The Vaccine Handbook:
A Practical Guide for Clinicians

Twelfth Edition

Gary S. Marshall, MD

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Marshall

12th
edition

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A Practical Guide for Clinicians

TWELFTH EDITION

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Norton Children's and
University of Louisville School of Medicine

PROFESSIONAL
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***The Vaccine Handbook: A Practical Guide for Clinicians*, 12th ed.**

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About the Pediatric Infectious Diseases Society

The Pediatric Infectious Diseases Society (PIDS) is the world's largest organization of professionals dedicated to the treatment, control and eradication of infectious diseases affecting children. PIDS membership encompasses leaders across the global scientific and public health spectrum, including clinical care, advocacy, academics, government, and the pharmaceutical industry. From fellowship training to continuing medical education, research, regulatory issues, and guideline development, PIDS members are the core professionals advocating for the improved health of children with infectious diseases both nationally and around the world, participating in critical public health and medical professional advisory committees that determine the treatment and prevention of infectious diseases, immunization practices in children, and the education of pediatricians.

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Foreword

The Vaccine Handbook: A Practical Guide for Clinicians—known widely as *The Purple Book*—has been in print for nearly two decades. Now in its 12th edition, the goal of *The Purple Book* is to provide concise, user-friendly, up-to-date information on vaccines to anyone who needs it, from physicians and nurse practitioners at the front line to trainees, nurses, pharmacists, and even interested patients and parents. Notably, the 12th edition will, for the first time, include a chapter on RSV as a vaccine-preventable disease—those of us here at the Pediatric Infectious Diseases Society (PIDS) have been waiting a long time for this. Along with progress has come increasing skepticism about the necessity for, and value of, vaccination in general, made all the more poignant in the post-pandemic environment. Not surprisingly, then, the longest chapter in *The Purple Book* is one that helps us navigate through this sea of vaccine hesitancy.

PIDS is thrilled to provide this resource as part of its ongoing efforts to improve vaccine education. *The Purple Book* is the foundation of the Collaboration for Vaccine Education and Research (CoVER) Program (see QR code below), an online curriculum for trainees and anyone else who wants to advance their knowledge of vaccines.

Inclusion, innovation, and impact—these are the identity of PIDS. *The Purple Book* showcases the innovation of the scientific community to which we belong, the impact of vaccines on human health, and our ability to reduce health disparities through access to immunizations.

Vaccines are part of the DNA of PIDS. They are one example of how, working together, we can provide patients, parents, and families an environment free of disease.

C. Buddy Creech, MD, MPH
President, Pediatric Infectious Diseases Society

For the PIDS Executive Committee
Kris Bryant, MD, PIDS Foundation President
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CoVER
Collaboration for Vaccine Education & Research

Preface

I'm sitting in Row 10, United 5450, ORD to SDF, unmasked, when an article in the New York Times[1] pops into view: *the number of Americans dying each day is back to normal*. At the height of the pandemic, there were weeks when the "excess death rate" in the US was almost 50 percent above normal.[2] By July 17, 2023—the date of that plane flight—COVID-19 had become an endemic respiratory illness. In thinking about how that happened—high transmission rates, widespread natural immunity, evolution of the virus, and so on—we cannot lose site of the fact that vaccines prevented 20 million premature deaths during the first year they were available.[3]

This past year, RSV gained a long-awaited seat at the Table of Diseases That Are Preventable Through Immunization (that would be both active [vaccines for adults] and passive [maternal vaccination or the monoclonal antibody for infants] immunization). While it's good to have new tools in our shed, we cannot rest on our vaccine laurels, because COVID-19 will not be the last pandemic, RSV is not the last infectious disease we need to prevent, and public sentiment is unpredictable.

Previous editions of The Purple Book have been dedicated to my vaccine heroes: Stanley A. Plotkin—7th edition (*My Max Gottlieb*); Kathy Edwards—8th edition (*Academic mother and medical conscience of so many*); and Paul Offit—9th edition (*Both versions*). The hero list has now grown to include Barney Graham, who figured out that prefusion stabilized viral proteins make better immunogens, a direct line to the RSV and COVID-19 vaccines[4]; Katalin Karikó and Drew Weissman, who rendered mRNA less toxic and more stable, opening the door to a new vaccine technology[5]; and the many people who labor behind the scenes in the private sector to move vaccines from benchtops into arms.

Which brings me to Penny Heaton, my first fellow (1994 to 1997). An academic at heart, Penny has spent her entire career in the private sector, her stated mission *to lead vaccines development from discovery through regulatory licensure and post-approval studies*. This is *translation*, and it requires nurturing strategic partnerships between academia, product developers, manufacturers, biotechnology firms, multinational companies, and governments. From leading the effort to license a second-generation rotavirus vaccine,[6] to testing novel constructs,[7] to thinking about the next generation of physician-scientists,[8] Penny is about getting things done.

She's had a lot of bosses (Bill Gates, for one). But she once told me about a woman she came across in Kenya, sitting on a bench, waiting to be seen in clinic, infant in arms. Every few minutes she bent down to place a rag in a puddle, soak up some water and squeeze it into her baby's dry mouth. "This woman," said Penny, "is my *real* boss."

— GSM (October 5, 2023)

Conventions Used in This Book

The nomenclature and abbreviations used in this book for disease agents and their respective vaccines are given in **Table 36.4**. In general, standards set by the Advisory Committee on Immunization Practices (ACIP) are followed (https://www.cdc.gov/vaccines/terms/vacc-abbrev.html; accessed October 5, 2023), with some modifications. For example, the proteins used in protein-polysaccharide conjugate vaccines are added to the abbreviations, as in "Hib-T" for "*Haemophilus influenzae* type b vaccine, tetanus toxoid conjugate" and "Hib-OMP" for "*Haemophilus influenzae* type b vaccine, outer membrane protein conjugate" (these are important to differentiate because the dosing schedules differ). There are times when vaccines are referred to in generic fashion, in which case the qualifier is dropped (eg, "Hib" for "*Haemophilus influenzae* type b conjugate vaccine").

In general, the abbreviation for the disease agent (eg, "HAV" for "hepatitis A virus") is different from the vaccine (eg, "HepA" for "hepatitis A vaccine"). In some cases, there is no abbreviation for the agent (eg, "human papillomavirus") so that an abbreviation can be used to refer to the vaccine (eg, "HPV" for "human papillomavirus vaccine"). The valency may get added to the end, as in "HPV9," which means "human papillomavirus vaccine, 9-valent." For some vaccines (eg, rabies vaccine), the abbreviation was made up (eg, "RAB"). Specific identifying characteristics, such as the cell type in which the vaccine was produced, may be indicated, as in "RAB-HDC," which means "rabies vaccine, human diploid cell." For COVID-19 vaccines (COV), the type of vaccine and the manufacturer's name are included to differentiate and avoid confusion. Thus, for example, "COV-mRNA (Pfizer-BioNTech) means "COVID-19 vaccine, mRNA-based, manufactured by Pfizer-BioNTech". The isolated abbreviation "COV" refers to "any vaccine against COVID-19".

Premixed combination vaccines are denoted by dashes between the components (eg, "DTaP-HepB-IPV" for Pediarix, which contains DTaP, HepB, and IPV). Combination vaccines that require reconstitution are denoted by a slash mark (eg, "DTaP-IPV/Hib," where the liquid DTaP-IPV is used to reconstitute the lyophilized Hib-T, creating the combination vaccine Pentacel). In general, vaccine trade names use initial capitals only, except where upper and lower-case letters are interspersed in the name, as in "RotaTeq." Trademark symbols are not used. Vaccines are referred to by their abbreviations (**Table 36.3**) without definition in the text.

In general, "age" means that the individual has passed one mark in time but has not yet reached the next relevant mark. For example, "2 months of age" means "at or beyond the 2-month birthday but not yet at the 3-month birthday". In tables, "days" is abbreviated "d"; "weeks", wk"; "months", "mo"; and "years,", "y". In addition, "2 months of age" is abbreviated as "2 mo", and so on. Age intervals may be indicated by a dash or the word "to"; thus, "4-6

y", "4-6 years of age" and "4 to 6 years of age" all mean "4 years of age through 6 years of age," or "from the 4th birthday until the day before the 7th birthday." As far as time is concerned, "weeks" are 7 days and, up to 4 months, "months" are 28 days; at 4 months and beyond, "months" are "calendar months," meaning an interval to the same date in the appropriate month (eg, for an infant vaccinated on January 6, an interval of 6 months would be to July 6). These definitions are particularly relevant when referring to age indications for vaccines and minimum intervals.

Many organizations provide guidance regarding immunizations. The most generally applicable, authoritative recommendations come from the ACIP, the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians. The recommendations from these organizations are usually very similar, and as such, ACIP recommendations are given in the book. Every attempt is made to highlight differences between ACIP recommendations and those of other agencies, and off-label recommendations are noted.

In *Section B: Diseases and Vaccines*, the cost of routinely recommended vaccines comes from the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html; accessed October 5, 2023). For other vaccines, retail prices are estimated from Internet sites like WebMDRx (https://www.webmd.com/rx; accessed October 5, 2023).

Disclaimers

Care has been taken to confirm the accuracy of the information presented herein and to describe generally accepted practices. However, the author, editor, and publisher are not responsible for errors or omissions or for any consequences from application of the information in this book and make no warranty, expressed or implied, with respect to the currency, completeness, or accuracy of the contents of the publication. Application of this information in a particular situation remains the professional responsibility of the practitioner.

The author, editor, and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accordance with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert and published or posted recommendations for each drug or vaccine discussed, being aware that there may be changes in indications, dosage, or schedule, and that added warnings and precautions may have been issued. This is particularly important when the recommended agent is a new or infrequently employed drug. Some drugs and medical devices presented in this publication may have US Food and Drug Administration (FDA) clearance for limited use in restricted research settings. It is the responsibility of health care providers to ascertain the FDA status of each drug or device planned for use in their clinical practice.

About the Author

Dr. Marshall received his undergraduate degree from the University of Pennsylvania and his medical degree from Vanderbilt University. He completed a pediatric residency at Vanderbilt and an infectious diseases fellowship at the Children's Hospital of Philadelphia, and in 1989 joined the faculty at the University of Louisville. Dr. Marshall currently serves as Chief of Pediatric Infectious Diseases at Norton Children's and the University of Louisville School of Medicine. He has received the Outstanding Clinical Professor and Educator of the Year Awards from the Department of Pediatrics, as well as the Distinguished Educator Award from the School of Medicine and the Educational Achievement Award from the Kentucky Medical Association. Dr. Marshall is a member of the Infectious Diseases Society of America and the Pediatric Infectious Diseases Society, among other organizations, and has authored over 200 scientific papers, many in the areas of vaccine development, advocacy, and education. In 2018, Dr. Marshall was honored to receive the Stanley A. Plotkin Lecture in Vaccinology Award from the Pediatric Infectious Diseases Society for "contributions to the field of vaccinology or areas of related science that have impacted the lives of children and the specific area of pediatric infectious diseases."

Acknowledgements

I am deeply indebted to the many individuals who have contributed to this work over the years. Special thanks go to the folks at CDC, AAP, and Immunize.org. I would also like to thank my Louisville colleagues, the Pediatric Infectious Diseases Society, and the industry partners who have (directly or indirectly) supported the book.

— GSM

Dedication

For Penny Heaton,
and her *real* boss

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Introduction to Vaccinology

Immunization

Immunization is the process of protecting individuals from disease by making them immune. This is most often accomplished *actively* through *vaccination*, the delivery of *antigens* (substances that are foreign to the host) contained in *vaccines* for purposes of stimulating an immune response (immunization can also be accomplished *passively* by the administration of antibodies). While not technically correct in all instances, the terms *vaccination* and *immunization* are often used interchangeably.

Table 1.1 shows one approach to classifying vaccines used in humans. Broadly speaking, vaccines are either *live* or *non-live;* **Table 1.2** lists generalizations about vaccines by type, which have practical consequences for storage, scheduling, efficacy, contraindications, and the potential for adverse reactions.

Live Vaccines

Live vaccines replicate in the host, stimulating immune responses that mimic those induced by natural infection. They are generally *attenuated*, or weakened, such that they cause subclinical infection with little risk of disease. There are several approaches to attenuation.

- *Serial passage*—This is the classical method of attenuating viruses, dating back to the 1930s when Thieler weakened yellow fever virus by serial passage in eggs. Serial passage causes the accumulation of mutations that, while adapting the virus to growth in vitro, render it less fit in vivo. Sabin developed the modern prototype of live attenuated virus vaccines by passaging poliovirus serially through monkey cells and demonstrating that oral administration of the attenuated virus protected against polio. Serial passage also was used to attenuate measles, mumps, and rubella viruses for use in vaccines. The virus used to make VAR was originally isolated from a child in Japan in the early 1970s; it was then serially passaged in human embryonic lung, embryonic guinea pig, and WI-38 (human diploid) cells to achieve attenuation. More recently, a strain of rotavirus that circulated in Cincinnati in the late 1980s was used to make RV1 by serial passage in Vero (African green monkey kidney) cells.

TABLE 1.1 — Classification of Vaccines Currently Available in the United States

Live			Non-Live						
	Attenuated				Subunit				
Not Attenuated	Classical	Engineered	Whole Agent	Viral, Non-Replicating	Toxoid	Purified	Engineered	In Vitro-Expressed	In Vivo-Expressed
Adenovirus[a]	MMR[b] RV1[c] Smallpox (ACAM2000)[d] VAR YFV	Cholera[e] Dengue[f] Ebola[g] LAIV[h] RV5[c] Ty21a[i]	HepA IPV JEV-VC RAB TBE	Smallpox (Jynneos)[j]	Diphtheria Tetanus	AVA[k] IIV[l] MenB-4C[m] Pertussis[n] PPSV23[o] TViPSV[o]	Hib[p] MenACWY[p] PCV[p]	COV-aPS[q] HepB[r] HPV9[s] rIIV[t] MenB-4C[m] MenB-FHbp[m] RSV[u] RZV[v]	COV-mRNA[w]

Listed vaccines are administered parenterally unless otherwise noted. The following vaccines are not available in the US: BCG (tuberculosis)—live attenuated, classical bacterial; cholera (WC/rBS)—inactivated, whole agent plus in vitro-expressed subunit, orally administered; COV-Ad26 (Janssen)—non-live, subunit, in vivo-expressed; hepatitis B (plasma-derived)—non-live, whole agent; Hib polysaccharide—non-live, purified subunit; HPV2 (human papillomavirus)—non-live, in vitro-expressed subunit (2-valent); influenza (whole virus)—non-live, whole agent; pertussis (whole cell)—non-live, whole agent; Lyme disease (rOspA)—non-live, in vitro-expressed subunit; MPSV4—non-live, purified subunit; OPV (polio)—live attenuated, classical viral; plague—non-live, whole agent; typhoid—non-live, whole agent; zoster vaccine live (shingles)—live attenuated, classical viral.

[a] Vaccine strains are not intrinsically attenuated, but do not produce disease because they are administered orally.
[b] Mixture of classically attenuated measles, mumps, and rubella viruses.
[c] RV1 contains a single strain of classically attenuated human rotavirus. RV5 contains 5 bovine-human reassortants. Both are orally administered.
[d] Vaccinia virus (which is related to cowpox and horsepox but does not exist in nature) produced in cell culture.
[e] CVD 103-HgR consists of serogroup O1 classical Inaba strain 569B with the catalytic domain of the ctxA genes deleted, rendering it incapable of producing active cholera toxin. The strain does produce the B subunit of cholera toxin, which is immunogenic but not toxic. The vaccine is orally administered.
[f] Dengue Tetravalent Vaccine, Live (Dengvaxia; Sanofi) consists of 4 chimeric strains of YFV (a live attenuated vaccine) in which the native pre-membrane and envelope protein genes were replaced by the corresponding genes from dengue virus serotypes 1, 2, 3, and 4.
[g] Ebola Zaire Vaccine, Live (Ervebo; Merck) consists of vesicular stomatitis virus (an animal pathogen) in which the native surface glycoprotein gene was replaced by the corresponding gene from Ebola virus (the substitution maintains replication competency but confers attenuation).
[h] Influenza virus engineered to attenuation, then reassorted to include hemagglutinin and neuraminidase of circulating strains.
[i] Mutagenized *S typhi*, selected for attenuation, orally administered.
[j] Modified Ankara-Bavarian Nordic strain of vaccinia virus that became replication incompetent for mammalian cells after serial passage in chick embryo fibroblasts. While Jynneos is replication competent in avian cells, it is classified here as non-live because it behaves like a non-live vaccine in human hosts. (Timing and Spacing of Immunobiologics, Table 3-1. CDC Web site. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html. Accessed July 13, 2023).
[k] Produced from cell-free filtrate of an avirulent strain of *B anthracis*.
[l] Physically purified hemagglutinin and neuraminidase from influenza virus.
[m] MenB-4C contains Factor H binding protein (subfamily B) and Neisserial heparin binding antigen fusion proteins and partial length Neisserial adhesin A expressed in *E coli*; a fourth component is physically purified outer membrane vesicles, which include PorA serosubtype P1.4. MenB-FHbp contains lipidated Factor H binding protein (subfamily A and B) expressed in *E coli*.
[n] Physically purified, inactivated pertussis toxin (arguably, this could be classified as a toxoid) and filamentous hemagglutinin; some pertussis vaccines also contain pertactin and fimbriae.
[o] Physically purified polysaccharide. Valency varies; for example, PPSV contains polysaccharide from 23 different pneumococcal serotypes, but TViPSV contains polysaccharide from only one strain of salmonella.

Continued

TABLE 1.1 — *Continued*

[p] Protein-polysaccharide conjugate. Valency varies; for example, Hib contains only one polysaccharide derived from the capsule of *H influenzae* type b, whereas MenACWY contains polysaccharide derived from the capsules of 4 different *N meningitidis* serogroups. Carrier proteins also vary. For example, Hib uses either tetanus toxoid or an outer membrane protein from *N meningitidis*; MenACWY uses either diphtheria toxoid, CRM (a mutant diphtheria toxin), or tetanus toxoid. PCV13, PCV15, and PCV20 use CRM as the carrier protein.

[q] The Novavax COVID-19 vaccine consists of recombinant-derived prefusion-stabilized S-protein assembled into nanoparticles and co-formulated with an adjuvant.

[r] Engerix-B, Heplisav-B, and Recombivax HB consist of hepatitis B surface antigen expressed in yeast. PreHevbrio consists of the small (S), middle (pre-S2) and large (pre-S1) hepatitis B surface antigens expressed in modified Chinese Hamster Ovary cells.

[s] L1 protein expressed in yeast, 9-valent.

[t] Hemagglutinin expressed in baculovirus-infected cells.

[u] The RSV vaccines from GSK and Pfizer consist of prefusion-stabilized F (fusion) protein (the Pfizer vaccine contains the F-protein from the A and B strains; the GSK vaccine contains the F-protein from the A strain and is adjuvanted).

[v] Surface glycoprotein E (gE) expressed in Chinese Hamster Ovary cells.

[w] These COVID-19 vaccines (Pfizer-BioNTech and Moderna) consist of mRNA that enters host cells and directs the expression of prefusion-stabilized S-protein. The mRNA is packaged in lipid nanoparticles to ensure stability and facilitate transfection.

Attenuation of bacteria dates to the mid-1800s, when Pasteur protected animals from anthrax using a form of the bacterium that had been weakened using chemicals. In vitro passage also has been used to attenuate bacteria. For example, Bacille Calmette-Guérin (BCG), a vaccine that protects against disseminated tuberculosis and is used outside the US, was a strain of *Mycobacterium bovis* (which is related to *M tuberculosis*) originally isolated from a cow in 1908 and passaged over 200 times in culture.

- *Heterologous host*—This method dates to the late 1700s, when Jenner used an animal poxvirus to protect humans from smallpox. Many animal viruses are naturally attenuated for humans. For example, RV5 was derived from a bovine strain of rotavirus (WC3) that replicates in humans but does not cause disease. The wild-type virus does not induce sufficient protective antibody against human strains, so it was altered to express immunogenic surface proteins of human rotaviruses. This was accomplished through *reassortment*, whereby the parental strain was co-cultured with natural human strains—bovine viruses that "accidentally" packaged genes for the human G or P proteins (dominant protective antigens) were selected and propagated. The vaccine strains consist of viruses that in every way are identical to the naturally attenuated bovine virus, except that each one expresses an immunogenic human protein instead of the corresponding bovine protein.
- *Engineered attenuation*—The attenuated phenotype can be purposefully introduced into an organism through mutagenesis and selection. An example of this is the oral typhoid vaccine Ty21a, which was derived from *Salmonella typhi* strain Ty2 after treatment with a mutagenic agent and selection for attenuation. Attenuation can also be introduced through genetic manipulation. An example of this is the Ebola vaccine that was approved in 2019. This *replication-competent viral vector* vaccine consists of vesicular stomatitis virus (an animal pathogen that can infect humans but usually does not cause disease) in which the native surface glycoprotein gene has been replaced by the gene for the immunodominant surface glycoprotein of Ebola virus. The substitution confers definitive attenuation on the virus, and the vector not only expresses the Ebola antigen of interest but also amplifies in the host.
- *Altered site of infection*—The attenuated phenotype can be achieved by something as simple as using an unnatural route of inoculation. The adenovirus vaccine, which is used in the military, consists of enteric-coated tablets, one containing live (non-attenuated) adenovirus type 4, and the other, type 7. When these viruses are delivered to the gastrointestinal tract, they replicate and stimulate an immune response without causing disease.

TABLE 1.2 — Generalizations About Vaccines by Type

Characteristic	Live	Non-Live
Immune response	Humoral and cell-mediated	Mostly humoral[a]
Dosing	One or 2 doses usually sufficient[b]	Multiple-dose series usually necessary[c]
Adjuvant	Not necessary	May be necessary[d]
Route of administration	Intranasal, oral, subcutaneous	Intramuscular, subcutaneous, intradermal[e]
Duration of immunity	Potentially lifelong	Booster doses may be necessary[f]
Person-to-person transmission	Possible[g]	Not possible
Effect of passively acquired antibodies	Inactivation possible	Interference possible
Use in immunocompromised hosts	May cause disease	May be less immunogenic
Use in pregnancy	Fetal damage theoretically possible[h]	Fetal damage theoretically unlikely
Rationale for storage requirements	Maintain viability	Maintain stability
Administration on the same day	Acceptable[i]	Acceptable[j]
Interval between doses of the *same* vaccine given in sequence	Minimum intervals apply[k]	Minimum intervals apply[l]
Interval between doses of *different* vaccines given in sequence	Minimum intervals apply[k]	No minimum intervals

[a] Non-live vaccines may stimulate limited cell-mediated immune responses through cross-presentation.

[b] RV5 and Ty21a are given orally in multiple-dose series; cholera vaccine is given as a single oral dose. Although 1 dose of MMR or VAR may be sufficient to induce long-lasting immunity, second doses are given before school entry to ensure that children who did not seroconvert to the first dose have another chance to do so. Since immunity to varicella zoster virus can wane after immunization, the second dose of VAR may also serve as a booster.

[c] Older adults may respond well to a single dose of a non-live vaccine because they have been previously primed by natural exposure. This might apply, for example, to PPSV23—adults who receive this vaccine have probably had prior exposures to *S pneumoniae*.

Continued

TABLE 1.2 — *Continued*

[d] Hib-T, IIV, MenACWY-D, MenACWY-CRM, MenACWY-T, PPSV23, IPV, RSV (Pfizer), and RAB do not contain adjuvants.

[e] Fluzone Intradermal (idIIV) was discontinued in 2017.

[f] Long-term protection has been demonstrated for some non-live vaccines, such as HepA and HepB, in the absence of booster doses.

[g] This is relevant for OPV, where horizontal transmission contributes to immunity at the population level, but also on rare occasion leads to disease in contacts. Transmission of vaccinia represents a real risk to susceptible close contacts. Transmission of cholera vaccine, LAIV, RV, and VAR has been documented, but is rare. Transmission of MMR, Ty21a, and YFV has not been documented.

[h] The possibility of fetal infection leads to the general recommendation that live vaccines should not be given during pregnancy (see *Chapter 6*: *Vaccination in Special Circumstances—Pregnancy, Postpartum, and Breast-Feeding*).

[i] Separate sites are always used for simultaneous administration. The only example of two live vaccines that cannot be given at the same time are VAR and smallpox (the concern is increased complications from smallpox vaccine).

[j] Separate sites are always used for simultaneous administration. Examples of two non-live vaccines that cannot be given at the same time are MenACWY-D and PCV13 in anatomically or functionally asplenic children (the concern is reduced response to pneumococcal antigens) and PCV13 and PPSV23 (the concern is interference).

[k] Replication of the first live vaccine can interfere with replication of a second live vaccine that is given within 4 weeks.

[l] Proper spacing between the doses is necessary to maximize the immune response.

Non-live Vaccines

Non-live vaccines have been referred to as *inactivated*, but that term is problematic. It is most accurate when referring to toxoids, which are "inactivated" toxins, although even here there is a problem—their toxicity is *inactivated* by chemical means, but toxoids are still *active* immunologically. Likewise, inactivated polio vaccine is noninfectious but still antigenic; in this context, "killed" might be a better descriptor. Some vaccines like HepB and HPV are made by in vitro expression of pathogen-derived genes; here, the vaccine antigens are not "inactivated" (they are natural proteins) or "killed" (they were not "live" to being with). For simplicity's sake, the term "non-live" is used herein to mean a vaccine that does not replicate in the same sense that a live virus or bacterium does.

- *Whole agent*—Non-live *whole agent* vaccines date back to the late 1800s, when Pasteur used killed rabies virus to protect animals and, eventually, humans from rabies. Salk developed the modern prototype of non-live whole-virus vaccines by growing poliovirus in cell culture, purifying it, inactivating it with formaldehyde, and demonstrating that intramuscular injection of the inactivated virus protects against polio. HepA, JEV, RAB, and TBE vaccine are made in much the same way. The modern prototype of non-live whole bacterial vaccines is whole-cell pertussis, which was made from suspensions of cultured *Bordetella pertussis* organ-

isms that were killed and detoxified. Because it contained every antigen from the live organism, this vaccine was both effective and reactogenic.

- *Subunit*—These vaccines use only a part of the pathogen instead of the whole organism.
  - *Toxoids*: These are protein toxins elaborated by bacteria that have been chemically modified to reduce pathogenicity while maintaining immunogenicity. The only current toxoid vaccines are those for diphtheria and tetanus (inactivated pertussis toxin is generally not referred to as a toxoid, although it is pretty much the same thing).
  - *Purified subunits*: In this case, an immunogenic component of the organism is physically purified and used (essentially in unmodified form) as a vaccine. Examples include the polysaccharide vaccines for *S pneumoniae* and *S typhi*, where the capsular polysaccharide is stripped from the cell surface and purified.
  - *Engineered subunits*: Polysaccharide vaccines induce only short-term immunity, do not produce memory, and are not immunogenic in young infants. These problems were overcome by chemically conjugating the polysaccharides to proteins (*see below*).
  - *In vitro-expressed subunits*: Subunits can be produced in vitro using recombinant DNA technology. The prototype here is recombinant-derived HepB, where the gene for hepatitis B surface antigen (HBsAg) was inserted into yeast cells, which produce large quantities of the protein for purification. A similar method was used to produce HPV. In this case, the gene for the L1 protein was expressed in either yeast (HPV4 and HPV9) or insect (HPV2) cells. L1 spontaneously aggregates into virus-like particles that look like viruses on the outside, are immunogenic, carry no genetic material and are incapable of replicating. In the case of COV-aPS (Novavax), the S-protein from SARS-CoV-2 is expressed in insect cells and formulated into a nanoparticle that stabilizes the antigen and presents it in similar fashion to a viral particle.[1] Genetically engineered Chinese Hamster Ovary cells are used to express the antigens that go into HepB3, RSV (GSK), RSV (Pfizer), and RZV. Recombinant DNA technology has also been used to make vaccines for *N meningitidis* serogroup B and influenza.
  - *In vivo-expressed subunits*: Subunits can also be expressed in vivo. mRNA-based technologies had been under development for 25 years when the COVID-19 pandemic hit in 2020, and they were used by Pfizer-BioNTech and Moderna to rapidly develop vaccines. Here, synthetically produced mRNA enters host cells through *transfection* at the site of inoculation or downstream in regional lymph nodes, directing cellular ribosomes to produce the protein of interest—in this case, the S-protein of SARS-CoV-2 (the virus that causes COVID-19), which mediates attachment and fusion and carries neutralizing epitopes. The protein expressed by host cells, especially dendritic cells and other professional antigen-presenting cells in lymph nodes and possibly even liver and spleen,[2] is then presented to immune effectors, which go on to generate specific adaptive immune responses. Hurdles had to be overcome before mRNA vaccines were ready for widespread use. For example, mRNA is rapidly degraded by ubiquitous ribonucleases and therefore had to be protected in some way. Moreover, there had to be a way to reliably get the mRNA into the cytoplasm. One solution to both problems was to package the mRNA in lipid nanoparticles; this stabilizes the molecule and facilitates endocytosis. Native mRNA can stimulate strong innate immune responses, and thus had to be modified to be less reactogenic. The mRNA sequences were also optimized for protein expression; this, combined with stimulation of innate immunity by the lipid package and the modified mRNA, leads to strong antibody responses.

Proteins made by mRNA vaccines undergo post-translational modification, folding, intracellular transport, and surface expression just like proteins made during natural infection; the similarity of vaccine-encoded antigen to native antigen ensures robust and relevant antibody responses. Proteins expressed in transfected cells are taken up by *antigen-presenting cells* (APCs), degraded into peptides, and presented to *helper T lymphocytes* (Th-cells) in the context of *MHC class II molecules* (MHC-II) (*see below*). APCs themselves may also be transfected and produce the protein internally, in which case fragments of the nascent polypeptide chain are loaded into *MHC class I molecules* (MHC-I) molecules for presentation to *cytotoxic T-cells* (Tc-cells). mRNA vaccines are thus capable of stimulating strong antibody responses as well as cellular immunity. mRNA vaccines are non-infectious, cannot cause the target disease, carry no risk of integrating into host genetic material, and are not affected by pre-existing immunity, as might be the case for viral expression vectors (*see below*). All that is needed to make a vaccine is the sequence of the target protein; this means that development can be expeditious (it also means that the vaccines can be modified quickly if new strains of the virus evolve). The SARS-CoV-2 genetic sequence was made available on January 11, 2020; by January 13, Moderna had finalized the mRNA sequence for its vaccine and by February 7 a clinical batch was ready for analytical testing. mRNA vaccines are also rapidly scalable—by July 2021, Phase 3 studies involving tens of thousands of subjects were underway, and by years' end millions of doses were ready for delivery.

Another way to express subunits in vivo is to deliver the instructions for making them through a *replication-incompetent viral vector*. As with mRNA vaccines, this technology had been under development when COVID-19 hit. The Janssen COVID-19 vaccine, which was no longer used in the US as of June 2023, is a recombinant adenovirus type 26 in which the E1 and E3 genes are deleted, rendering it incapable of replicating, and into which the S-protein gene is inserted. Host cells are infected and produce the S-protein, conferring the same advantages as for mRNA vaccines. The vaccine virus itself does not replicate; for production, the vaccine is grown in cells that complement the function of the deleted genes.

In *classical vaccinology*, the immunogenic subunits of a pathogen are identified, physically purified, and injected into animals to measure the immune response. *Reverse vaccinology* starts with the genotype (the genes) rather than the phenotype (the antigens), looking for genes that code for molecules that are likely to be important in immunity (ie, they are expressed on the cell surface and have a critical role in infectivity). The genes are then expressed, and the resultant antigens screened for immunogenicity in animals. Going forward, the identification of optimal antigens for use in vaccines may depend on *systems immunology*, a holistic picture of the immune response that is now possible with techniques like next-generation sequencing, protein and peptide microarrrays, flow and mass cytometry, and metabolomics, as well as advances in data processing and analysis.[3]

Passive Immunization

Passive immunization is the process by which short-term protection from disease is conferred by administration of antibodies. This process occurs naturally during the last 2 months of pregnancy, when large quantities of IgG are transferred across the placenta to the fetus, and it explains the relative protection that newborns have against invasive *S pneumoniae* and *H influenzae* type b infections, among others. Passive immunization is necessary for patients with humoral immune defects who cannot synthesize their own antibody. *Polyclonal immune globulin* is used to prevent specific infections such as measles and hepatitis A in vulnerable hosts, as the level of antibody against these viruses in pooled blood donations is sufficiently high. In some cases, *hyperimmune globulin* is used; this is derived from donors with high antibody levels to the pathogen (examples include varicella zoster immune globulin and hepatitis B immune globulin). Hyperimmune globulins contain antibodies to agents in addition to the one they target; while selected for their high specific antibody levels, the donors also have antibodies to other organisms. Antibodies also can be *engineered* for prevention of specific diseases, as in the case of the monoclonal antibody products against RSV and SARS-CoV-2. *Antitoxins*, also known as *heterologous hyperimmune sera*, are also used for passive immunization. These are produced in animals like horses and target toxins such as diphtheria, botulinum, and tetanus.

Passively acquired antibodies can inactivate live vaccines. MMR and VAR are not routinely given in the first year of life to avoid inactivation by maternal antibodies (these degrade sufficiently by 12 months of age). Likewise, administration of MMR and VAR is deferred in persons who receive blood products (which contain antibodies; see **Table 5.2**). Maternal antibodies also can interfere with the response to some non-live vaccines[4]; this is one reason why HepA is usually given in the second year of life. Passively acquired antibodies do not appear to interfere with vaccines administered at mucosal surfaces, which is why RV can be given as early as 6 weeks of age.

Basic Vaccine Immunology

Vaccines are designed to generate pathogen-specific antibodies and T-cells by stimulating the *adaptive immune system*, which recognizes and remembers specific pathogens and learns to respond to them more strongly after each exposure. What follows is a simplified version of the immune mechanisms that underpin vaccination.[5] These concepts shed light on the differences between various types of vaccines, the duration of protection, dosing schedules, and other aspects of vaccine practice.

Antibodies

Antibodies are proteins that bind to conformational, 3-dimensional patterns called *epitopes* that are present on antigens. They constitute the humoral, or soluble, arm of the adaptive immune system and are produced as different immunoglobulin *isotypes* (IgG, IgA, IgM, IgE, IgD) that have different functions. A given antibody with a given antigenic specificity can be produced as one of several different isotypes. Antibody binding is specific in that each antibody molecule binds best to one epitope; any given antigen may express many different epitopes, and any given organism may have hundreds of different antigens. The possible consequences of antibody binding to bacteria are illustrated in **Figure 1.1**. Virus-infected cells may also be flagged for destruction by phagocytes or natural killer cells, a process known as *antibody-dependent cell-mediated cytotoxicity* (ADCC). The Holy Grail of vaccine development is the identification of epitopes expressed on pathogens that elicit *broadly neutralizing antibodies*—those that can take out many different strains of the organism.[6]

Antibody is the only element of the adaptive immune system that can *prevent* viral infection because it can neutralize a virus before it has a chance to replicate in cells. It is also the mainstay of protection against bacterial invasion since it can facilitate destruction of the organism before it has a chance to replicate. The battle between

FIGURE 1.1 — Antibody Functions

Neutralization refers to the inactivation of pathogens and toxins. *Opsonization* refers to coating of the organism with antibody, resulting in removal through phagocytosis. *Complement activation* leads to the deposition of proteins on the organism that form a *membrane attack complex*, causing *complement-mediated lysis*. Complement activation also enhances opsonization.

Adapted from Murphy K. *Janeway's Immunobiology*. 8th ed. New York, NY: Garland Science; 2011.

antibodies and pathogens takes place at different sites. At mucosal surfaces, where most pathogens attempt to gain entry, secretory IgA and serum-derived IgG antibodies are important. Live vaccines that replicate at mucosal surfaces (eg, RV and LAIV) have the advantage of inducing strong local IgA responses that can neutralize pathogens before attachment. Vaccines given parenterally are not as good at generating mucosal IgA, although many do. A vaccine that induces high levels of serum IgG not only protects against bloodstream invasion and infection of extravascular spaces, but also blocks infection at mucosal sites before the organism gains a foothold.

Antibodies are produced by plasma cells, which are derived from B-lymphocytes or *B-cells*. B-cells have immunoglobulins on their surface (mostly IgM, also referred to as the *B-cell receptor*) that express one and only one antibody specificity. During ontogeny, genetic rearrangements lead to a diverse repertoire of B-cell clones, each with its own unique antibody specificity (B-cells that emerge from this process with receptors that recognize self-antigens are deleted). B-cells that leave the bone marrow and do not encounter their cognate antigen are short-lived, but new B-cells with new specificities are generated every day; in this way, the B-cell repertoire is continuously refreshed. People are, therefore, walking around with millions of B-cells, each pre-committed to recognizing one and only one epitope. Theoretically, humans even have B-cells capable of recognizing the Andromeda strain,[7] should it happen to (again) fall to earth. The point is that the B-cell repertoire theoretically covers every possible antigen—extant or imagined—that is not self. When a given B-cell finds its antigenic match, it is activated and proliferates; this is known as *clonal expansion*. The daughter cells eventually differentiate into plasma cells, which secrete large amounts of antibody.

There are two basic pathways through which antibody production occurs, and the differences between them are important to understanding how vaccines work.

The Extrafollicular Reaction

The extrafollicular reaction is best exemplified by the immune response to polysaccharides (**Figure 1.2**, **Panel A**). A pre-committed B-cell encounters its polysaccharide match (at the site of vaccination or in a lymph node to which the vaccine antigen was transported). This leads to activation, proliferation, and differentiation into plasma cells that migrate predominantly to the red pulp of the spleen and intramedullary areas of lymph nodes, where they begin producing antibodies. It is important to understand that these are *germline* antibodies, ie, antibodies transcribed from genes that were present in the B-cell to begin with. Germline antibodies have low affinity for their corresponding antigens because the genes encoding them are created by a random process during the B-cell's development. These B-cells (and their genes) are selected during their development because they do not recognize self antigens, not because they will

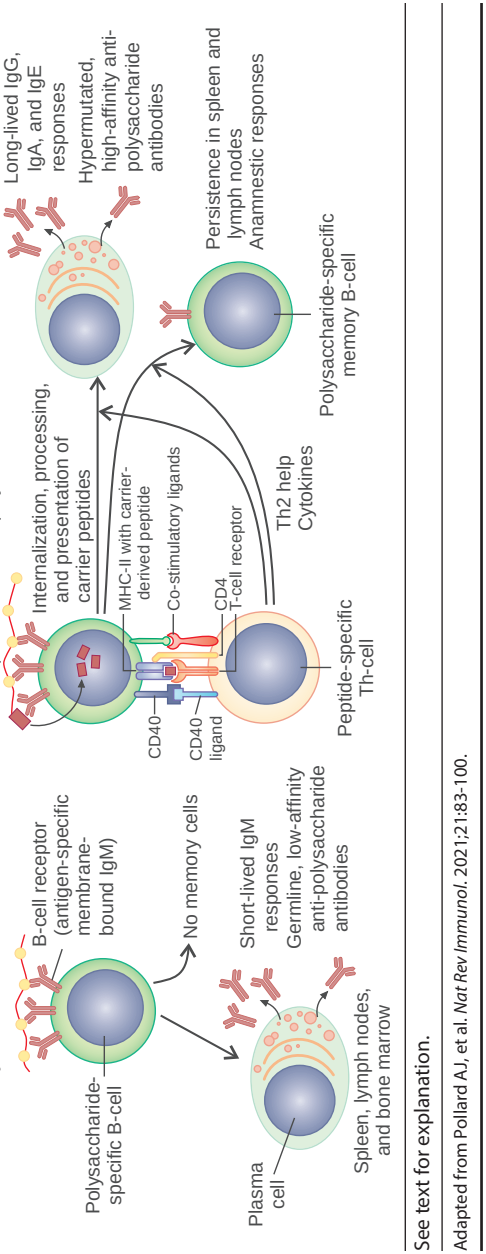


FIGURE 1.2 — Extrafollicular and Germinal Center Reactions

See text for explanation.

Adapted from Pollard AJ, et al. *Nat Rev Immunol*. 2021;21:83-100.

someday bind especially tightly to foreign antigens. Furthermore, most of the antibodies produced in the extrafollicular reaction are of the same isotype that was present on the B-cell surface, namely IgM, which does not offer the functional benefits of other isotypes like IgG. Finally, plasma cells produced through the extrafollicular reaction ultimately die out—no more antibodies produced, no more protection, no ability to remember the encounter and respond more quickly or decisively the next time.

This is called the *extrafollicular reaction* because it takes place outside of the germinal centers of lymph nodes. Antigens that elicit this response are called *T-cell independent* because the responding B-cells differentiate without much T-cell interaction. The characteristics of T-cell independent responses—rapid production (days to weeks) of short-lived, low-affinity, predominantly IgM antibodies without induction of memory—are hallmark features of the response to polysaccharide antigens, such as those in PPSV23. Children <2 years of age do not mount robust T-cell independent responses, making polysaccharide vaccines poor immunogens in that age group.

Another problem with polysaccharides is *hyporesponsiveness*—individuals who initially receive polysaccharide vaccines respond less well to subsequent polysaccharide challenge.[8] It appears that the initial exposure to antigen "uses up" some of the pre-existing antigen-specific B-cell pool.[9] Interestingly, infants receiving PCV7 have decreased responses to the *S pneumoniae* serotypes with which they are colonized at the time they are immunized, suggesting that colonization—a natural form of exposure to capsular polysaccharide—also induces hyporesponsiveness.[10]

It is important to point out that there is some crossover between immunologic pathways. For example, some degree of T-cell help (*see below*) may be available to extrafollicular B-cells, such that some isotype switching occurs and some memory may be generated.

The Germinal Center Reaction

Underpinning the adaptive immune system is the more primitive *innate immune system*, which initiates the battle against invading microorganisms in a nonspecific fashion. Cells of the innate immune system—most notably dendritic cells and monocytes—carry receptors that recognize conserved patterns among pathogens (*pathogen-associated molecular patterns*, or PAMPs) that are not found in self-tissues. Among these are *Toll-like receptors* (TLRs), each of which recognizes a different PAMP. TLR3, for example, recognizes double-stranded viral RNA; TLR4—endotoxin; TLR5—bacterial flagellins; TLR7—single-stranded RNA; TLR9—double-stranded DNA.[11] Engagement of pattern-recognition receptors activates the cell, which then secretes *cytokines* (intercellular communication molecules) that activate and recruit other cells, setting up an inflammatory reaction. The result might be destruction of the invader through processes such as phagocytosis. Importantly, this

is a one-time occurrence—once the pathogen is destroyed, there is no pathogen-specific memory of the encounter that might facilitate a response the next time around (although there is evidence that innate immune cells can be "trained" to be better killers and to more effectively trigger adaptive responses[12]).

The innate immune system is critically important because its activation can trigger and augment the adaptive immune response. The key link is provided by APCs, the most important of which are dendritic cells. Immature APCs circulate through the body or reside in tissues (immature dendritic cells in the dermis are called *Langerhans cells*). When a PAMP is encountered—in the form, for example, of a vaccine—the APCs begin to mature, express new receptors on their surface, and migrate through lymphatic vessels to regional lymph nodes. Some of them also engulf the vaccine antigens, degrade the proteins into small peptides, load the peptides into the groove of MHC-II, and express those molecules on their surface.

The mature APCs are now *activated* (secreting proinflammatory cytokines and expressing co-stimulatory molecules), *flagged* (by surface expression of antigen-derived peptides in the context of MHC-II), and have *migrated* to the follicular region of the lymph node. At this stage, the APCs are ready to engage immature Th-cells by interacting with the *T-cell receptor* (TCR) and the *CD4 co-receptor* (both are on the Th-cell). Each Th-cell is predetermined to recognize a particular peptide:MHC-II flag by virtue of its TCR and CD4 molecule. Each TCR has a unique antigenic specificity that was generated during development by a random process, much like the generation of germline antibodies (T-cells that emerge from this process with receptors that recognize self-antigens are deleted or inactivated). Through soluble cytokines and co-stimulatory receptor-ligand interactions, contact with the right APC results in activation and maturation of the Th-cell into antigen-specific subtypes that differ in their cytokine profiles and functions. The most important of these are Th1-cells, which help establish cellular immunity, and Th2-cells, which help establish humoral immunity (others include Th17-cells, which are involved in mucosal immunity, and Th follicular-cells, which help in affinity maturation). Several factors determine whether a Th-cell differentiates into a Th1- or Th2-cell during immunization; among these are the dose of antigen, route of administration, and the effect of adjuvants (*see below*). These factors, therefore, also determine whether humoral or cellular responses predominate.

Th1-cells have some direct antimicrobial functions. More importantly, though, Th1-cells seek out Tc-cells and macrophages, coaxing them into performing cytotoxic functions (*see below*). Th2-cells also have some direct antimicrobial functions, particularly against parasites. More importantly, though, Th2-cells seek out their unique B-cell matches to help them make antibody (to the antigen from which the peptide in the MHC groove was originally derived). B-cells are primed to be helped by engulfing some of the

bound antigen, digesting the proteins, and presenting the peptides on their surface in the context of MHC-II, much like dendritic cells do (**Figure 1.2**, **Panel B**). As further evidence of the interaction between the innate and adaptive immune systems, there is evidence that neutrophils (which are part of the innate immune system) are involved in stimulating antibody responses to vaccines.[13]

The interaction between B-cells and Th-cells takes place in the germinal centers of lymph nodes. The signals provided by Th2-cells, as well as the persistence of antigen shuttled there by APCs, drive B-cells to undergo massive clonal proliferation—producing millions of daughter cells capable of making the same antibodies. As they proliferate under these conditions, the B-cells undergo a process of *somatic hypermutation*, whereby the genes encoding the immunoglobulin-combining region mutate at exceptional rates, randomly producing a spectrum of antibodies with varying affinities for the antigen. Those B-cells expressing high-affinity antibodies are selected for and clonally expanded. The result is a set of dominant B-cell clones that produce high-affinity antibodies, ones that bind the antigen better than the germline antibodies (this is referred to as *affinity maturation*). This process takes a week or two.

Interestingly, the genes encoding TCRs do not undergo somatic hypermutation as do the genes encoding antibodies. One reason for this is the central role that T-cells play in adaptive immunity—they are involved in both humoral and cellular responses, and constraining their diversity helps limit autoimmunity. While we "want" TCR diversity so we can respond to a variety of foreign antigens, TCRs must also recognize MHC molecules as part of the antigen presenting complex; too much diversity could result in T-cells that are prone to self-recognition, leading to autoimmunity. On the other hand, we do not want T-cells that *fail* to recognize the MHC portions of the antigen-presenting complex, because then adaptive immune responses would be suboptimal.

In the germinal center, signals from Th2-cells drive *isotype switching* (from IgM to other isotypes) as B-cells transform into plasma cells. The result is large numbers of plasma cells that migrate to the bone marrow and produce high-affinity IgG, as well as other isotypes. Th2-cells also drive the evolution of *memory B-cells*, which migrate to the spleen and lymph nodes and wait there—sometimes for decades—until they again encounter their cognate antigen, at which time they rapidly proliferate and differentiate into antibody-producing plasma cells. This is called the *anamnestic response*. Memory Th-cells are also generated, but their numbers wane with time.

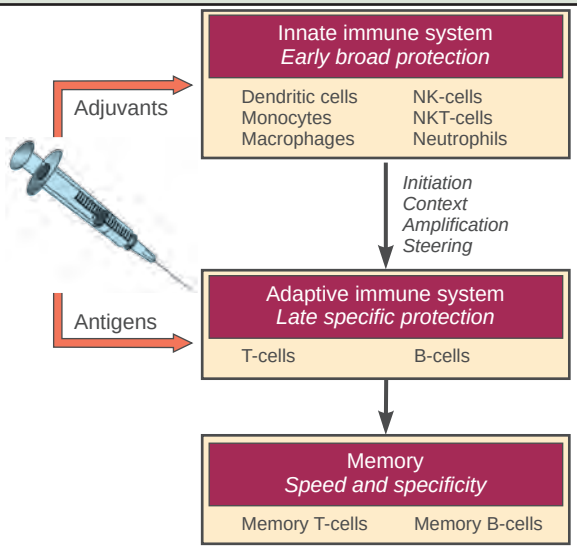
The germinal center reaction has implications for vaccination.

- *Stimulating innate immunity*—The more innate immunity is stimulated, the more robust the adaptive immune response will be. For example, intradermal vaccination may stimulate more robust responses than intramuscular injection because there

are more immature dendritic cells in the dermis.[14] As another example, live viral vaccines are more immunogenic than non-live ones because they can disseminate and encounter dendritic cells at many sites, ultimately establishing multiple foci of germinal center reactions. Live vaccines also express PAMPs that can activate innate immune cells.

- *Adjuvants*—Adjuvants are substances that potentiate the immune response to vaccine antigens (**Figure 1.3**). They are necessary for some non-live subunit vaccines, but they are not necessary for live vaccines because these stimulate innate immune responses on their own. For many decades, the only adjuvant used in human vaccines was alum, but the last decade has seen growth in the number of available adjuvants, improvement in potency, development of adjuvant systems (combinations of immune stimulants) and targeting of specific elements of the immune system (**Table 1.3**). Adjuvants may allow for *antigen sparing*; for example, an adjuvanted version of IIV is just as immunogenic as a non-adjuvanted version, even though it contains one-fourth the amount of antigen.[15] Adjuvants also may cause *epitope spread*, a broadening of the antibody repertoire such that more epitopes on a given antigen are recognized.[16]

FIGURE 1.3 — Adjuvants and Antigens



See text for explanation.

Adapted from O'Hagan DT, et al. *Nat Rev Drug Discovery*. 2003;2:727-735.

- *Priming and boosting*—Ultimately, the magnitude and duration of the antibody response to non-live vaccines depends on the "immunologic set point" following primary immunization. In other words, the more germinal centers that are formed, the more long-lived plasma cells and memory B-cells there will be. In addition to optimizing antigen dose and using adjuvants, *primary immunization* is enhanced by multiple doses of the vaccine given in succession, classically separated by 1 or 2 months (as in the 2-, 4-, and 6-month schedule for PCV). These doses are given too soon to exploit memory responses, but they *do* drive the process of affinity maturation. Following priming, vaccine schedules take advantage of anamnestic responses, which boost the level of high-quality antibody (**Figure 1.4**)[17]; in general, the longer the interval to boosting, the better the antibody response.[18] The need to wait until the germinal center reaction is complete explains the longer interval between the primary series of a vaccine and the booster doses (as in the 12- to 15-month dose of PCV). The response to booster doses of vaccine mimics what happens when the natural pathogen is encountered.

A good example of a booster is Tdap, which boosts the immunity to tetanus, diphtheria, and pertussis that has waned since the childhood series was completed (see *Chapter 14: Diphtheria, Tetanus and Pertussis*). One might notice that the package insert for Infanrix (a brand of DTaP) states that the doses given at 2, 4, and 6 months of age constitute a "primary series" for pertussis and the toddler and school-aged doses are "boosters". The Daptacel (another brand of DTaP) package insert states that the primary series for pertussis is 4 doses (2, 4, 6, and 15 to 20 months), and only the school-aged dose is considered a booster (similar language is contained in the package insert for Pentacel and Vaxelis, vaccines that are based on Daptacel). The reasons behind this have more to do with regulatory precedent and interpretation than they do with the biology of immune responses; arguably, the long interval between Doses 3 and 4 of Daptacel takes advantage of priming, B- and T-cell memory, and anamnestic responses, all characteristics of "boosters."

There may be a downside to the *immunological set point* when it comes to protection against pathogens that evolve antigenically over time. It was known as far back as the 1940s that prior exposure to, or vaccination with, one strain of influenza virus can impair the response to a new related but antigenically distinct strain, a phenomenon referred to *as original antigenic sin.*[19] It's as if the first exposure to antigen imprints on the immune system what the antibody repertoire *ought to be* in response to subsequent exposure to a similar antigen; however, if the new antigen is sufficiently different, the antibody response, which is biased towards the previous antigen, might be less effective

TABLE 1.3 — Adjuvants Used in the United States

Name	Description	Vaccines[a]	Year Approved	Proposed Mechanisms of Action
Alum	Amorphous mixture of aluminum salts[b]	AVA DTaP, DT, Td Hib-OMP HepA HepB (Engerix-B, Recombivax HB, PreHevbrio) HPV9 JEV-VC MenB-FHbp, MenB-4C PCV13, PCV15, PCV20 TBE	1930s	Antigen stabilization Inflammasome activation Increased uptake by APCs Induction of DAMPs Depot effect
AS04	3-O-desacyl-4′-monophosphoryl lipid A[c] adsorbed to aluminum hydroxide	HPV2[d]	2009	Effects of alum, as above Engagement of TLR4
AS03	Oil-in-water emulsion consisting of squalene, alpha-tocopherol, and polysorbate 80	A(H5N1) IIV[e]	2013	Increased uptake by APCs Activation of regional lymph nodes Perturbed lipid metabolism in monocytes, causing endoplasmic reticulum stress and activation
MF59	Oil-in-water emulsion consisting of squalene, polysorbate 80, and sorbitan trioleate	aIIV A(H5N1) IIV[e]	2015 2019	Increased trafficking of APCs Increased differentiation of APCs Increased uptake by APCs
$AS01_B$[f]	3-*O*-desacyl-4′-monophosphoryl lipid A[c] and QS-21[g], liposomal formulation using dioleoyl phosphatidylcholine and cholesterol	RZV	2017	Antigen protection Increased delivery to APCs Induction of DAMPs Enhanced cross-presentation Engagement of TLR4
$AS01_E$[f]	3-*O*-desacyl-4′-monophosphoryl lipid A[c] and QS-21[g], liposomal formulation using dioleoyl phosphatidylcholine and cholesterol	RSV (GSK)	2023	Antigen protection Increased delivery to APCs Induction of DAMPs Enhanced cross-presentation Engagement of TLR4
CpG 1018	22-mer phosphorothioate linked oligodeoxynucleotide[h]	HepB-CpG (Heplisav-B)	2017	Engagement of TLR9
Matrix-M	Fraction-A and Fraction-C of *Quillaja saponaria* Molina extract[g]	COV-aPS (Novavax)	2022	Interaction with T-cell surface co-stimulatory ligands Enhanced processing of endocytosed antigens in dendritic cells

Continued

TABLE 1.3 —*Continued*

APC, antigen-presenting cell; DAMP, damage-associated molecular pattern; TLR, Toll-like receptor

[a] Corresponding combination vaccines include the same adjuvants.
[b] Includes aluminum hydroxide, aluminum phosphate, and aluminum hydroxyphosphate sulfate
[c] A derivative of bacterial lipopolysaccharide (endotoxin)
[d] HPV2 (Cervarix) is no longer distributed in the US but is used elsewhere in the world.
[e] The AS03-adjuvanted A(H1N1) vaccine is manufactured by ID Biomedical Corporation and distributed by GSK; the MF59-adjuvanted vaccine is manufactured by CSL Seqirus. Neither is commercially available.
[f] $AS01_B$ and $AS01_E$ differ only in the amount of the various constituents.
[g] Saponins purified from plant extract *Quillaja saponaria* Molina
[h] A DNA molecule that mimics unmethylated cytosine-guanuine dinucleotides common in bacteria

Adapted from De Gregorio E, et al. *Front Immunol.* 2013; 4:214; Dowling DJ, et al. *Pediatr Infect Dis J.* 2015;34:1395-1398; Bonam SR, et al. *Trends Pharmacol Sci.* 2017;38:771-793; Laupèze B, et al. *Vaccine.* 2019;37:5670-5680; Marciani DJ. *Trends Pharmacol Sci.* 2018;39:573-585.

FIGURE 1.4 — Time Course of Antibody Responses

See text for explanation.

against the new version, at least when compared to the response of naïve individuals. The key to this phenomenon lies in the germinal center and the continuous mutation and selection process that the B-cell receptor undergoes.[20] *Imprinting* could in part explain why individuals vaccinated against the ancestral strain of SARS-CoV-2 early in the pandemic were so easily infected with later variants[21]; at the same time, vaccinated people were protected against severe disease, because T-cells, unlike B-cells, are long-lived, do not undergo somatic mutation after they leave the thymus, and are broadly reactive.

- *Specificity*—Hypermutated, high-affinity antibodies target single epitopes. For this reason, most non-live vaccines are very specific in the protection they afford. For example, IPV contains formalin-inactivated, disrupted viral particles from three different serotypes of poliovirus because the antigens from any given serotype do not induce antibodies that will neutralize the other serotypes. Germinal center reactions by and large generate homotypic responses, ie, responses directed against the antigen used as the vaccine. *Heterotypic*, or *cross-protective*, responses occur only if there is sufficient similarity between the antigens of different strains, or if there is a common antigen between them. Tc-cells offer much more potential for cross-strain protection (*see below*). One of the biggest questions about the first COVID-19 vaccines, which were based on antigens derived from the original strain of SARS-CoV-2, is whether they would protect against emergent strains. Those strains emerge under the immunologic pressure represented by populations previously infected with and/or immunized to the original strain, among other evolutionary forces[22]; the extent to which emergent strains are antigenically different from the original—yet still fit for replication and transmission—is called *antigenic escape.*
- *Persistence of antibody*—The germinal center reaction peaks in several weeks, after which it is terminated. The mechanisms by which serum antibodies persist for long periods of time—something so critical to maintaining protection—are not yet fully understood.[23] Some models suggest that there is constitutive differentiation of memory B-cells into plasma cells, stimulated by persistent antigen, reinfection, or exposure to cross-reactive antigens. Other models propose nonspecific, or so-called "bystander," activation of memory B-cells. These models have important implications for vaccine programs. For example, early studies of VAR showed persistent if not *rising* titers of antibody over time. But these studies were done at a time when the wild-type virus was still circulating; therefore, immunized individuals might have experienced repeated subclinical reinfections with natural virus, coaxing memory B-cells to differentiate into plasma cells and boosting antibody production. As transmission of natural varicella decreased, some studies began to show waning immunity over time (this observation made it less likely that antibody persisted because of boosting from periodic reactivation of latent vaccine virus). Although initially intended to immunize those who failed to seroconvert after the first dose (so-called *primary vaccine failures*), the second dose of VAR also serves to boost immunity in those individuals whose antibody levels have fallen low enough to allow *take*, or replication of the vaccine virus.

  Other models suggest that plasma cells derived from the germinal center reaction can live for a very long time. Either

way, for some vaccines, it is necessary to periodically stimulate an anamnestic response through booster vaccination. One thing is clear—to prevent serious infections that have a short incubation period (invasive meningococcal disease is a good example), one must have enough circulating antibody when the pathogen is encountered. Anamnestic responses, while brisk, are not fast enough to be of much help when dealing with rapidly replicating bacteria. They may be sufficient, however, for pathogens with longer incubation periods. Thus, for example, although antibodies to HBV may wane with time, protection against disease does not wane—there is plenty of time for memory responses to kick in before the virus can do damage.

- *Making better immunogens*—As mentioned above, polysaccharides are poor immunogens. Vaccinologists have learned, however, to harness the power of the germinal center reaction to enhance polysaccharide immunogenicity (**Figure 1.2**, **Panel B**). The polysaccharides are chemically attached to protein carriers—among the variety of carriers used are an outer-membrane protein from *N meningitidis* (Hib-OMP [PedvaxHIB]); the mutant diphtheria toxin CRM (PCV13-CRM [Prevnar 13], PCV15-CRM [Vaxneuvance], PCV20-CRM [Prevnar 20], and MenACWY-CRM [Menveo]); tetanus toxoid (Hib-T [ActHIB, Hiberix], MenACWY-T [MenQuadfi]); and diphtheria toxoid (MenACWY-D [Menactra]). B-cells that are pre-committed to producing anti-*polysaccharide* antibody are stimulated by their encounter with the antigen (stimulation occurs through cross-linking of the B-cell receptor on the cell surface). They also engulf the bound antigen, digest it, and present peptides from the *protein* portion of the vaccine on their surface in the context of MHC-II (there is some evidence that B-cells and other APCs can also present polysaccharide antigens that are attached to peptides[24]). So, what you have is a B-cell committed to making anti-*polysaccharide* antibodies that is displaying a *peptide*:MHC-II flag on its surface. All it takes now is for APCs to display the same peptides in the context of MHC-II, stimulating Th2-cells, which then find their B-cell matches and help them make antibody through the germinal center reaction. In essence, the Th2-cells "think" they are helping B-cells make antibodies to the *protein* antigen from which the peptides were derived, when, in fact, the flagged B-cells make polysaccharide antibody. By converting a *T-cell independent* response to a *T-cell dependent* one, the antigenic shortcomings of polysaccharides are overcome (**Table 1.4**).

Cytotoxic T Cells

Tc-cells are the main effectors of the adaptive cellular immune response. Like Th-cells, they express the TCR on their surface, which has a unique antigenic specificity encoded in the germline. Unlike Th-cells, which express CD4, Tc-cells express the CD8 co-receptor,

TABLE 1.4 — Advantages of Protein-Polysaccharide Conjugate Vaccines

Property	Type of Vaccine	
	Polysaccharide	Protein-Polysaccharide Conjugate
B-cell response	T-cell independent	T-cell dependent
Pathway	Extrafollicular	Germinal center
Antibody generation in young infants	No	Yes
Induction of immune memory	No	Yes
Anamnestic or booster responses	No	Yes
Long-term protection	No	Yes
Reduced carriage of the organism at mucosal surfaces	No	Yes[a]
Herd immunity	No	Yes[b]

[a] Serum-derived IgG can kill colonizing bacteria at mucosal surfaces.
[b] Fewer colonized people means less transmission of the pathogen from person to person, indirectly protecting people who are not immune.

which directs engagement with MHC-I. Like MHC-II, MHC-I loads pathogen-derived peptides into its groove and presents those peptides on the cell surface. However, instead of coming from the digestion of exogenous proteins that were engulfed by the cell, the peptides loaded into MHC-I are, for the most part, made inside the cell—by infecting viruses or other intracellular pathogens.

MHC-I is expressed on all nucleated host cells, including APCs. Naïve Tc-cells, predetermined to recognize a particular peptide:MHC-I flag, engage infected APCs that express those peptides in the context of MHC-I (**Figure 1.5**). While this leads to activation of the Tc-cell, the Tc-cell does not become a killer until it receives additional signals—those coming in the form of cytokines from Th1-cells, which in turn have been activated by engagement of APCs expressing pathogen-derived peptides in the context of MHC-II (Th1-cells have other functions as well, such as activation of macrophages). The respective, critical role of the two different types of Th-cells is obvious—Th2-cells help B-cells produce high-quality antibodies and memory cells, and Th1-cells help Tc-cells become killers (and memory cells).

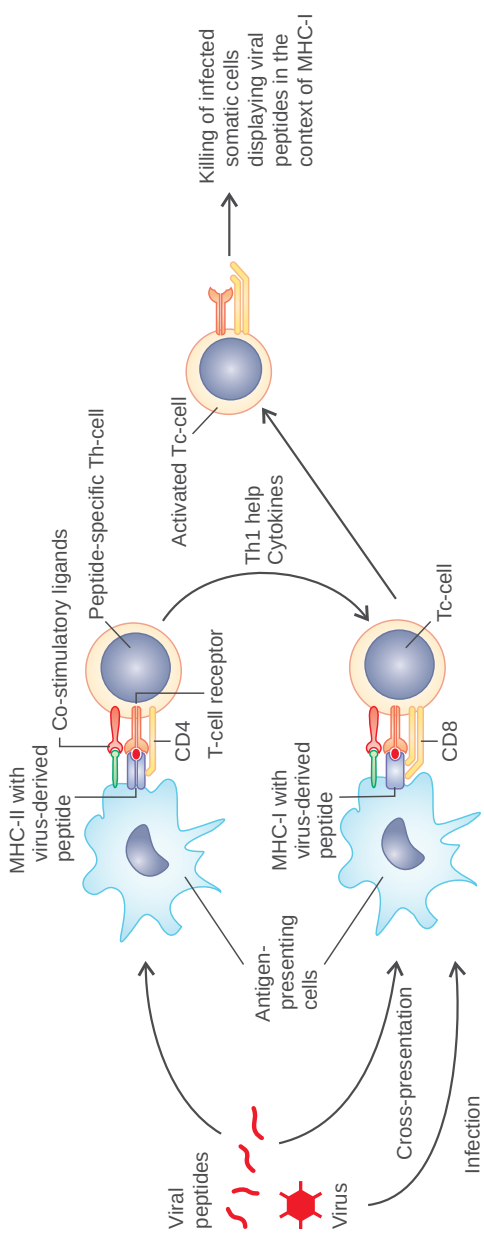


FIGURE 1.5 — Cytotoxic T-Cell Response

See text for explanation.

Pollard AJ, et al. *Nat Rev Immunol*. 2021;21:83-100.

Tc-cells find and destroy infected cells that express pathogen-derived peptides on their surface in the context of MHC-I. Killing occurs through the release of *cytotoxins* that create holes in the cell membrane, and by induction of *apoptosis*, or programmed cell death, through receptor-ligand interactions and the release of certain enzymes.

The unique characteristics of Tc-cells and their generation have several implications for vaccination.

- *Viruses vs bacteria*—Tc-cells are more important in controlling viral rather than bacterial infections. This is because most bacteria replicate outside of cells, and therefore do not generate cells flagged with endogenously derived peptide:MHC-I molecules. Viruses, on the other hand, only replicate inside cells by usurping the machinery for protein synthesis; infected somatic cells routinely carry endogenously derived peptide:MHC-I flags on their surface and are therefore recognizable by Tc-cells. Certain APCs, like dendritic cells, can cull peptides from the extracellular environment and present them in the context of MHC-I, enabling them to stimulate Tc-cells without themselves being infected; this process is called *cross-presentation*[25] (dendritic cells can even acquire the entire peptide:MHC complex from other APCs in a process called *cross-dressing*[26]).

  Vaccines against bacteria are designed to maximize high-quality antibody production, partly through the generation of large pools of Th2-cells. The ideal vaccine for a virus would maximize high-quality antibody production (to inactivate the inoculum, thereby *preventing* infection), as well as generate Tc-cells (to kill infected cells, thereby *controlling* infection).

- *Preventing infection vs limiting disease*—Tc-cells operate *after infection* has taken place; they limit but do not prevent infection. Unlike antibody, a Tc-cell cannot kill a free virion—it must wait until a cell is infected and expressing viral peptides. If a vaccinated person is exposed to a virus, the first line of defense is the antibody that resides in the immediate local environment. That antibody can neutralize the virus and prevent *infection*. If it does not, the virus enters cells and expresses proteins; this activates memory Tc-cells, which limit *disease* by destroying those cells (in some cases, however, the inflammation caused by activated Tc-cells may contribute to disease manifestations). Antibody may also play a role in the destruction of infected cells through ADCC.

  Certain differences between varicella and zoster vaccines are instructive. VAR is designed to stimulate antibodies that can prevent primary infection (varicella, or chickenpox). Herpes zoster, or shingles, results from reactivation of endogenous VZV that has been latent since the person had varicella. As such, zoster vaccine is designed to expand the pool of memory Tc-cells that can be stimulated by cells expressing viral peptides on their surface as reactivation begins. RZV, a non-live vaccine containing one surface glycoprotein from the virus, expands memory Tc-cells through cross-presentation (*see below*) and the guiding power of a strong adjuvant.

- *Live vs non-live vaccines*—Live viral vaccines infect cells and direct the synthesis of virus-specific proteins; peptides from nascent polypeptide chains are loaded into MHC-I molecules and expressed on the cell surface in the MHC-I context, stimulating strong T-cell responses. Live vaccines are also able to amplify and disseminate antigens, and they stimulate strong innate immune responses. Peptides from non-live protein vaccines can be presented on the cell surface in the context of MHC-I through cross-presentation. Whereas this process is less efficient, it nevertheless explains how some non-live vaccines can induce Tc-cell responses. mRNA vaccines mimic live vaccines in that they direct endogenous protein synthesis and stimulate strong cellular responses,[27] but they do not replicate. Non-replicating vectored viral vaccines act similarly.

- *Broad protection*—Tc-cells recognize peptides that are derived from any protein made by the pathogen, some of which are well-conserved between strains. Thus, Tc-cells stimulated by vaccination might be able to limit disease caused by a variety of strains, even when the elicited antibodies are strain-specific.

Correlates of Protection

Ideally, vaccines are shown to be effective in randomized, blinded, placebo-controlled trials, where one group of subjects gets vaccine, another gets placebo, and the measured outcome is *efficacy*, or ability to prevent disease (or infection). This works if the disease is prevalent, such that the number of subjects needed in a clinical trial is within reach. For diseases that are relatively rare, demonstrating efficacy may not be feasible.[28] In these situations, *immunogenicity*, or the ability to generate an immune response, is relied upon as a predictor of efficacy. The concept of *correlates of protection* (CoP, also known as *correlated immune marker*) connects the measured immune response to the predicted efficacy.[29] CoP may be mechanistic, ie, biologically responsible for protection (also referred to as a *protective immune marker*), or non-mechanistic, ie, statistically related to protection but not biologically responsible (also referred to as a *surrogate immune marker*). A good example of a mechanistic CoP is bactericidal antibody to *N meningitidis* (the antibody being measured is the one that kills the bacterium). However, for many pathogens, the mechanism of protection is multi-dimensional, involving everything from innate immune training to the role of complement and antibody effector functions.[30] A good example of a non-mechanistic CoP is the antibody response to RZV as measured by enzyme-linked immunosorbent assay (the protection against zoster is mediated by

T-cells). Studies suggest that hepatitis B surface antibody (HBsAb) levels ≥10 mIU/mL perfectly prevent HBV infection. In as much as the measured antibodies neutralize the viral inoculum, HBsAb ≥10 mIU/mL can be considered a mechanistic CoP. However, studies also show that protection persists even when antibody levels wane to <10 mIU/mL. Therefore, there must be other CoP that come into play besides circulating antibody at the time of exposure—for example, the existing level of memory and the ability to mount an anamnestic response.

CoP against a disease are useful for other reasons as well. For example, it may not be possible to study vaccine efficacy in every population that will ultimately be targeted for immunization. However, if we know which immunologic results predict protection, we can extrapolate that protection is likely to ensue if those criteria are met. CoP also drive preclinical development, in the sense that scientists choose antigens, delivery systems, and dosing schedules that maximize immune responses thought to be important in protection. They are also critical in quality assurance—each new production lot of vaccine cannot be studied for efficacy, but it can be studied for immunogenicity. Likewise, there are many vaccination scenarios that must be studied in practice. For example, a new vaccine might be effective in clinical trials, but in real life, it needs to be given concomitantly with other vaccines. It would be difficult to study efficacy under every permutation of concomitant use; instead, investigators rely on CoP to determine if concomitant use is likely or unlikely to compromise protection. In general, statistical noninferiority with respect to a relevant immune response must be demonstrated (see *Chapter 2: Vaccine Infrastructure in the United States—Vaccine Development and Licensure*).

CoP are imperfect. To give one example, studies in the prevaccine era showed that children who had naturally occurring antibody to the *H influenzae* type b capsular polysaccharide (polyribosylribitol phosphate [PRP]) in amounts ≥0.15 mcg/mL were protected from invasive disease; those with levels <0.15 mcg/mL were not. Studies utilizing the unconjugated PRP vaccine showed that antibody levels ≥1.0 mcg/mL immediately following vaccination correlated with protection against disease. So, which is the protective antibody level, 0.15 mcg/mL, or 1.0 mcg/mL? Some have referred to 0.15 mcg/mL as the "short-term" correlate, meaning that this is the level of circulating anti-PRP antibody you need at any given time to kill any *H influenzae* type b that happens to show up; 1.0 mcg/mL is referred to as the "long-term" correlate, meaning that this is the amount of antibody you need after vaccination with a *polysaccharide* vaccine to be protected for a long time. The question is, what antibody levels are necessary immediately after vaccination with a *conjugate* vaccine to achieve long-term protection? One cannot directly infer this from studies of polysaccharide vaccine because conjugate vaccines induce higher quality antibodies.

Protection undoubtedly involves interplay between humoral and cellular mechanisms and may be difficult to reduce to a simple antibody concentration. Moreover, serological CoP may depend on host factors in addition to properties of the organism.[31] Protection may be mediated at the site of mucosal colonization, but little is known about mucosal CoP. Serum antibody may confer protection at mucosal surfaces and reduce colonization; however, the serological correlate of mucosal protection may be much higher than that of protection against invasive disease.[32] Inoculum size (the number of organisms to which a person is exposed) plays into this; higher inoculums may be able to overcome existing immunity (and may also be associated with more severe disease).[33]

It also depends how antibodies are measured. For example, we are much more interested in the levels of serum bactericidal antibodies to *N meningitidis*, a functional immune response endpoint, than we are in quantitating antibody binding to the capsular polysaccharide; bactericidal assays, however, are difficult to standardize and are labor-intensive. Quantitation of antibodies that neutralize viruses in vitro might be more relevant than measurement of antibodies that bind to viral proteins—unless one knows exactly which proteins are involved in generating neutralizing antibody. Even then, there is no guarantee that a protein-binding assay will measure antibodies that bind to the neutralizing epitopes, and that binding to those epitopes correlates with neutralization in a functional assay (to make matters worse, some viruses do not grow well in cell culture, making functional assays difficult to design). For some infections (eg, tetanus), antibodies to the *organism itself* are not relevant, but antibodies to toxins produced by the organism are. Finally, for some diseases, protection may be mediated as much by Th- and Tc-cells as by antibody. In as much as Th-cells help B-cells make antibodies, antibody levels may be an indirect measure of cellular immunity.

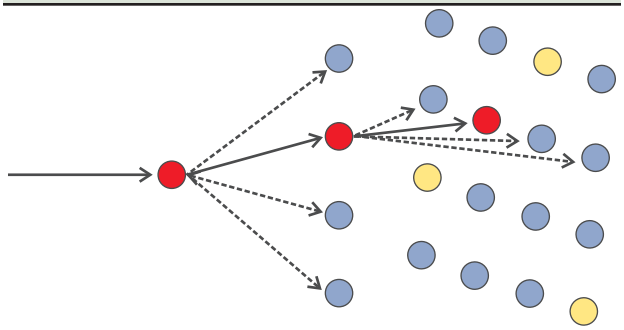
Fortunately, vaccine development does not depend on establishing CoP. For example, there is no consensus on CoP against rotavirus, even though highly effective vaccines have been developed. Likewise, debate continues about the CoP against pertussis, yet pertussis vaccines have been in use since the 1940s—licensed based on demonstrated efficacy against disease endpoints. Interestingly, Tdap was licensed without proof of efficacy against pertussis—and even though there are no agreed-upon CoP. The basis for licensure was the demonstration of levels of antibody to pertussis antigens that were similar to the levels found in infants who had received DTaP, a vaccine already proved to be effective. Similarly, MenACWY-D was licensed because the levels of antibody following vaccination were equivalent to those achieved after immunization with MPSV4 (a pure polysaccharide vaccine that is no longer available), which was known to be protective. MenACWY-CRM, in turn, was licensed after demonstration of noninferiority with MenACWY-D.

Epidemiological Concepts

Vaccines protect people by stimulating adaptive immunity; the level of protection depends on the quality, magnitude, and duration of the person's response. Since no vaccine is 100% effective, even vaccinated individuals can become infected—*if* they are exposed. Exposure, in turn, depends on transmission of the pathogen from person to person (an exception is tetanus, which is acquired from the environment, not other people). This, then, brings up the second way that vaccines protect people—by interrupting disease transmission.

Topley and Wilson coined the term *herd immunity* in 1923 to draw a distinction between (but acknowledge the relatedness of) the immunity of individuals and protection of the community in which the individuals live (synonymous terms include *community immunity, community protection*, and *population immunity*). It refers to the fact that susceptible members of "the herd" are protected by the presence and proximity of immune members who prevent propagation of the infection (**Figure 1.6**).[34] For many diseases that are transmitted from person to person, there is a *herd immunity threshold*—a critical proportion of the population that must be immune to prevent sustained disease transmission (**Figure 1.7**). Although simple in concept, the herd immunity threshold depends on a complex interplay of many

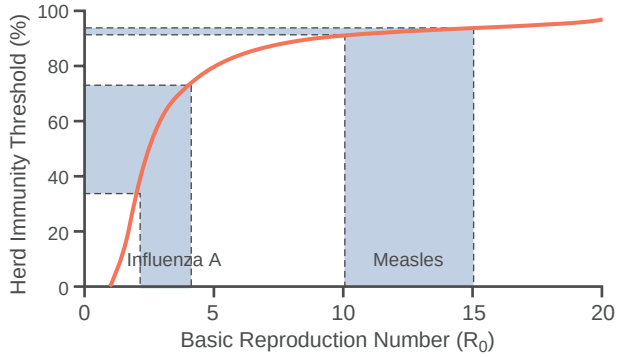
FIGURE 1.6 — Herd Immunity



The figure illustrates introduction of a hypothetical infection (solid arrows) into a population with 75% immunity. The infection has a basic reproduction number (R_0) of 4, meaning that the first case (the first red circle) would result in 4 secondary cases if all members of the population were susceptible. Here, however, there is only one secondary case (second red circle) because 3 out of 4 individuals are immune (blue circles) and transmission to them is unsuccessful (dashed arrows). Similarly, the secondary case gives rise to only one tertiary case. The 3 yellow circles represent susceptible individuals who do not get infected because of herd immunity.

Adapted from Fine P, et al. *Clin Infect Dis*. 2011;52:911-916.

FIGURE 1.7 — Herd Immunity Threshold



The figure illustrates the relationship between the basic reproduction number (R_0) and the herd immunity threshold for measles and influenza A. Because measles is more contagious (has a higher R_0), the herd immunity threshold is higher (a larger proportion of the population must be immune to prevent sustained transmission). This model assumes a randomly mixing homogenous population.

Adapted from Zepp F. *Vaccine*. 2010;28S:C14-C24.

factors. One is the contagiousness of the pathogen, often expressed as the *basic reproduction number* (R_0, pronounced *R-naught*)—the average number of secondary cases that arise from an index case when all members of the population are susceptible. Another is the *force of infection* (λ), which refers to the rate at which susceptible individuals become infected (synonymous terms include *infection hazard, person time incidence rate,* and *susceptible attack rate*).[35] Still another is the *overdispersion factor* (k)—a measure of individual-level variation in the distribution of secondary cases (the lower the value, the more variation). These parameters were critical to understanding the epidemiology of COVID-19 and the effectiveness of the corresponding vaccination campaign. Early estimates of R_0 ranged from 2.4 to 3.4—on average, one case in a naïve population resulted in 2 to 3 secondary cases (note that the average R_0 of the later Omicron variant was estimated to be 8.2[36], demonstrating evolution towards higher transmissibility during the pandemic). The virus was, however, highly overdispersed, with k estimated to be around 0.1; this meant that 80% of secondary cases were caused by 10% of index cases, leading to the concept of "superspreading" individuals and events.[37] Non-pharmaceutical interventions—masking and lock-downs, for example—decreased λ, likely leading to improved estimates of vaccine effectiveness.[38] Whereas COVID-19 serves to illustrate many of these epidemiologic parameters, it is also, unfortunately, an example

of a disease for which the concept of herd immunity may not fully apply.[39]

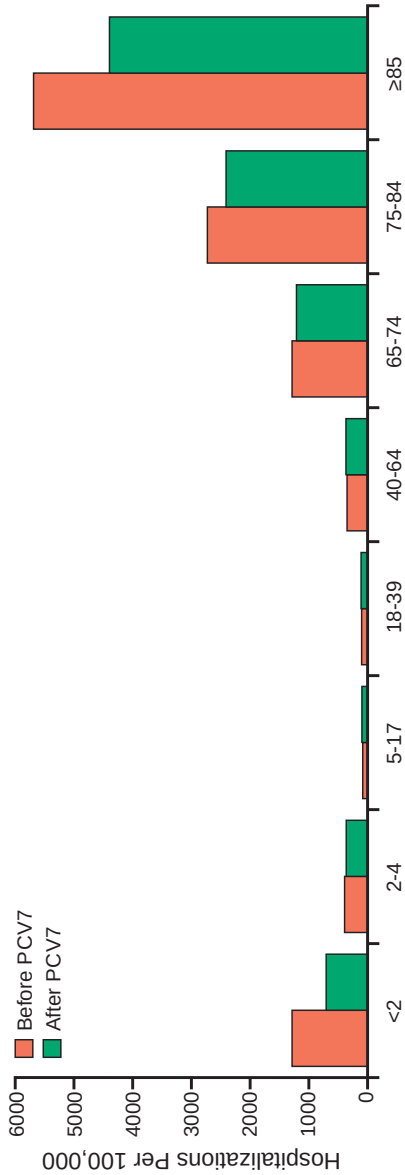
Ideally, one would want to know what proportion of a population needs to be vaccinated to protect the entire population. This will depend on the above factors, as well as on the efficacy of the vaccine and the reality that neither vaccination nor exposure is evenly distributed within a population (for example, there may be pockets of susceptible individuals, such as under-vaccinated inner-city residents, or foci of close contact, such as college dormitories).

In addition, the ecology and virology of the pathogen must be considered. For measles virus, there is no carrier state and there is no reservoir per se; the virus is phenotypically stable and protective immunity is long-lived. Thus, a vaccine that prevents individual infection will prevent transmission and amplify the protective effect on individuals in a community. SARS-CoV-2, on the other hand, exhibits characteristics that make herd immunity elusive: short-term immunity, for example, and the continued evolution of variants. For *H influenzae* type b, there is a reservoir—the nasopharynx of young children. A vaccine that prevents invasive infection, but not nasopharyngeal colonization arguably would not result in herd immunity, since transmission could still occur from vaccinated children who remain colonized. Fortunately, protein-polysaccharide conjugate vaccines are very effective at reducing colonization. In the case of Hib, the herd immunity effects were dramatic. A Danish study, for example, estimated that by 3.5 years of age, the protection afforded unvaccinated children through herd immunity was about the same as the direct protection afforded through vaccination (approximately 94%).[40]

In the early 1990s, the incidence of hepatitis A in Butte County, California, was six times higher than in the state as a whole. Beginning in 1995, children 2 through 17 years of age were routinely immunized with HepA. Within 5 years, the incidence of hepatitis A had fallen dramatically among children, as one might have expected. However, the incidence also had fallen in all other age groups—groups that were not targeted for immunization.[41] Preventing hepatitis A in children was enough to prevent transmission to, and infection among, adults. Economic models suggest that herd immunity effects more than double the cost savings from universal HepA immunization of young children.[42]

Figure 1.8 illustrates the impact that routine childhood PCV7 immunization had on pneumonia hospitalization rates among unimmunized older persons. In this case, herd immunity was mediated by decreases in nasopharyngeal colonization among vaccinated children.[43] However, there is a cautionary tale here. Vaccination only affects colonization with vaccine serotypes. When these serotypes disappear from the nasopharynx, other serotypes take over, something called *serotype replacement.*[44] Some of those serotypes—19A, for example, in the case of *S pneumoniae*—are themselves capable of

FIGURE 1.8 — Herd Immunity: *S pneumoniae*



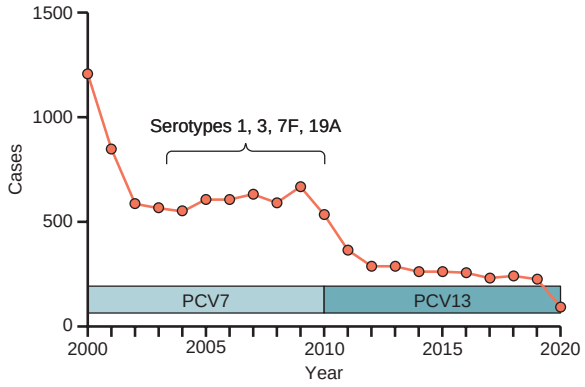
The graph shows the average annual rates of hospitalization in the US related to pneumonia from any cause, 3 y before and 7–9 y after introduction of PCV7. Routine use of PCV7 at 2, 4, 6, and 12-15 mo was introduced in 2000. The reduction in hospitalization rates among children was due to both direct and herd effects. The reduction in older adults was due to herd effects alone, since adults were not being immunized with PCV7.

Adapted from Griffin MR, et al. *N Engl J Med.* 2013;369:155-163.

causing invasive disease. In fact, invasive disease due to non-vaccine serotypes *increased* in the PCV7 era, although the overall rate of invasive disease (all serotypes included) declined (**Figure 1.9**).[45] The challenge is to stay one step ahead of the organism by developing vaccines that include the remaining and emerging serotypes; for *S pneumoniae,* this accomplished with PCV13, PCV15, and PCV20. Interestingly, widespread *H influenzae* serotype replacement has not occurred in the vaccine era, despite similar effects of Hib on nasopharyngeal colonization with that organism[46,47]; this may be because *H influenzae* type b occupied a smaller microbial "niche" in the nasopharynx and the non-b strains are less virulent.

Some diseases, such as measles, rubella, and varicella, are more severe when acquired after childhood. Widespread childhood immunization has the potential to shift the epidemiology of infection towards older people, who may experience more severe disease. Thus, ironically, as the herd immunity threshold for these diseases is approached, the number of cases goes down but the severity of illness

FIGURE 1.9 — Serotype Replacement



The graph shows the number of cases of invasive pneumococcal disease (IPD) in persons <18 y at Active Bacterial Core surveillance sites in the US. Dramatic declines were seen after the introduction of PCV7 into the routine childhood schedule. Within a few years, however, invasive disease due to serotypes not represented in PCV7 (eg, serotypes 1, 3, 7F and 19A) began to emerge. A further decline in IPD was seen after the introduction of PCV13, which includes those serotypes (among others). The sharp decline in 2020 was likely due to the implementation of non-pharmaceutical interventions in response to the COVID-19 pandemic (Prasad N, et al. *J Infect Dis*. 23;227:907-916).

Adapted from Active bacterial core surveillance (ABCs). CDC Web site. https://www.cdc.gov/abcs/reports-findings/surv-reports.html. Accessed June 15, 2023.

in those who do get infected may go up.[48] This phenomenon, which raises the stakes for those who are not vaccinated, has been termed the *herd severity effect.*[49]

Future Vaccinology

Immune responses depend on the interplay of various cells that engage each other through MHC molecules loaded with peptides derived from the pathogen (or vaccine). The genes encoding MHC molecules demonstrate a large degree of diversity, such that one person's MHC molecules might be better able to present a given peptide than another person's. Thus, for example, individuals with a particular HLA allele called DQB1*0303 appear to be less competent at producing mumps antibody after 2 doses of vaccine than those who possess other alleles.[50] Other HLA alleles are associated with lower lymphoproliferative responses. Polymorphisms in cytokine and cytokine receptor genes may also predict immune responses. Polymorphisms may also predict breakthrough disease; for example, children who develop invasive *H influenzae* type b disease despite immunization may have polymorphisms in genes that control intracellular signal transduction from TLR2 and TLR4, or polymorphisms in the promoter region of the IL-10 gene.[51] Importantly, these polymorphisms are not something you would necessarily know about ahead of time, since they (probably) do not result in a particular disease phenotype. *Vaccinomics*—the application of genetic analyses to predicting immune responses and adverse events after vaccination—may someday lead to vaccines that are optimized for individual people or groups.[52,53]

The "old vaccinology" was dependent on antigens that are native to the organism. However, many of those antigens, while playing a critical role in infection, evolved to evade immune responses, not induce them.[54] This reality (among others) has given rise to the concepts of *rational vaccine design* and *precision vaccinology*—the application of structural biology, systems immunology, bioinformatics, molecular engineering, new delivery technologies and adjuvants to improving, honing, and tailoring vaccine immune responses. The new "golden age" of vaccinology will move us beyond the empiricism of the past to a future of directed vaccine development and use.[55]

Vaccines and Public Health

Goals of Immunization Programs

Some historians believe that smallpox killed more people since civilization began than all other infectious diseases combined. In 1967, the World Health Assembly (WHA) resolved to eradicate the disease—increased funding was secured; large amounts of stable, lyophilized vaccines were manufactured; reference testing centers

were established; the bifurcated needle was adopted for administration; and the strategy of ring vaccination (vaccinating the contacts around index cases) was developed. As a result, the last natural case of smallpox on the planet occurred in 1977, and in 1980 the world was certified smallpox-free.[56] It was remarked at the time that smallpox eradication was one of the few things that needed to be done only once in the history of the world.

Vaccination programs move from *control* of disease to *elimination* of disease and infection to *eradication*, defined as a permanent reduction to zero of the worldwide incidence of infection as the result of deliberate efforts.[57] Because there is no reservoir of variola virus in nature and there is no human carrier state, the eradication of smallpox was considered definitive, standing as one of the best examples of the power that vaccines have to improve human health. In the US, routine vaccination of civilians ceased in 1972, health care personnel (HCP) in 1976, and military personnel in 1990. Until 2001, the only persons in the US who continued to be vaccinated were laboratory and animal care workers with potential exposures to orthopox viruses and HCP conducting clinical trials with recombinant vaccinia virus vaccines. Between 1984 and 2001, no country routinely immunized civilians.

The terrorist attacks of September 11, 2001, raised concern that the endgame for smallpox should not have been eradication but rather *extinction*, where the agent no longer exists, anywhere. Today, there are two places where stocks of variola virus are known to exist: the World Health Organization (WHO) Collaborating Centre on Smallpox and Other Poxvirus Infections at the Centers for Disease Control in Atlanta, and the WHO Collaborating Centre for Orthopoxvirus Diagnosis and Repository for Variola Virus Strains and DNA at the Russian State Research Centre of Virology and Biotechnology in Koltsovo, Novosibirsk Region, Russian Federation. It is now known that the Soviet Union had an active program to weaponize variola virus, and with the political unrest and economic hardship that ensued in Russia during the 1990s, it remains possible that the virus and the technology to deliver it may have fallen into the hands of terrorists or rogue nations. Also unsettling was the discovery in 2014 of vials containing variola virus in a freezer at the National Institutes of Health. These had probably been there, unbeknownst to anyone, since the 1950s, leading to speculation that other stocks may exist and fueling the debate about what to do with the last remaining known stocks.[58] Destroying all vestiges of the natural virus (provided we know where those are) would forever rid the world of smallpox, although reconstructing the virus from its genomic sequence is, technically speaking, feasible.

In 2015, there was another victory in the worldwide fight against vaccine-preventable diseases: the planet was certified free of type 2 polio (the last known case was in 1999). By 2016 all countries on Earth had switched to using either bivalent OPV (containing polio types 1 and 3) or inactivated polio vaccines.[59] Here's the reason—in the absence of circulating wild-type virus, most cases of polio are caused by vaccine-derived strains, and most of those are type 2 OPV that has reverted to virulence. In 2019, there was yet another victory: the planet was certified free of type 3 polio (the last known case was in 2012).[60] The case of vaccine-derived polio type 2 in an unimmunized adult in New York in 2022, and the fact that the virus was found in sewage in both New York and London, underscores the importance of maintaining a high level of population immunity.[61]

Many diseases have been *controlled* through vaccination. Polio, measles, and rubella have been *eliminated* from the US, meaning that indigenous cases no longer occur. Because infection can still be imported from outside the country, elimination should be viewed as a step along the way to the ultimate goal of eradication. Worldwide efforts to eliminate and ultimately eradicate hepatitis B, measles, rubella, and polio are under way.

What does it take to eliminate or eradicate a vaccine-preventable disease? First, it takes favorable disease characteristics, including a readily recognizable clinical syndrome, easy diagnosis, few subclinical infections, a short period of contagion, absence of persistence and nonhuman reservoirs, little strain variability, and lifelong immunity after natural infection. Then it takes a safe, effective, stable, easily stored and transported, cheap vaccine. Then it takes political will and the collaboration of governments, organizations, and many individuals. Finally, eradication takes money—while it requires intensive effort and expense over a short period of time, eradication can be viewed as very cost-effective when you consider that once achieved, vaccination may no longer be necessary.

Public Health Impact of Vaccines

It is difficult to summarize the impact that vaccines have had on our general well-being. Vaccination ranks among the top achievements in public health during the 20th century and is partially responsible for the dramatic increase in life expectancy that was seen during that period of time.[62] Great public health benefits continued to be realized on a global scale in the first decade of the 21st century[63]; worldwide, over 30,000 vaccine doses are delivered every second, preventing up to 3 million premature deaths each year.[64] It's no wonder that the International Covenant on Economic, Social and Cultural Rights holds immunization as a fundamental right of all people and sets immunization programs as an obligation for signatory states.[65] **Table 1.5** lists some of the historic triumphs of vaccination programs. The power of vaccination to preserve life and health is underscored by the extraordinary impact of the COVID-19 program, shown in **Table 12.3**.

As shown in **Figure 1.10**, the decline in cases of vaccine-preventable diseases has been nothing short of spectacular; com-

TABLE 1.5 — Triumphs Over Vaccine-Preventable Diseases

Disease	Year Eliminated From the United States	Global Progress
Smallpox[a]	1949	1977—Last case of smallpox in the world
		1980—Planet certified as smallpox-free
		2023—Extinction still debated
Polio[b]	1979	1999—Last case of type 2 polio in the world
		2012—Last case of type 3 polio in the world
		2015—Planet certified as type 2 polio-free
		2019—Planet certified as type 3 polio-free
Measles[c]	2000	2002—Last endemic case in the Region of the Americas
		2016—Region of the Americas certified as measles-free
Rubella[d]	2004	2009—Last endemic case in the Region of the Americas
		2015—Region of the Americas certified as rubella-free

[a] Smallpox. World Health Organization Web site. http://www.who.int/csr/disease/smallpox/en/. Accessed July 8, 2023.
[b] Global Polio Eradication Web site. http://polioeradication.org. Accessed July 8, 2023.
[c] Pan American Health Organization Web site. http://www.paho.org/hq/index.php?option=com_content&view=article&id=12528%3Aregion-americas-declared-free-measles&Itemid=1926&lang=en. Accessed July 8, 2023.
[d] Pan American Health Organization Web site. https://www3.paho.org/hq/index.php?option=com_content&view=article&id=10798:2015-americas-free-of-rubella&Itemid=1926&lang=en. Accessed July 8, 2023.

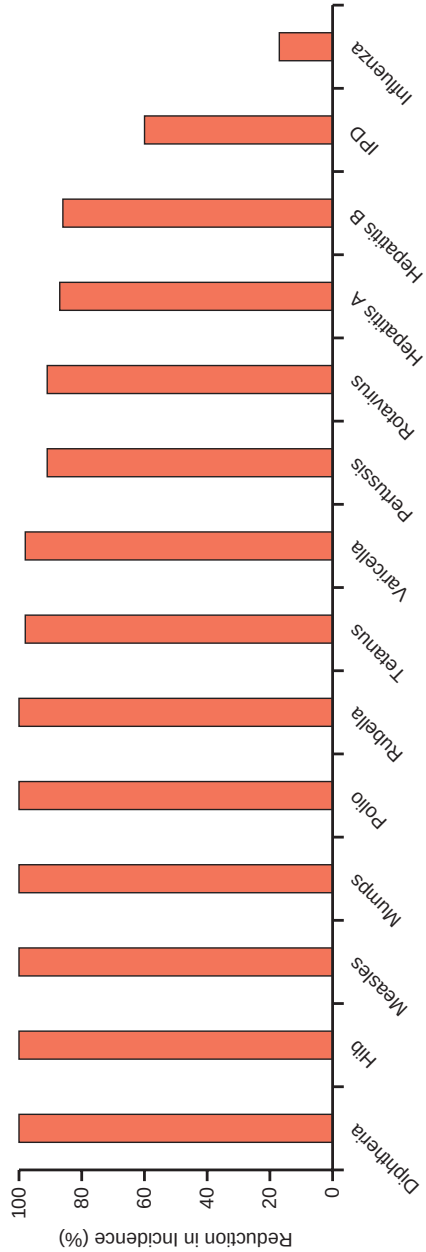


FIGURE 1.10 — Impact of Routine Childhood Immunization in the United States

Hib, (invasive) *Haemophilus influenzae* type b (disease); IPD, invasive pneumococcal disease

The graph shows the reduction in overall disease-specific incidence rates from the prevaccine era through 2019.

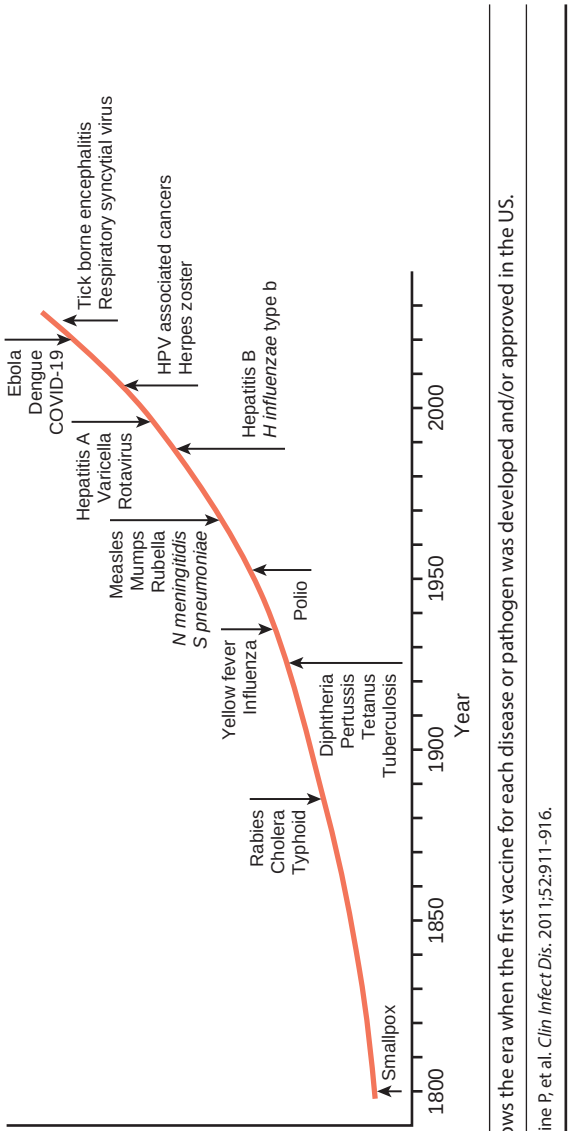
Adapted from Talbird SE, et al. *Pediatrics*. 2022;150:e2021056013.

placency, however, is ill-advised. Pertussis, for example, declined to historic lows in the 1970s but resurged after 1980. Some part of this resurgence was due to increased awareness, active surveillance, and better diagnostic tools. Part of it was also the fact that acellular vaccines are not as immunogenic as whole-cell vaccines, and immunity induced by childhood vaccination wanes[66,67] (even booster responses to Tdap appear to wane with time[68]). Other potential factors include antigenic changes in circulating strains, increased toxin production by current strains, and the inability of vaccines to prevent infection as opposed to disease.[69] The mid-2000s also saw an abrupt resurgence of mumps, probably due to a virus imported from Europe. Waning vaccine-induced immunity and the close-contact living situation of college students drove that outbreak, which disproportionately affected young adults. And measles, despite being eliminated from the US in 2000, continues to pop up and wreak havoc, largely because of intentional avoidance of vaccination.[70]

New strategies have been adopted for diseases that stubbornly persisted after vaccination programs were rolled out. For example, HepA targeted at high-risk individuals and communities could only bring us so far; the adoption of a universal childhood immunization program in 2006 brought the number of cases down much further. Similarly, the one-dose VAR program initiated in 1995 was very successful, but, because of breakthrough disease in vaccinees, could only bring us so far; the adoption of a routine 2-dose childhood schedule and catch-up immunization for everyone else should close the deal.

The number of vaccines in our armamentarium has grown exponentially (**Figure 1.11**), and studies have shown that the *clinically preventable burden*—the proportion of disease aborted by a preventive service in usual practice—is higher for the routine childhood immunization schedule than for virtually every other routine public health intervention.[71] There are many indirect benefits of vaccination programs as well; for example, reducing the number of disease cases also reduces the use of antibiotics, potentially helping to prevent the emergence of antimicrobial resistance.[72] **Table 1.6** shows the tremendous clinical and economic impact of the routine childhood vaccine schedule in the US.

FIGURE 1.11 — Vaccine-Preventable Diseases Timeline



The figure shows the era when the first vaccine for each disease or pathogen was developed and/or approved in the US.

Adapted from Fine P, et al. *Clin Infect Dis*. 2011;52:911-916.

TABLE 1.6 — Lifetime Impact of Routine Childhood Immunizations: United States, 2017 Birth Cohort

Outcome	Without Routine Vaccination	With Routine Vaccination
VPD cases	21.2 million	3.4 million
VPD-related deaths	33,000	1600
QALYs lost due to VPD	931,400	39,800
Lifetime societal VPD-related costs	$66.8 billion	$3.2 billion
Societal costs of vaccine program	—	$8.5 billion

QALYs, quality-adjusted life years; VPD, vaccine-preventable disease

The impact of routine childhood immunizations (DTaP, HepA, HepB, Hib, IPV, MMR, PCV13, RV, and VAR; influenza not included) was modeled for the 2017 birth cohort (N=3,855,500) through its lifetime. Outcomes were compared if the routine childhood vaccination schedule was not (second column, above), or was (third column), implemented, adjusted for current coverage rates and effectiveness estimates. Costs are reported in 2019 USD. Program costs included vaccine acquisition, administration, and adverse events.

Adapted from Carrico J, et al. *Pediatrics*. 2022;150:e2021056007.

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Vaccine Infrastructure in the United States

Vaccine Development and Licensure

It takes a lot to go from identifying the cause of an infectious disease to having a vaccine that can prevent it. The biology of the infectious agent and pathogenesis of the disease must be elucidated. Correlates of immunity, and the laboratory tools to measure them, must be developed. Animal models of vaccine efficacy need to be investigated. Issues such as immunopotentiation, formulation, and delivery need to be worked out, and consistent test lots must be produced. As illustrated in **Figure 2.1**, these steps take place in academia, industry, governmental research institutions, and/or collaborations between these groups.

Whereas the testing of candidate vaccines in humans is rigorously overseen by the US Food and Drug Administration (FDA),[1] it is important to understand that public health emergencies aside (*see below*), the financial risk of clinical development is largely borne by industry. That risk is substantial—for example, the estimated, inflation-adjusted, capitalized, total research and development costs for RotaTeq (RV5) were as high as $644 million (2008 dollars)[2]—and there was no guarantee that the investment would pay off. In fact, for every one vaccine development success, there are eight failures, and development takes an average of 14 years.[3] Even successful development programs can fail, at least from a business perspective. For example, costly development programs successfully extended the age indication for MenACWY into infancy, but routine use in infants was recommended against.[4]

The FDA group that sets the standards for vaccine development is the Center for Biologics Evaluation and Research (CBER). Laboratory testing for purity and consistency is required before and after licensure, and an intensive search is performed for the presence of adventitious agents. Potency tests are applied, and biochemical identity is assured. Manufacturers are required to conform to Good Manufacturing Practices (GMPs), a collection of rules and guidance that cover everything from raw-materials quality assurance to record keeping, cleanliness standards, personnel qualifications, in-house testing, process controls, warehousing, and distribution. Manufacturers must also adhere to Good Laboratory Practices (GLPs), analo-

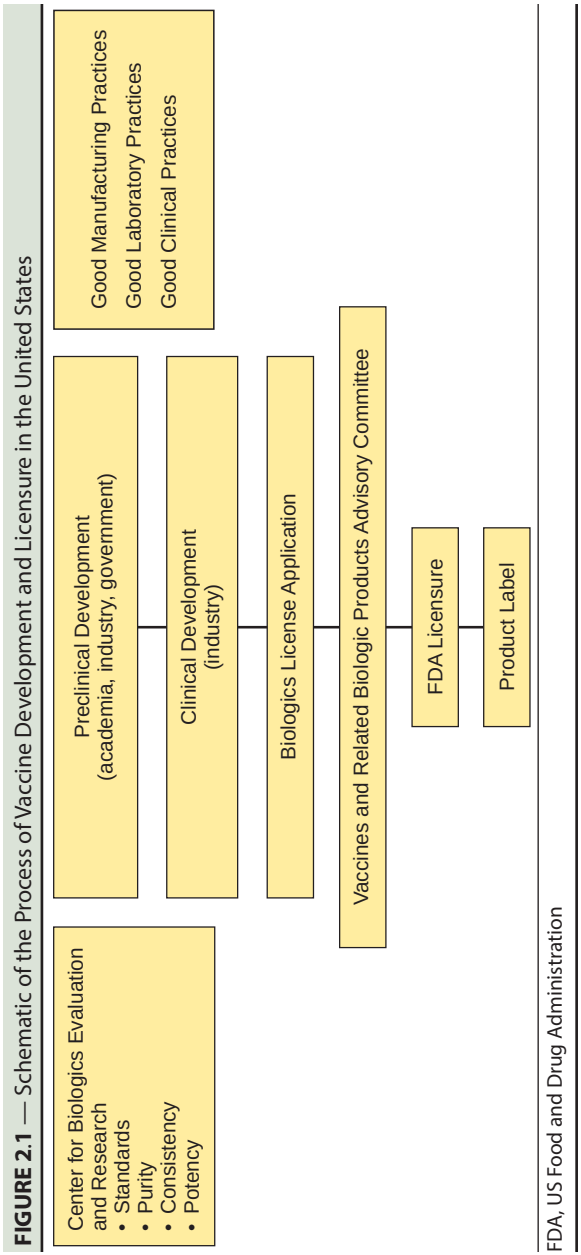


FIGURE 2.1 — Schematic of the Process of Vaccine Development and Licensure in the United States

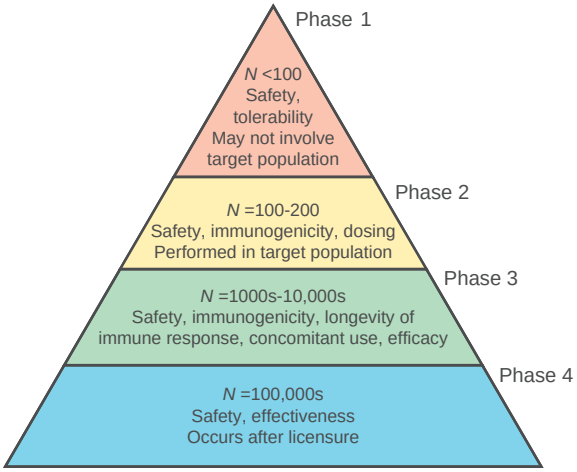
gous guidance that involves everything from assay reproducibility to interpretation. Several large lots of vaccine with identical potencies and demonstrated safety must be produced in a manner that is consistent and reliable. In addition, manufacturers are required to provide information regarding appropriate storage and handling.

After a candidate vaccine is approved as an investigational new drug for use in clinical trials, studies of safety, immunogenicity, and (if possible) efficacy are performed. The Code of Federal Regulations (eg, 21CFR314.126) and Good Clinical Practice (GCP) guidance from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use[5] set the standards for conduct of clinical trials. Some trials are sponsored by the National Institutes of Health (NIH) through Vaccine and Treatment Evaluation Units, all of which are associated with academic medical centers. Other studies, generally involving more mature candidate vaccines, are conducted at academic medical centers or private offices by pharmaceutical companies (or clinical research organizations contracted by these companies) using local principal investigators who are overseen by institutional review boards. Strict federal guidelines apply regarding the protection of human subjects and the management of potential conflicts of interest.

Prelicensure trials proceed in phases (**Figure 2.2**)[6]:

- *Phase 1*—These trials usually involve <100 volunteers and are intended to provide basic information on safety and tolerability. Because of their small size, they can detect only common adverse events. Subjects are often not drawn from the intended target population; for example, pediatric vaccine candidates might undergo initial testing in adults until basic safety is assured.
- *Phase 2*—These trials enroll hundreds of subjects and provide information about the vaccine's immunogenicity, dosing, and common side effects. Studies are usually performed in the proposed target group.
- *Phase 3*—These studies enroll thousands to tens of thousands of subjects—sample sizes large enough to ensure that questions about safety and efficacy (or surrogates of efficacy) will be answered (these are often referred to as *pivotal studies*). Subjects are carefully followed for adverse events in the immediate post-vaccination period and sometimes as long as 42 days. Longer periods of observation allow for assessment of persistence of immune responses, protection from disease, insidious side effects and adverse events of special interest. Large trials also evaluate the consistency of responses and look at concomitant use with other vaccines. This phase of development includes the transfer of manufacturing to full-scale facilities, which must operate under GMPs and are subject to rigorous inspections (the physical plant itself must be licensed).

FIGURE 2.2 — Sequential Stages in the Testing of Vaccines in Humans



Phase 3 trials of vaccines for diseases that previously were not vaccine-preventable typically include placebo recipients so that efficacy can be directly determined. Phase 3 trials of new versions of existing vaccines generally pit the new vaccine against the existing one. Here, prevention of disease may not be a feasible endpoint, since the disease itself may be rare. The endpoint, therefore, may be immunogenicity, the inference being that if the new vaccine is as immunogenic as the existing one, which is already known to be protective, it should also be protective—this is called *immunogenicity bridging*. The statistical paradigm used in these evaluations is called *noninferiority*, which determines whether the new vaccine achieves the immunogenicity of the established vaccine within a predetermined, acceptable, and agreed-upon margin of error.[7] The new vaccine must also be noninferior for safety endpoints.

Pressure to make sure that vaccines are as safe as possible before licensure has driven the size of Phase 3 trials upward—the studies that led to the licensure of RV5 and RV1, for example, each involved about 70,000 children. As illustrated in **Table 2.1**, huge numbers of subjects are needed to detect adverse events that have a low background rate in the general population and a rare association with vaccination. Trials of that magnitude are rarely feasible, necessitating postmarketing safety surveillance mechanisms (*see below*). At some point in the future, safety may be established using surrogate biomarkers.

TABLE 2.1 — Number of Subjects Needed to Test for Increased Relative Risk of an Adverse Event Compared to Background Rates

Background Rate in General Population	Rate in Vaccinated Population		
	2-Fold Higher	10-Fold Higher	100-Fold Higher
1 in 10,000	141,000	5,500	500
1 in 100,000	1,238,000	53,500	2,500
1 in 1,000,000	12,951,500	532,500	23,500

Adapted from Evans D, et al. *J Infect Dis*. 2009;200:321-328. Assumes a 5% risk of committing a Type I error and 90% power to detect a difference.

- *Phase 4*—In addition to very rare side effects, prelicensure trials may not be able to detect adverse events with delayed onset and reactions in culturally or ethnically diverse populations. Formal *postmarketing* studies are designed to detect such rare events. Guidance for postmarketing activities is provided by Good Pharmacovigilance Practices (GPPs), which are analogous to GCPs. These studies are supplemented by the surveillance systems described below.

  Postmarketing studies also may look at *effectiveness*, that is, the extent to which a vaccine performs in real life (not to be confused with *efficacy*, which is how the vaccine performs in controlled clinical trials). Effectiveness assesses the net balance between the benefits and risks of a vaccination program, not just the potency of the vaccine itself; in addition, because it is assessed at the population level, effectiveness includes the contribution of herd effects. Many other factors affect vaccine effectiveness, including coverage rates, population mixing, host factors, and the prevailing force of infection (see *Chapter 1: Introduction to Vaccinology—Epidemiological Concepts*).

  Determining true vaccine effectiveness can be tricky. For example, vaccine effectiveness appeared to wane over time during successive waves of the COVID-19 pandemic.[8] Some of this may have been due to our inability to deploy updated vaccines fast enough to hold a rapidly evolving pathogen in check. However, vaccine effectiveness must be understood as the relative risk reduction in a given outcome among vaccinated people compared to unvaccinated people.[9] As the pandemic continued, more and more unvaccinated people acquired immunity from natural infection, diminishing the relative advantage conferred by vaccination. This has been called the *depletion of susceptibles bias* in effectiveness studies.

A special type of effectiveness study that is particularly applicable to diseases like influenza is the *test-negative design*. Here, effectiveness estimates are derived by comparing vaccination status among cases of influenza-like illness who test positive for influenza and those who test negative.[10] Some of the reasons why a vaccine might not work in real life are listed in **Table 2.2**.

Ultimately, what we are really interested in is the *impact* of a vaccine program, that is, the reduction of disease at the population level after a vaccine is introduced.[11] Impact is determined by vaccine effectiveness, coverage rates, and herd effects.

After Phase 3 studies are completed, the manufacturer submits a Biologics License Application (BLA) to the FDA, which contains all the data necessary to determine if a license should be granted. The license, technically speaking, grants permission for the manufacturer to introduce the product into interstate commerce. The content of the BLA file is determined in a dynamic process of give and take between CBER and the manufacturer. Around the time of the BLA submission, the manufacturing facilities are inspected, and all aspects of vaccine production are evaluated. Once the BLA is accepted, the formal evaluation process begins—a process that generally takes a year or two, depending on whether supplemental information or additional studies are requested. If, after review, a product is deemed not ready for approval, the FDA issues a Complete Response Letter, which describes specific deficiencies and outlines recommended actions that could lead to licensure. The FDA has a series of programs designed to expedite drug development for serious conditions, including breakthrough therapy designation, fast track designation, accelerated approval, and priority review; these pathways may be warranted for certain vaccines.[12]

Manufacturers may be invited to present the case for licensure to the Vaccines and Related Biological Products Advisory Committee (VRBPAC), especially if the vaccine is the first in a class or if there are questions about safety or efficacy. VRBPAC members are appointed by the FDA Commissioner; most of them have recognized expertise in fields related to vaccinology, although one member who is identified with consumer interests may be appointed. In addition, a nonvoting representative of the pharmaceutical industry also may be invited, ensuring that all interested parties have input into licensure decisions. VRBPAC makes recommendations to the FDA Commissioner regarding whether the product should be licensed, what the indications should be, and whether any additional data are needed.

In some situations, efficacy studies are unethical; a good example is the use of anthrax vaccine for postexposure prophylaxis against inhalation anthrax. Here, the FDA employed the Animal Rule, which allows for approval of products that are critical to public health and national security based on efficacy data in animals combined with immunogenicity and safety data in both animals and humans.[13]

Along with licensure of the vaccine, the FDA approves a *package insert* (PI), also referred to as the *product information*, *prescribing information*, or *label*. The PI has two main sections: Highlights, which provides immediate access to the most important information that providers need and lists the original date of approval, recent major changes, and contact information in the event of adverse reactions; and Full Prescribing Information, which contains official indications; efficacy data; contraindications; warnings; precautions; information about adverse events; instructions for storage, handling, and administration; details on composition; and presentation and packaging, among other things.[14] When people refer to *labeled indications*, they are referring to the specifics contained in the PI. The labeled indications are based on data in the BLA. So, for example, if the studies on file only include persons in a certain age group, the label specifies approved use only in that age group. That will not change, even if new studies are published, unless the manufacturer submits a supplemental BLA that is approved. The PI also determines how a vaccine can be advertised and marketed. Companies must restrict their claims about the product to the information contained in the PI (guidance from the FDA now allows for the dissemination of data *consistent with* the label, even if those data are not contained *in* the label[15]). Likewise, promotional programs must remain within the label, and it must be specified during continuing medical education programs when off-label uses of a product are to be discussed. It is important to understand that the PI is a regulatory document, and its content is prescriptive. For example, adverse events that have been reported postlicensure are listed, *whether or not there is evidence of a causal relationship with vaccination*; this can lead to unnecessary concern, since in truth there may be no causal relationship.

It is also important to understand the difference between *labeled indications* and *official recommendations*. Labeled indications derive strictly from the PI and are based on information in the BLA; recommendations derive from authoritative bodies (*see below*) and sometimes differ from labeled indications (**Table 2.3**). Most people would agree that recommendations, as opposed to labeled indications, set the standard of care because they are based on a more comprehensive dataset and represent the opinion of medical peers.

Emergency Preparedness and Response

Until 2004, the only mechanism for making unlicensed medical products available to patients was the Investigational New Drug (IND) designation, which essentially handled administration of the product as a research activity.[16] This meant that an Institutional Review Board had to approve the protocol; patients needed to sign informed consent documents; and there were substantial requirements for record-keeping and patient follow-up. After the September 11, 2001, terrorist attacks, it became clear that these procedures

TABLE 2.2 — Causes of Vaccination Failure

Category	Example
Vaccine Failure	
Host-related	
Immunodeficiency	HIV-infected children may have suboptimal responses to certain vaccines[a]
Poor immune response	8% of vaccinees <40 y do not achieve protective levels of antibody after the 3-dose HepB series[b]
Immune senescence	Efficacy of ZVL against herpes zoster is 64% at 60-69 y and 38% at ≥70 y[c]
Waning immunity	Immunity to pertussis after the childhood DTaP series wanes before adolescence[d]
Poor health status	Patients with end stage renal disease may have decreased responses to IIV[e]
Interference by infectious agents	Concurrent enteric infections inhibit the response to OPV[f]
Immunological interference	Transplacentally derived maternal antibodies blunt the response of infants to HepA[g]
Pre-existing infection	Females who are infected with human papillomavirus before immunization are at risk for cervical cancer[h]
Vaccine-related	
Vaccines are not 100% efficacious	Influenza vaccine efficacy is only about 60% in adults 18-65 y[i]
Antigenic variation	Influenza vaccine has decreased efficacy against "drifted" strains[i]
Antigenic interference	Response to VAR is impaired if it is given within 28 d of receipt of MMR[j]
Suboptimal manufacturing	Inadvertent release in 1998 of HepA with decreased antigen content[k]
Failure to Vaccinate	
Usage Issues	
Administration error	Decreased response to HepB when it is given in the buttock[l]
Non-compliance	Invasive *H influenzae* type b disease in infants who had not received Hib[m]

Continued

TABLE 2.2 — *Continued*

Category	Example
Inadequate storage	Freezing pertussis vaccine can decrease immunogenicity[n]
Expiration	18% of 4,699 VAERS reports regarding LAIV from 2007-2014 involved administration of expired vaccine[o]
Programmatic Issues	
Suboptimal recommendation	3-dose infant Hib schedule (without a booster dose) in the United Kingdom before 2006[p]
Shortage of vaccine	Increased invasive pneumococcal disease associated with PCV7 shortage[q]

VAERS, Vaccine Adverse Event Reporting System

[a] Bekker V, et al. *Pediatrics*. 2006.118:e315-e322.
[b] Averhoff F, et al. *Am J Prev Med*. 1998;15:1-8.
[c] Oxman MN, et al. *N Engl J Med*. 2005;352:2271-2284.
[d] Tartof SY, et al. *Pediatrics*. 2013;131:e1047-e1052.
[e] Watcharananan SP, et al. *Transplant Proc*. 2014;46:328-331.
[f] Parker EPK, et al. *J Infect Dis*. 2014;210:853-864.
[g] Bell BP, et al. *Pediatr Infect Dis J*. 2007;26:116-122.
[h] Muñoz N, et al. *Lancet*. 2009;373:1949-1957.
[i] Osterholm MT, et al. *Lancet Infect Dis*. 2012;12:36-44.
[j] Verstraeten T, et al. *Pediatrics*. 2003;112:e98-e103.
[k] Jäger G, et al. *Hum Vac*. 2006;2:233-236.
[l] de Lalla F, et al. *Eur J Epidemiol*. 1988;4:256-258.
[m] CDC. *MMWR*. 2009;58:58-60.
[n] Boros CA, et al. *Vaccine*. 2001;19:3537-3542.
[o] CDC. *MMWR*. 2014;63:773.
[p] Ladhani S, et al. *Clin Ther*. 2012;34:385-399.
[q] Abuelreish M, et al. *Clin Pediatr*. 2007;46:45-52.

Adapted from Heininger U, et al. *Vaccine*. 2012;30:1265-1268.

would not work for rapid development and deployment of critical drugs and vaccines in a strategic emergency. Congress therefore passed to Project BioShield Act of 2004 (P.L. 108-276), which established the Emergency Use Authorization (EUA) program; subsequent legislation has expanded and strengthened the EUA authority.[17]

EUA is functionally equivalent to FDA licensure, allowing a previously unlicensed product to be distributed and used before it achieves full approval (an EUA can also be used to expand the indication for a currently licensed product). For an EUA to be granted, the Secretary of Health and Human Services (HHS) must first declare a public health emergency. The FDA then evaluates clinical data on the product in consultation with the Centers for Disease Control and Prevention (CDC) and NIH. An EUA is issued if the agent listed in the public health emergency causes a serious disease;

TABLE 2.3 — Notable Differences Between Product Labels and Official Recommendations

Vaccine(s)	Product Label(s)	ACIP Recommendation(s)
Many products	Limited information on concomitant administration of other vaccines	Virtually all vaccines can be given concomitantly
DTaP-HepB-IPV (Pediarix)	Indicated for infants of HBsAg-negative mothers	May be used to complete HepB series in infants of HBsAg-positive mothers
HepA	Indicated for persons ≥12 mo	Use in infants 6-11 mo before international travel
Hib-T (ActHIB, Hiberix)	Booster dose at 15-18 mo	Booster dose at 12-15 mo
IIV	Some brands contraindicated in persons with severe egg allergy	All brands may be used in persons with severe egg allergy
MenACWY-D (Menactra)	2 doses at 9-23 mo 1 dose at 2-55 y 1 booster dose at 15-55 y	2-dose primary series for persons with reduced immune response Revaccination every 5 y for high-risk persons
MenACWY-CRM (Menveo)	4-dose series in infants 2 doses at 7-23 mo 1 dose at 2-55 y 1 booster dose at 15-55 y	
MenACWY-CRM (MenQuadfi)	1 dose at ≥2 y 1 booster dose at ≥15 y	
MenB-FHbp (Trumenba) and MenB-4C (Bexsero)	1 series at 10-25 y	Use in high-risk persons ≥10 y Revaccination every 2-3 y
MMR (M-M-R_{II} and Priorix)	Indicated for persons ≥12 mo	Use in infants 6-11 mo during outbreaks and before international travel
MMR (M-M-R_{II} and Priorix) and VAR (Varivax)	Contraindicated in primary or acquired immunodeficiency states	May be used in certain primary and acquired immunodeficiency states
RAB (Imovax Rabies and Rabavert)	5-dose series for postexposure prophylaxis	4-dose series for postexposure prophylaxis
RV1 (Rotarix)	First dose beginning at 6 wk, last dose ≤24 wk	First dose at 6-14 wk 6 d, last dose at <8 mo 0 d
RV5 (RotaTeq)	First dose at 6-12 wk, last dose ≤32 wk	
Tdap (Adacel)	1 dose at 10-64 y A second dose may be administered ≥8 y after Dose 1	Use in children 7-9 y who are not complete on pertussis immunization Adacel may be given to adults ≥65 y Use during every pregnancy May be used for decennial tetanus and diphtheria boosters throughout adulthood
Tdap (Boostrix)	1 dose at ≥10 y	

ACIP, Advisory Committee on Immunization Practices; HBsAg, hepatitis B surface antigen

the scientific evidence suggests that the product may be effective in diagnosing, preventing, or treating the disease; the benefits are likely to outweigh the risks; and there is no approved alternative product. Certain conditions for use may be specified under an EUA, such as how the product may be distributed. Patients should be informed that a product is approved under an EUA and should be told the potential benefits and risks. Safety and efficacy are rigorously monitored, such that the EUA could be revoked at any time if the risk/benefit calculus changes. Manufacturers and those who administer vaccines under an EUA are protected from liability (see *Chapter 3: Standards, Principles, and Regulations—Public Readiness and Emergency Preparedness* [*PREP*] *Act*). Recent public health emergency declarations relevant to vaccine-preventable diseases include the influenza A(H1N1) pandemic (April 26, 2009), COVID-19 pandemic (January 31, 2020), and mpox outbreak (August 4, 2022).

The usual mechanisms for vaccine development would not work in the event of an emergent biological threat. Therefore, in 2006, HHS established the Biomedical Advanced Research and Development Authority (BARDA), which is responsible for (among other things) sponsoring the development and stockpiling of vaccines for public health emergencies.[18] Activities include supporting innovative research, nonclinical development (eg, animal models), fill and finish capacity, and clinical studies. For influenza, elements of this effort have included the development of new technologies like cell-culture, adjuvants, and recombinant DNA. Moreover, BARDA acts to secure year-round supplies of eggs for manufacturing and provides cost-sharing support for modification of existing facilities and building new ones.

The response to the 2009 A(H1N1) pandemic attests to the effectiveness of these strategies.[19] At that time, existing technologies, platforms, manufacturing methods and facilities were leveraged to produce vaccines. At the time of the COVID-19 pandemic, however, no such infrastructure or history existed. The response, therefore required an unprecedented martialing of effort—termed Operation Warp Speed (OWS)—from government, industry, academia, and other partners. The initial investment was $10 billion, with the goal of having tens of millions of doses of a safe and effective vaccine authorized for use by the end of 2020, and 300 million doses available for distribution to the US population by mid-2021.[20]

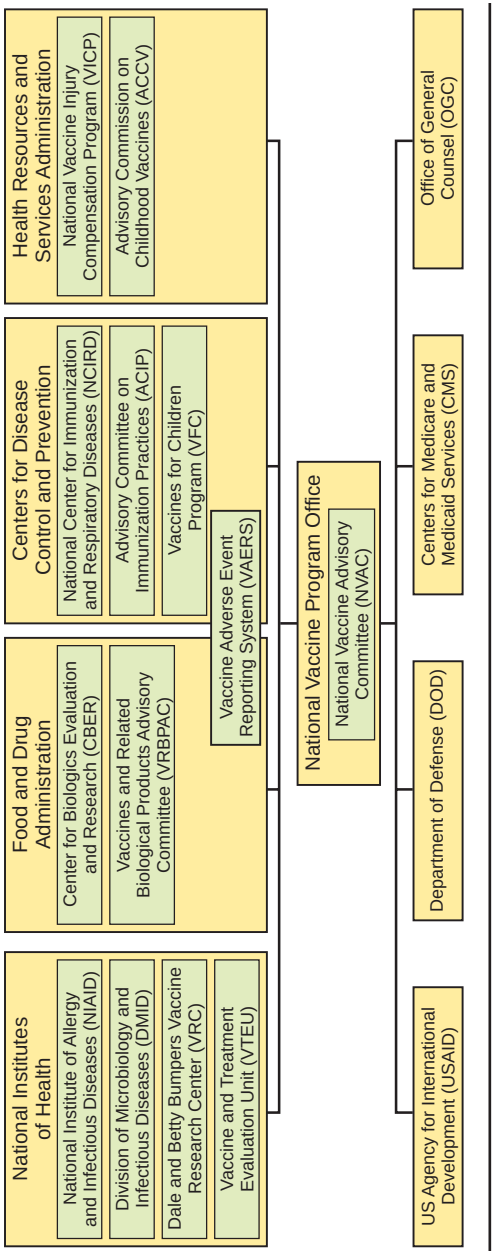
It is difficult to fully comprehend the challenge that OWS faced. In the first year of the pandemic there were over 100 million cases worldwide (over 25 million in the US) and 2.2 million deaths (430,000 in the US).[21] The disease was caused by a novel virus, SARS-CoV-2, whose closest relatives—SARS-CoV-1 and MERS—had caused severe but circumspect outbreaks. The virus was highly contagious and lethal; the correlates of protective immunity were not known and, in fact, reinfections and antigenic escape (see *Chapter 1: Introduction to Vaccinology—Basic Vaccine Immunology*) had been documented, suggesting that a vaccine might need to protect better than natural immunity. Given this, and the need to rapidly scale-up manufacturing, 4 platforms were chosen for development: mRNA; replication-defective live vector; recombinant, subunit, adjuvanted protein; and attenuated replicating live vector. Some of these technologies had never been used to manufacture a routinely administered human vaccine (see *Chapter 1: Introduction to Vaccinology—Non-live Vaccines*), and the fact that not every candidate vaccine was found to be sufficiently immunogenic underscores the reality that—theory and animal data aside—limited early phase human trials are needed before large-scale studies are warranted. Massive Phase 3 clinical trials involving 30,000 to 50,000 volunteers were needed for each candidate vaccine (see *Chapter 12: COVID-19*). Moreover, to facilitate rapid deployment, manufacturing needed to commence in parallel with these trials, based on the premise that a candidate vaccine might work, at tremendous financial risk. Finally, the challenges of implementation, not the least of which was public concern and skepticism, would need to be overcome (see *Chapter 7: Addressing Concerns About Vaccines—COVID-19 Vaccines*).

Policy and Recommendations

Figure 2.3 gives an overview of the various agencies and committees involved in vaccine policy in the US; **Table 2.4** summarizes the functions and work products of some of those bodies. The CDC includes the National Center for Immunization and Respiratory Diseases (NCIRD), an interdisciplinary program that merges vaccine-preventable disease science and research with immunization program activities. NCIRD provides leadership in the planning, coordination, and conduct of immunization activities throughout the country. It assists health departments in implementing immunization programs, supports establishment of vaccine supply contracts for state and local programs through the Vaccines For Children Program (VFC), assists in the development of information-management systems, administers research and operational programs, provides clinician educational programs, and supports surveillance for vaccine-preventable diseases.

The Advisory Committee on Immunization Practices (ACIP) is the principal body that makes recommendations for vaccine use.[22,23] It provides advice and guidance to the Secretary of HHS, the Assistant Secretary, and the Director of the CDC regarding the most appropriate application of vaccines and related agents to control communicable diseases in the civilian population. ACIP recommendations also provide an evidence base for providers and programs regarding how vaccines should be used. The committee has 15 voting members, including infectious diseases specialists and persons who are knowledgeable about consumer perspectives and/or social and community aspects of immunization programs. In addition,

FIGURE 2.3 — Governmental Agencies and Advisory Committees Involved in Vaccine Development, Policy, and Implementation



there are *ex officio* members representing a variety of governmental agencies, as well as nonvoting liaison members from professional organizations. Rigorous safeguards are in place to minimize actual or perceived conflicts of interest. For example, individuals employed by (or whose immediate family members are employed by), or those on the Board of Directors of, vaccine manufacturers, as well as those who hold patents on vaccines or related products, are excluded from membership. Study investigators may become ACIP members, but they cannot vote on recommendations related to the vaccines they are studying, or other vaccines made by the sponsor of the research, or even other vaccines related to the one under consideration.

The committee meets in February, June, and October of each year, with ad hoc interval meetings as needed (eg, meetings were held at least monthly beginning in June 2020 to deal with the rapidly evolving COVID-19 pandemic). ACIP meetings are open to the public and are broadcast on the Internet, and there are opportunities for oral and written public comment (during the COVID-19 pandemic, all meetings were held virtually). In making recommendations, the ACIP considers a product's labeled indications and dosing schedule, disease burden, safety data, feasibility, programmatic issues, equity of access, stewardship of public funds, and input from other stakeholder groups. Whereas a standardized approach to the presentation of health economics studies has been in place since 2008,[24] it is understood that economic models are subject to their input assumptions and must be interpreted in the context of appropriate sensitivity analyses. Herd effects are notoriously difficult to consider.[25]

Oftentimes, data that are not included in the BLA are considered, which explains why the recommendations may differ from the label. The process usually involves the formation of working groups on specific topics; these groups are chaired by ACIP members but often include outside experts. For some issues, such as vaccination during pregnancy and breast-feeding, specific guiding principles have been adopted.[26] **Figure 2.4** illustrates how vaccine-preventable diseases may differ from one another in terms of disease burden and how correspondingly difficult it may be to develop immunization policy.

There are several permanent working groups:

- *Combined Child/Adolescent and Adult Immunization Schedule*—This group recommends changes to the routine child/adolescent and adult schedules, which are published around the beginning of each year in their characteristic graphic layout (see *Chapter 8: Routine Schedules*). Beginning in 2023, addenda to the schedules have been posted year round on the CDC Web site to reflect incremental ACIP recommendations.
- *Influenza Vaccines*—This group makes recommendations regarding influenza immunization for the upcoming influenza season, which are usually published in late spring or early summer.

TABLE 2.4 — Terms Used in Reference to Vaccine Policy

Characteristic	Term		
	"Indication"	"Recommendation"	"Requirement"
Principal agency	FDA	CDC, as advised by ACIP	State or local governments Companies and hospitals Universities
Synonym	Label	Guideline	Mandate
Seat of authority	Federal law	Federal law	State or local law Employment Matriculation
Output	Package Insert Product Information Prescribing Information	Publication in MMWR	Statute and regulation[a] Contract Policy
Constituency	Manufacturers Recommending bodies	Providers State and local health departments	Citizens Employees Students
Common implication	What manufacturers can claim about their vaccine Starting point for drafting recommendations	Who providers should immunize How vaccines should be used	Which vaccines a person needs to attend school or work
Caveats	Some CDC recommendations may differ from the indications The indications are based solely on data submitted by the manufacturer[b]	Recommendations are not *requirements*, but they are considered the *standard of care* Other agencies contribute to drafting recommendations issued by CDC, and those agencies usually reissue the same recommendations There may be minor differences between CDC recommendations and those issued by partner agencies	Exemptions for medical reasons are generally offered Exemptions for nonmedical reasons may be available

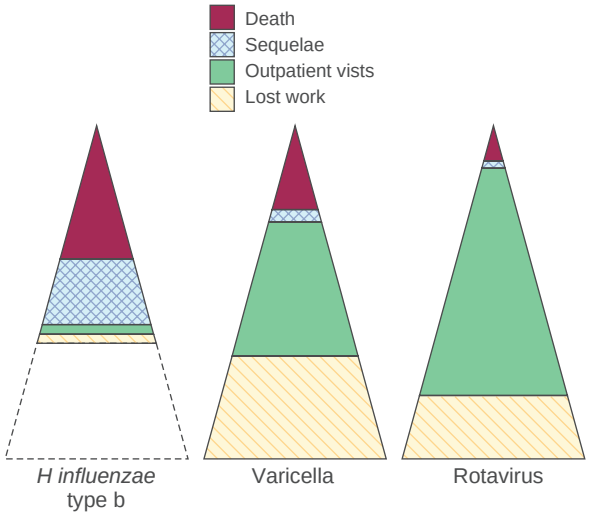
ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; FDA, US Food and Drug Administration; MMWR, *MMWR Morbidity and Mortality Weekly Report*

[a] Statutes are formal laws written by a legislative body. Regulations are laws promulgated under delegated authority, usually by government agencies.

[b] For example, postmarketing data on safety or effectiveness may be available, but are not included in the Package Insert unless formally submitted by the manufacturer and approved by the FDA.

Adapted from Pickering LK, et al. *Vaccine*. 2017;35:5027-5036.

FIGURE 2.4 — Considerations in Making Vaccine Recommendations



The figure illustrates just how different the clinical and societal burden was among various diseases before vaccines were available. Some diseases like varicella were universal and, while resulting in occasional deaths and permanent sequelae, took their toll to a large extent in terms of outpatient visits and lost work. Others like invasive *H influenzae* type b infection were less common but resulted in significant morbidity and mortality. The justification for each respective immunization program had to take these characteristics into account.

Adapted from Black S. *Vaccine*. 2013;31:6046-6049.

- *General Recommendations*—This group maintains the *General Best Practice Guidelines for Immunization*, an on-line document that provides background and technical guidance regarding vaccination.[27] Topics include timing and spacing of doses, contraindications and precautions, adverse reactions, vaccine administration, storage, and handling, altered immune competence, special situations, record keeping, vaccination programs, and sources of information (see *Chapter 5: General Recommendations*).

Starting in 2023, new recommendations are posted on the ACIP Recommendations Web site (https://www.cdc.gov/vaccines/acip/recommendations.html) immediately after each meeting. Whereas these are "official" recommendations that are approved by the CDC director, more background and guidance is contained in the full recommendations that are subsequently published in the *Morbidity and Mortality Weekly Report* (*MMWR*) and on the CDC Web site. Occasionally, informational items ("Notice to Readers") are also published in the MMWR. The CDC Director may, on occasion, modify the recommendations of the ACIP before they are rendered "official"; in September 2021, for example, the Director expanded the ACIP recommendations for a booster dose of COV-mRNA (Pfizer-BioNTech) to include adults at increased risk for exposure and transmission because of their occupational or institutional setting.[28] The ACIP Web site houses a comprehensive, up-to-date archive of disease-specific recommendations[29] and a summary of recommendations for common diseases is maintained in *Epidemiology and Prevention of Vaccine-Preventable Diseases*, also known as the "Pink Book."[30]

The process by which ACIP recommendations are made, and the final format of those recommendations, are codified. Relevant evidence is ranked using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[31] approach (**Table 2.5**). After this, the Evidence to Recommendations (EtR)[32] framework (**Table 2.6**) is used to consider the public health importance of the disease, the desirable and undesirable effects of a vaccination program, relevant values, acceptability to stakeholders, resources, equity, and feasibility. The elements of the EtR framework are difficult to weigh, and there is no prescribed formula. Recommendations for the prevention of invasive meningococcal disease (IMD) provide a good example of the challenges that the EtR framework presents. For one, the disease is rare (see *Chapter 23: Neisseria meningitidis*) and the cost of immunization is high. Whereas that would seem to make routine immunization unfavorable, studies show that the U.S. public values protection against low-incidence, severe-outcome diseases (like IMD) as much as it does protection against high-incidence, less-severe diseases (like influenza).[33] For another, any incremental recommendations would need to address disparities in coverage rates that have arisen across racial, ethnic, socioeconomic, and geographic lines.[34]

Recommendations fall into the categories shown in **Table 2.7**. ACIP may decide not to issue a recommendation; in such cases, VFC will not cover the vaccine and insurance may not. As more vaccines become available for the same disease, there are likely to be instances when one vaccine may be preferred over another. Recent examples of *preferential recommendations* for older adults include the preference for RZV over ZVL for prevention of zoster, and for higher dose and adjuvanted IIVs over standard vaccines for prevention of influenza. As of 2023, there is no accepted framework for arriving at preferential recommendations.[35]

Recommendations *for* or *against* vaccination are straightforward; recommendations for *shared clinical decision-making* (SCDM)

TABLE 2.5 — GRADE Approach to Quality of Evidence[a]

Level	Source of Evidence
1	Randomized controlled trials
	Overwhelming observational evidence
2	Randomized controlled trials with important limitations
	Exceptionally strong observational evidence
3	Observational studies
	Randomized controlled trials with notable limitations
4	Clinical experience
	Controlled or observational studies with major limitations

GRADE, Grading of Recommendations, Assessment, Development and Evaluation

[a] Health economics analyses are not subjected to the GRADE process.

Adapted from Ahmed F, et al. *Vaccine*. 2011;29:9171-9176.

take no position on whether to vaccinate. Instead, they place the vaccination decision in the context of the therapeutic relationship between individual providers and patients. Importantly, SCDM recommendations are intended to move patients and providers beyond the status quo, which is, technically, that any vaccine may be given to any person who falls within the labeled indications.[36] Under SCDM, the ACIP not only acknowledges this, but also encourages that a discussion take place about the vaccine and the disease it is intended to prevent. Under SCDM, it seems reasonable that all eligible patients be informed about the disease and the availability of a vaccine; otherwise, disparities may arise between the "information haves" (those who know about the disease and vaccine) and the "information have-nots" (those who do not know about the disease or vaccine).[37] Considerations in the SCDM discussion include evidence regarding who may benefit; patient characteristics, values and preferences; clinical discretion of the provider; and characteristics of the vaccine.[38] SCDM in medicine is most appropriate when there is uncertainty and more than one reasonable choice[39]; it requires that the values, risks, benefits, and consequences of different decisions be clearly delineated for the patient.[40] Arguably, the trade-offs when it comes to vaccination are fairly simple—a sore arm and protection against disease at little or no cost (vaccines recommended under SCDM are covered by insurance and VFC) versus no sore arm and vulnerability to disease.

Table 2.8 lists the SCDM recommendations as of July 2023. It should be noted that some recommendations are not routine, use

TABLE 2.6 — EtR Framework

Problem
- Is the problem of public health importance?

Benefits and Harms
- How substantial are the desirable anticipated effects?
- How substantial are the undesirable anticipated effects?
- Do the desirable effects outweigh the undesirable effects?
- What is the overall certainty of this evidence for the critical outcomes?

Values
- Does the target population feel that the desirable effects are large relative to undesirable effects?
- Is there important uncertainty about or variability in how much people value the main outcomes?

Acceptability
- Is the intervention acceptable to key stakeholders?

Resource Use
- Is the intervention a reasonable and efficient allocation of resources?

Equity
- What would be the impact on health equity?

Feasibility
- Is the intervention feasible to implement?

ACIP, Advisory Committee on Immunization Practices; EtR, Evidence to Recommendation; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; PICO, Population, Intervention, Comparisons, Outcome

Overarching policy questions are formulated in PICO format. After addressing each of the factors listed in the box, the committee determines the balance between desirable and undesirable consequences and whether there is sufficient information to move forward with a recommendation. Recommendations take the forms listed in **Table 2.7**. The GRADE and EtR processes are more about providing transparency into how ACIP recommendations are developed, as opposed to a formulaic, algorithmic, or mathematical approach to reaching conclusions (in other words, there is still some subjectivity involved).

Adapted from ACIP Evidence to Recommendations Framework. CDC Web site. https://www.cdc.gov/vaccines/acip/recs/grade/downloads/acip-evidence-recs-framework.pdf. Accessed July 10, 2023.

TABLE 2.7— ACIP Recommendations

Category	Interpretation	Typical Language	Older Terminology	Insurance and VFC
Routine Catch-up Risk-based	Vaccination is recommended for all persons in a specified age or risk group	Recommend Should	Routine Category A	Yes
Recommendation against	Vaccination is not recommended in a specified group	Recommend against Should not	—	No
Shared clinical decision-making	The vaccination decision is informed by evidence regarding who may benefit; the person's characteristics, values, and preferences; the provider's clinical discretion; and characteristics of the vaccine	May	Permissive Category B	Yes

ACIP, Advisory Community on Immunization Practices; VFC, Vaccines for Children Program

TABLE 2.8 — SCDM Recommendations as of June 2023

Vaccine	Vaccination Recommended Under SCDM	Years in Place or Year Initiated
Historical		
HPV[a]	Males 9-21 y Males 22-26 y	2010-2011 2010-2019
HepB[b]	Persons ≥60 y with diabetes	2011-2022
PCV13[c]	Persons ≥65 y	2019-2021
Standing as of 2023		
MenB[d]	Persons 16-23 y	2015
HPV[a]	Persons 27-45 y	2019
Smallpox[e]	Jynneos for HCP who administer ACAM2000 or care for patients infected with orthopoxviruses	2022
PCV20[f]	Persons ≥65 y who previously received PCV13 and received PPSV23 at ≥65 y	2023
RSV[g]	Persons ≥60 y	2023

ACIP, Advisory Committee on Immunization Practices; SCDM, shared clinical decision-making

[a] In 2010, ACIP issued a permissive recommendation for use of HPV in males 9-26 y (CDC. *MMWR*. 2010;59:630-632). In 2011, routine vaccination of males at 11-12 y (starting as early as 9 y) was recommended, with catch-up through 21 y (Dunne EF, et al. *MMWR*. 2011;60:1705-1708). In 2019, routine vaccination of males 22-26 y was recommended, and vaccination of females and males 27-45 y was recommended under SCDM (Meites E, et al. *MMWR*. 2019;68:698-702).

[b] In 2011 the ACIP issued a routine recommendation for diabetics 19 to 59 y and a permissive recommendation for diabetics ≥60 y (Sawyer MH, et al. *MMWR*. 2011;60:1709-1711). As of 2022, routine vaccination of all persons 19 to 59 y and diabetics ≥60 y was recommended (Murthy N, et al. *MMWR*. 2022;71:229-233).

[c] From 2014-2019, PCV13 was routinely recommended in sequence with PPSV23 (Tomczyk S, et al. *MMWR*. 2014;63:822-825). In 2019, the recommendation for PCV13 was changed to SCDM (PPSV23 was still routinely recommended) (Matanock A, et al. *MMWR*. 2019;68:1069-1075). In 2022, these recommendations were replaced with a routine recommendation for either PCV20 alone or PCV15 followed by PPSV23 (Kobayashi M, et al. *MMWR*. 2022;71:109-117).

[d] In 2015, MenB was recommended for all healthy adolescents under "Category B", later known as SCDM (MacNeil JR, et al. *MMWR*. 2015;64:1171-1176).

[e] Rao AK, et al. *MMWR*. 2022;71:734-742.

[f] Adult immunization schedule by age. CDC Web site. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html. Accessed July 28, 2023.

[g] Meeting of the Advisory Committee on Immunization Practices, June 21, 2023. CDC Web site. https://www.cdc.gov/vaccines/acip/meetings/index.html. Accessed June 25, 2023.

the term "may receive", and require a discussion between provider and patient—but they are not specifically labeled "SCDM". This includes certain travel recommendations and other special circumstances.[41]

The American Academy of Pediatrics (AAP) Committee on Infectious Diseases also develops policy recommendations on the use of vaccines, subject to approval by the AAP Board of Directors. While these are developed independently, attempts are made to achieve congruity with ACIP recommendations. From time to time, however, there are subtle but important differences. AAP recommendations are included in the *Report of the Committee on Infectious Diseases* (commonly called the "Red Book"), a comprehensive summary of infectious diseases that is published in hard copy every 3 years and is available online.[42,43] The AAP also partners with the CDC in the Childhood Immunization Support Program, with goals to promote quality improvement and best immunization practices, improve delivery, and enable effective communication.

The ACIP has another important function: it determines which vaccines should be added to VFC (*see below*). For a vaccine to be covered under VFC, a specific resolution must be passed, which generally happens if the vaccine has been recommended. In 2023, the ACIP recommended nirsevimab (Beyfortus), a long-acting monoclonal antibody against respiratory syncytial virus (RSV), for all infants, and a VFC resolution was also passed. This was the first time a passive immunization product was essentially handled as a "vaccine".

The National Vaccine Program Office (NVPO) coordinates the activities of all federal agencies in developing and implementing the National Vaccine Plan, which was created in 1994, updated in 2010, and reformulated into the Vaccines National Strategic Plan in 2021.[44,45] The NVPO strives to improve collaboration with the commercial vaccine industry, global organizations, consumer groups, and academic institutions.

The National Vaccine Advisory Committee (NVAC) makes recommendations to the NVPO regarding the supply of safe and effective vaccines, research priorities, areas of cooperation, and ways to achieve optimal prevention of infectious diseases through vaccine development while minimizing adverse reactions. Members include physicians, researchers, representatives from parent organizations, and people involved in manufacturing and public health.

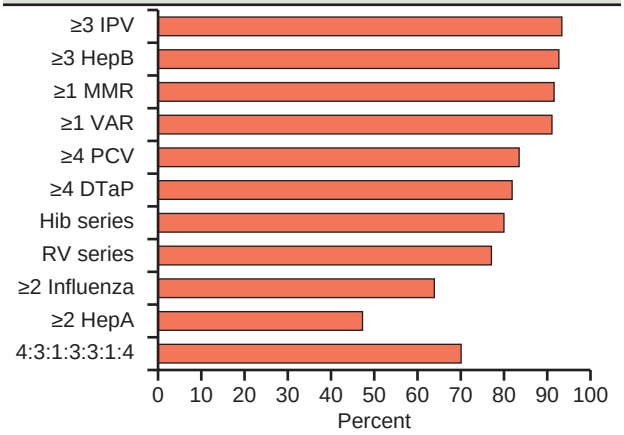
Monitoring Delivery

A substance is not a vaccine until it has been administered to a person.[46] Knowing who receives vaccines, and when they receive them, is a critical function of public health infrastructure, helping to identify disparities, assess the effectiveness of intervention programs, and establish best practices. The *coverage rate* is the proportion of

eligible persons who receive a recommended vaccine. The most recent coverage rates for children, adolescents, and adults are shown in **Figures 2.5**, **2.6**, and **2.7**, respectively. *Timeliness* refers to how often vaccinated persons receive the recommended doses of a vaccine within the recommended age ranges. As illustrated in **Figure 2.8**, delayed doses lead to periods of vulnerability to disease. In an analysis of 2014 data, only 58% of children were up-to-date with all recommended vaccines by 19 to 35 months of age.[47] The link between poor timeliness and disease risk is clear—in a study that involved over 300,000 children born or living in Washington State between 2008 and 2017, the adjusted relative risk of pertussis was 4.8 times higher among young children who were undervaccinated or delayed for the primary series as compared to those with age-appropriate immunization.[48]

Table 2.9 shows the major systems used to monitor vaccine delivery in the US. Additional methods include periodic school surveys (for example, state and local assessments of coverage rates among kindergarteners[49]), special area and population surveys (for

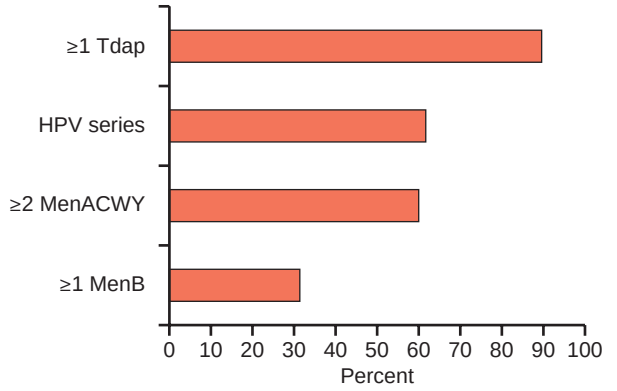
FIGURE 2.5 — Immunization Coverage Rates by 24 Mo for Children Born in 2018-2019



The graph shows the proportion of children in the US who received the indicated vaccines. While coverage for individual vaccines like DTaP remains high, coverage for the whole early childhood series (≥4 DTaP + ≥3 IPV + ≥1 MMR + ≥3 Hib + ≥3 HepB + ≥1 VAR + ≥4 PCV, or 4:3:1:3:3:1:4) is only around 70%. About 1% of young children are completely unimmunized (data not shown). For Hib and RV, the number of doses for series completion depends on the product used.

Data from Hill HA, et al. *MMWR*. 2023;73:33-38.

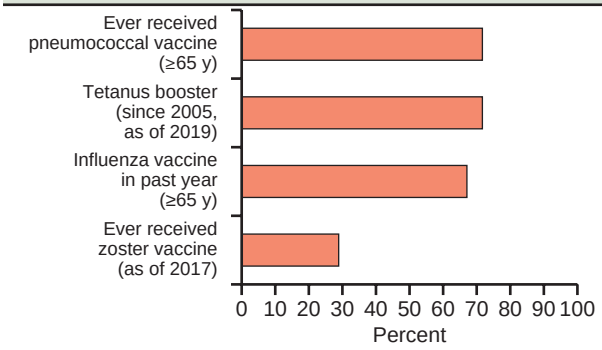
FIGURE 2.6 — Immunization Coverage Rates for Adolescents 13-17 y, 2021



The graph shows the proportion of adolescents in the US who received the indicated vaccines. While coverage for Tdap is high, coverage for the HPV series and MenACWY (doses at 11-12 and 16 y) remains low. Coverage for MenB is also low, but that, unlike HPV and MenACWY, MenB is recommended under shared clinical decision-making. For HPV, the number of doses for series completion depends on the age at initiation.

Data from Pingali C, et al. *MMWR*. 2022;71:1101-1108.

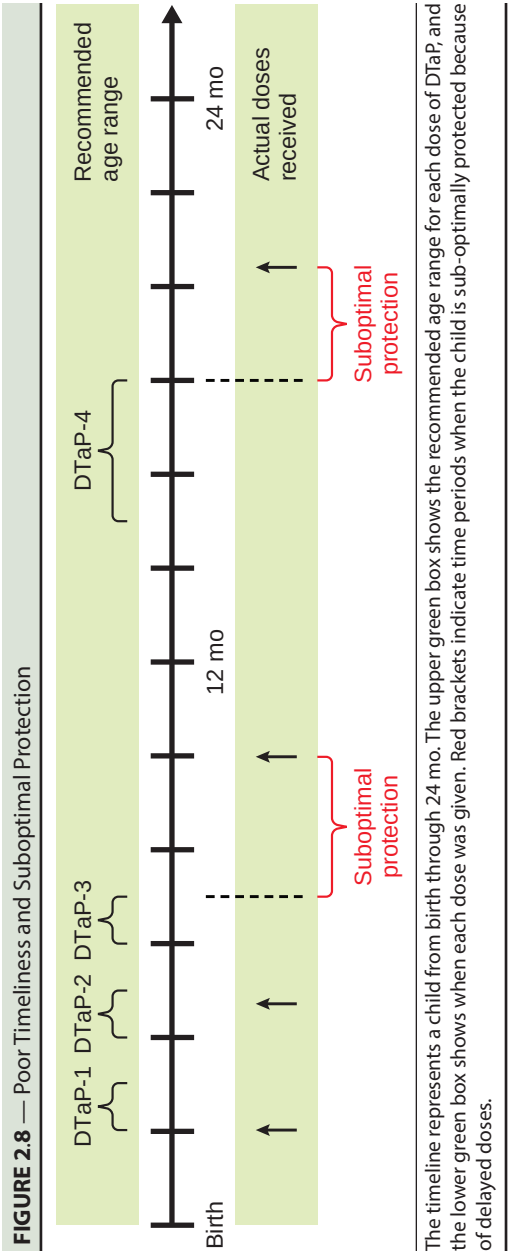
FIGURE 2.7 — Immunization Coverage Rates for Adults, 2021



The graph shows the proportion of adults in the US who received the indicated vaccines.

Data from BRFSS prevalence and trends data. CDC Web site. https://www.cdc.gov/brfss/brfssprevalence/index.html. Accessed June 8, 2023.

FIGURE 2.8 — Poor Timeliness and Suboptimal Protection



The timeline represents a child from birth through 24 mo. The upper green box shows the recommended age range for each dose of DTaP, and the lower green box shows when each dose was given. Red brackets indicate time periods when the child is sub-optimally protected because of delayed doses.

TABLE 2.9 — Principal Systems for Monitoring Vaccine Delivery in the United States

System	Characteristics	Annual Sample	Vaccinations Covered
National Immunization Surveys[a]	Random telephone interviews with validation through provider records	30,000 children 20,000 adolescents	Recommended vaccines for children 19-35 mo and adolescents 13-17 y COV for all persons in eligible age groups
Behavioral Risk Factor Surveillance System[b]	Random telephone interviews	>400,000 adults	Influenza, tetanus, and pneumococcus
National Health and Nutrition Examination Survey[c]	Face-to-face interviews and physical examinations	5000 children, adolescents, and adults	Hepatitis A, hepatitis B, and HPV
National Health Interview Survey[d]	Face-to-face interviews	9000 children 30,000 adults	Influenza, pneumococcus, zoster, tetanus, HPV, COV

[a] https://www.cdc.gov/vaccines/imz-managers/nis/index.html
[b] https://www.cdc.gov/brfss/index.html
[c] https://www.cdc.gov/nchs/nhanes/index.htm
[d] https://www.cdc.gov/nchs/nhis/index.htm

Adapted from Roper L, et al. *J Infect Dis*. 2021;224:S443-S451. All web sites accessed July 10, 2023.

example, the National Nursing Home Survey[50]), and the Healthcare Effectiveness Data and Information Set (HEDIS), which monitors the performance of managed health care plans.[51] During the pandemic, the CDC created an online clearinghouse[52] to receive, de-duplicate, and de-identify COVID-19 vaccination data for tracking purposes; sources of information included the Vaccine Administration Management System, immunization information systems (IISs), pharmacies, the Vaccine Tracking System, and VaccineFinder.

Disease Surveillance

Vaccine-preventable disease activity is monitored to assess the impact of immunization programs. Efforts are coordinated by the CDC's Epidemiology Program Office and the NCIRD, in collaboration with groups such as the Council of State and Territorial Epidemiologists. Approximately 100 infectious diseases, some of which are vaccine-preventable, are reportable through the National Notifiable Disease Surveillance System (NNDSS).[53] Reporting of diseases is mandated through legislation or regulation at the state level. Reporting to the CDC occurs weekly through the National Electronic Telecommunications System for Surveillance; the CDC analyzes the data and launches investigations when appropriate. Active surveillance systems are used to supplement reporting; a good example of this is the Active Bacterial Core surveillance (ABCs) system, which collects isolates and demographic data on patients with invasive bacterial infections, including *S pneumoniae*, *H influenzae*, and *N meningitidis*.[54] In 2015, the CDC implemented an enhanced meningococcal disease surveillance program to collect more complete data, acquire isolates for study, and inform policy decisions.[55]

The New Vaccine Surveillance Network (NVSN) was established in 1999 to evaluate the impact of new vaccines and new recommendations.[56] The network consists of seven academic medical centers that conduct inpatient and outpatient surveillance for vaccine-preventable diseases, including seasonal acute respiratory illness and acute gastroenteritis. Special targeted studies look at vaccine effectiveness.

Other systems contribute to our understanding of changes in disease burden after immunization programs are implemented. For example, the impact of rotavirus vaccine has been monitored using the National Respiratory and Enteric Virus Surveillance System (NREVSS), a passive laboratory system that provides data on rotavirus testing.

The Vaccine Safety Net

There is an inherent tolerance for risk with therapeutic interventions for sick people. The tolerance for risk with preventive interventions like vaccines is much lower because these involve healthy people. Moreover, everyone gets vaccines, but only selected people get medicines; therefore, the consequences of even rare adverse events are significant at the population level. It has been said that when a *medicine* is given, *disease is treated*, but when *vaccines* are given, *nothing happens*. The truth is, of course, that something *does* happen—disease is prevented. The difference is that with drugs like antibiotics, it is about what you see happen (*the pneumonia improves*), whereas with vaccines, it is about what you do not see happen (*the disease does not occur*).

An *adverse event following immunization* (AEFI) is any untoward medical occurrence—including a symptom, sign, disease, or laboratory abnormality—that happens after receipt of a vaccine. The categories of AEFI recognized by the World Health Organization as causally related are shown in **Table 2.10**. Monitoring for safety begins as soon as a candidate vaccine is proposed for testing and continues throughout its life cycle (**Figure 2.9**).[57,58] Prelicensure evaluation is described earlier in this chapter. Aspects of postlicensure safety monitoring are described below. Many examples of the safety net in action are described in *Chapter 7: Addressing Concerns About Vaccines*.

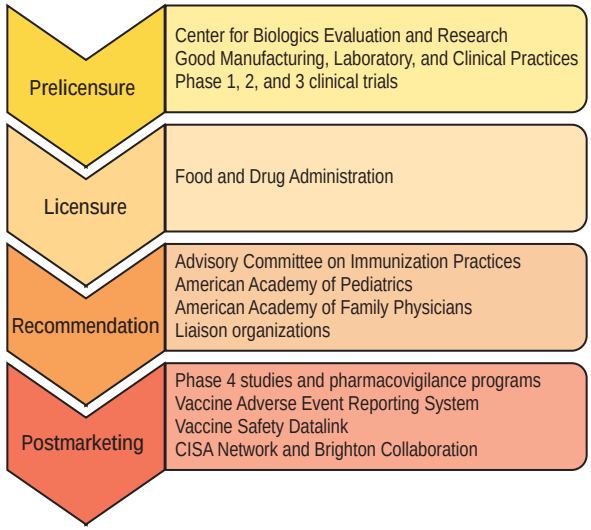
TABLE 2.10 — Causally-Related Adverse Events Following Immunization

Type	Characteristics
Vaccine product-related reaction	Caused or precipitated by a vaccine due to one or more of the inherent properties of the product itself
Vaccine quality defect-related reaction	Caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including the administration device, as provided by the manufacturer
Immunization error-related reaction	Caused by inappropriate vaccine handling, prescribing or administration
Immunization anxiety-related reaction[a]	Arising from anxiety about immunization
Coincidental event	Caused by something other than the vaccine product, immunization error or immunization anxiety

[a] The term *immunization stress-related response* has been proposed to convey the spectrum of reactions more accurately in this category, which are caused by the *process* of vaccination, not the vaccine *product* itself (Gold MS, et al. *Vaccine*. 2020;38:3015-3020).

Adapted from Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification. World Health Organization Web site. https://apps.who.int/iris/bitstream/handle/10665/259959/9789241513654-eng.pdf?sequence=1&isAllowed=y. Accessed July 10, 2023.

FIGURE 2.9 — Vaccine Safety Net in the United States



From 1996 to 2015, 57 vaccine products were licensed by the FDA (21 were influenza vaccines).[59] Only 25 products underwent safety-related label changes in the years following approval, the majority of which involved population restrictions (eg, immunocompromised patients, persons with pre-existing medical conditions, premature infants, and pregnant women), allergy (eg, changes in latex-containing packaging), or syncope. Only one vaccine—RRV-TV—was withdrawn for safety reasons (see *Chapter 7: Addressing Concerns About Vaccines—Intussusception*). This experience attests to the rigor of premarket vaccine review as well as the robustness of the post-marketing safety net, described below.

Vaccine Adverse Event Reporting System (VAERS)

VAERS is a postmarketing surveillance system established by the National Childhood Vaccine Injury Act of 1986 and coadministered by the FDA and CDC. Anyone can submit a report about any event related to vaccination, and reporting of certain events is mandated by

law (see *Chapter 3: Standards, Principles, and Regulations—National Vaccine Injury Compensation Program [VICP]*). Information from VAERS reports is entered into a database, and selected serious events and deaths are compiled and analyzed. Hundreds of thousands of events have been reported to VAERS since its inception in 1990[60]; the vast majority are mild, including fever, local reactions, crying, and irritability. From 2011 to 2014, 38% of VAERS reports were submitted by health care personnel, 30% by vaccine manufacturers, and 14% by patients and parents.[61]

A significant limitation of VAERS is that it only receives information regarding vaccinated persons in whom an adverse event has occurred. Because it does not receive information about the number of vaccine doses administered or the occurrence of adverse events in unvaccinated persons, causal relationships between vaccines and particular adverse events cannot be established. In addition, underreporting, poor data quality, incomplete reports, differences between public and private sector reporting rates, lack of consistent diagnostic criteria for disease, and simultaneous administration of multiple vaccines limit the inferences that can be derived from VAERS. Moreover, significant reporting biases exist (for example, increased reporting is seen immediately after licensure and when particular vaccines are "in the news"). VAERS is therefore a vital mechanism for hypothesis *generation*, but it is not useful for hypothesis *testing*.

Despite these limitations, VAERS is the only surveillance system that covers the entire US population, and it includes the largest number of case reports temporally associated with vaccination. It serves to generate the signal that warrants further investigation and can provide early warning of potential problems. A good example of the utility of VAERS data was in prompting investigation of the relationship between the rhesus rotavirus vaccine and intussusception (see *Chapter 7: Addressing Concerns About Vaccines—Intussusception*). Unfortunately, VAERS data have also been misunderstood by the media and misused by antivaccine activists, who have made the erroneous supposition that temporal association means causation.

Vaccine Safety Datalink (VSD)

The VSD is an active surveillance system created by the CDC in 1990 and operated by the CDC's Immunization Safety Office.[62] Information regarding vaccination, medical outcomes, birth history, and census is collected through large, linked, computerized databases from eight managed healthcare organizations across the country. Over 9 million people of all ages are studied through this process, amounting to 3% of the entire US population. Given these numbers, relatively rare adverse events can be detected. Since the VSD includes control data (eg, information about unvaccinated persons, as well as data on individuals in the weeks preceding vaccination), it is an excellent place to test hypotheses and determine if relationships between vaccines and adverse events are causal or coincidental.[63] The database is replete with information, including demographics, hospitalizations, outpatient and emergency room visits, and mortality; pharmacy, laboratory, and radiology data also can be collected to validate outcomes and vaccination history. *Rapid cycle analysis*, wherein events after vaccination are monitored continuously and compared to the expected number of events, is used to prompt further investigation.

Other Components of the Vaccine Safety Net

Other components of the U.S. vaccine safety monitoring system include:

- *Postlicensure Rapid Immunization Safety Monitoring* (*PRISM*) *system*—PRISM was created in 2009 to monitor the safety of the pandemic A(H1N1) vaccine program.[64] Now a part of the Sentinel System[65] funded by the FDA, PRISM uses data from national health insurance plans and local and state immunization information systems, making it the largest and most diverse vaccine safety surveillance system in the US.
- *Clinical Immunization Safety Assessment* (*CISA*) *Project*—CISA is a partnership between medical research centers and the CDC designed to systematically evaluate patients who experience AEFIs, was created in 2001. It offers consultation on individual clinical vaccine safety issues, develops assessment strategies for individuals who may be at increased risk for AEFIs, and conducts studies to identify risk factors and preventive strategies, especially in special populations.[66] CISA centers follow an algorithmic approach to assessing causality.[67]
- *Defense Medical Surveillance System* —This is a central repository of medical surveillance data for the US military operated by the Department of Defense (DOD). The health records of approximately 1 million men and women in uniform are available to study AEFIs.[68] The Veterans Administration has also been involved in surveys among veterans and Veterans Administration employees.
- *Brighton Collaboration*—Launched in 2000, Brighton is an international organization that aims to facilitate the development, evaluation, and dissemination of high-quality information about the safety of vaccines.[69] Participants are volunteers from patient care, public health, pharmaceutical, regulatory, scientific, and professional organizations. The primary objective is to develop standardized definitions of AEFIs to enhance comparability of data.[70] In addition, Brighton establishes guidelines for collection, analysis, and presentation of safety data and offers protocols for collection, analysis, and presentation of data in clinical studies[71] and surveillance systems.[72]
- *Special surveillance efforts*—The 2009 A(H1N1) influenza immunization campaign, during which tens of millions of

individuals were vaccinated in a short period of time, called for unprecedented safety surveillance efforts, especially in light of the association between the 1976 swine flu vaccine and Guillain-Barré syndrome (GBS) (see *Chapter 7: Addressing Concerns About Vaccines—Guillain-Barré Syndrome*). Existing systems were enhanced and new systems were deployed in this effort, including: VAERS reporting, facilitated by vaccination report cards and collaboration with the American Academy of Neurology; rapid-cycle analysis by the VSD; surveillance through the Vaccine Analytic Unit, a collaboration between the CDC, FDA, and DOD; GBS case finding through the Emerging Infections Program, a collaboration between the CDC and state health departments; the Real Time Immunization Monitoring System, a Web-based active surveillance system developed by Johns Hopkins University and sponsored by the CDC; surveillance through the Indian Health Service; near real time active surveillance of Medicare recipients; and PRISM, which linked health plan and Immunization Information System (IIS) data to look for unexpected risks.[73] Similar surveillance initiatives have been used to monitor the safety of COVID-19 vaccines.[74] Novel approaches have also been used, including *v-safe*, a confidential smartphone-based system that provides personalized health check-ins after vaccination and allows for real-time adverse event surveillance.[75]

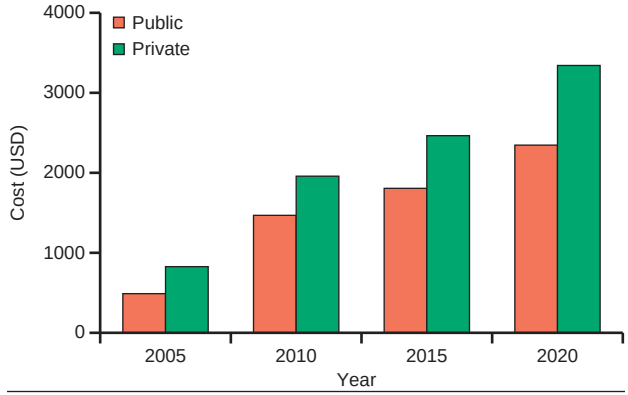
- *Ad-hoc committees and task forces*—Ad-hoc committees and task forces are constituted to address specific issues. The Task Force on Safer Childhood Vaccines, for example, issued a report in 1998 that emphasized the need to assess and address public concerns about the risks and benefits of vaccines, conduct research on the biological basis for vaccine reactions, foster partnership between stakeholders, enhance the ability to detect adverse events, and improve coordination of effort between agencies.[76] The Immunization Safety Review Committee (ISRC), convened in 2001 by the Institute of Medicine (IOM; now known as the National Academy of Medicine), reviewed nine different vaccine safety hypotheses, finding little evidence to support most of them.[77] In August 2011, the IOM released a Consensus Report that looked at eight specific vaccines and over 150 vaccine-adverse event pairs.[78] For some events—like deltoid bursitis from injectable vaccines and disseminated disease from VAR or MMR in immunodeficient persons—the IOM found convincing evidence for a causal relationship. For others—like transient arthralgia in women from MMR—it suggested that the evidence favored acceptance of a causal relationship. For still others—in particular, autism and type 1 diabetes from MMR—the IOM felt that the evidence favored rejection of a causal relationship. In January 2013, the IOM released the most comprehensive review ever conducted of the childhood schedule as a whole, finding that "the lack of conclusive evidence linking adverse events to multiple immunizations or other schedule exposures suggests that the recommended schedule is safe."[79]

Financing

Figure 2.10 illustrates the increasing cost of vaccines—the cumulative effect of more vaccines, more doses, and increased cost per dose. Layered on top of the purchase price for the vaccines themselves are the costs associated with administration, from personnel time, storage, and equipment to wastage and insurance.

The system for financing immunizations in the US rests on a unique partnership between the public and private sectors. Whereas most of the vaccinating is done in private settings, the purchase cost of routine childhood vaccines is split evenly between the public and private sectors.[80] Historically, many states had laws requiring insurers to cover childhood immunizations, at least to some degree, but insurance plans differed in terms of which vaccines they covered for both children and adults and to what extent they reimbursed for vaccine administration. The Patient Protection and Affordable Care Act (ACA) [PL 111-148] of 2010 contained many provisions

FIGURE 2.10 — Cost of Vaccines in the Routine Childhood Schedule



The figure shows the total cost of all recommended vaccines for one female child as specified by the routine schedule in the given year. Assumptions included the birth dose of HepB and use of DTaP-HepB-IPV, RV5, a 4-dose Hib series, monovalent MMR and VAR, and MenB in year 2020. The least expensive products were used in the calculations.

Adapted from VFC CDC Vaccine Price List Archives. CDC Web site. https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/archive.html. Accessed July 10, 2023.

aimed at improving immunization delivery. For one, it required new employer and individual health plans to cover all ACIP recommended immunizations, without deductible, copay, or coinsurance, when delivered by in-network providers. This includes vaccines recommended for adults.

Public sector funds for vaccination of children include the following sources:

- *The Vaccines for Children Program* (*VFC*)—Created in 1993, VFC is a federal program that guarantees immunization services for children ≤18 years of age who are 1) eligible for Medicaid, the public health insurance program for low-income people; 2) uninsured; 3) underinsured and receiving immunizations at federally-qualified health centers or rural health clinics; or 4) American Indian or Alaska Native. "Underinsured" means that the child's insurance does not cover vaccines, or does not cover certain vaccines, or has a cap on vaccine coverage and the cap has been reached (most plans today fall under the ACA mandate that immunizations be covered). Through this program, vaccines are purchased by the CDC at reduced rates and provided to participating private practices and public clinics free of charge. Providers are required to screen for eligibility and to offer vaccine proactively to eligible children, and they are prohibited from charging the patient for the vaccine itself. Whereas they *can* charge patients administration fees, within limits established by the Centers for Medicare and Medicaid Services, they cannot *deny* vaccination if the patient cannot pay the fee (claims for these fees can still be submitted to Medicaid for those children who are enrolled). There are no regulations regarding charges for the visit itself or other services. Any private provider can participate in the program—this has resulted in a shift toward private sector delivery of vaccines, establishing an anchor point for the medical home for many children. Moreover, VFC has reduced disparities across racial, ethnic, and socioeconomic lines.[81]

  VFC is an *entitlement program*, which means that Congress is obligated to appropriate the funds necessary to purchase the covered vaccines, no matter how much they cost. Covered vaccines are determined by ACIP resolutions; this makes ACIP one of the few civilian bodies that can mandate federal spending. In fact, one intent of VFC was for the ACIP to make recommendations based only on issues of public health and medicine, not cost.[82] That being said, economic analyses do play a part in ACIP decisions in the context of its responsibility to conscientiously steward public funds.[83] VFC resolutions pertain to all ACIP recommendations, including those based on SCDM. Even when a VFC resolution is passed, significant delays in securing a federal contract may occur. During such delays, state Medicaid programs must cover ACIP-recommended vaccines. Common questions about VFC coverage are addressed in **Table 2.11**.

- *Section 317 Funds*—States, territories, protectorates, and several designated cities may purchase vaccines through block grants under Section 317 of the Public Health Service Act. Most of these funds are used for childhood immunization, but adolescent and adult programs may be supported as well. Section 317 funds also may be used to support infrastructure and programmatic activities such as quality assurance, IISs, disease surveillance, and school- or community-based delivery services. The main intent of the 317 program is to provide vaccines to people who fall outside of VFC. This program—in contrast to VFC—represents *discretionary federal spending*, and the amount allocated by Congress, therefore, varies from year to year.[84] Section 317 funds cannot be used to cover routine vaccinations in persons who have public or private insurance that covers vaccination.[85]
- *State and Local Funds*—States may appropriate funds to support both childhood and adult immunizations, but in general the contribution of this source to the whole funding picture is small. The Children's Health Insurance Program (CHIP), enacted in 1997, is a federal block grant program targeted to low-income children who are not eligible for Medicaid and are otherwise uninsured. States can use CHIP funds to expand Medicaid or to create separate, freestanding children's insurance programs.
- *Universal Purchase States*—A minority of states have some type of universal purchase policy, whereby federal, state, and local monies are used to purchase childhood vaccines at the CDC-negotiated price and distribute them to providers for administration to children free of charge, regardless of insurance status.

There is no VFC-equivalent for adults. Fortunately, most private insurance plans cover adult vaccination.[86] Medicare, a federal insurance program for adults ≥65 years of age, covers influenza vaccine, PCV, PPSV23, and HepB (for persons of any age with end-stage renal disease or other high-risk conditions) under Part B (medical insurance), with no cost sharing. Part B may also cover vaccines that are indicated because of injury or exposure (eg, Tdap for wound prophylaxis or RAB after an animal bite). As of January 1, 2023, Medicare Part D (outpatient prescription drug coverage) covers, without cost sharing, all vaccines not covered under Part B that are recommended by the ACIP for prevention of disease in adults (patients may have to pay administration fees up front, but these are reimbursable under the plan).[87] As of October 1, 2023, state Medicaid programs must cover all ACIP-recommended vaccines (including those that are not routine) for adults with no cost sharing.[88]

TABLE 2.11 — Common Questions About VFC

Question	Answer
Are providers required to post a sign stating that eligible children will not be denied vaccine?	No
Can a provider refuse to administer VFC vaccine to an eligible child?	Private VFC providers, unless otherwise required by state law, do not have to vaccinate walk-ins who are not established patients. For established patients, vaccination cannot be denied because of inability to pay the administration fee.
How does a medical or health savings account affect eligibility?	Patients with such accounts must also be insured. If their insurance does not cover vaccines, they can receive VFC vaccine at Federally-Qualified Health Centers or Rural Health Clinics.
Is an uninsured child eligible if his parents plan to insure him in the near future?	Yes. Eligibility is determined on the day of vaccination. Eligibility screening must take place at every vaccination visit.
Are all children from birth through 18 y who are enrolled in Medicaid automatically eligible?	Yes
What about children who have Medicaid as a secondary insurance?	Yes, they are also eligible.
If a child starts a vaccine series at 18 y, can the series be completed with VFC vaccine if he turns 19?	No
Are American Indian/Alaska Native children still eligible for VFC vaccine even if they have insurance?	Yes
If a child's insurance covers a percentage of the cost of vaccination, can he receive VFC vaccine?	No
If a child's insurance covers vaccines but a claim will not be paid because the deductible has not been met, is he eligible for VFC vaccine?	No
Can all children at a school-based clinic receive VFC vaccine?	No. They must still be screened for eligibility (this can be incorporated into the consent process).
If a child has exceeded his insurance coverage for provider visits in a given year, is he considered underinsured for VFC purposes?	Yes

Continued

VFC, Vaccines for Children Program

Adapted from About VFC: CDC Web site. http://www.cdc.gov/vaccines/programs/vfc/about/index.html#f1. Accessed July 10, 2023.

Throughout the pandemic and as of July 2023, COVID-19 vaccines were administered to eligible persons free of charge by providers enrolled in the CDC COVID-19 Vaccination Program.[89] Vaccines were purchased by the federal government and supplied to enrolled providers, who could not charge recipients for the vaccine or for administration fees, copays, or coinsurance. Providers also could not deny vaccination to anyone who is uninsured, underinsured, or out of network. In addition, providers could not charge for an office visit if the only service provided is a COVID-19 vaccination. If a vaccine recipient had health coverage, providers could seek reimbursement for administration fees, but they could not bill the recipient for any balance that was not covered by the recipient's plan. Commercialization of COVID-19 vaccines—in this context, the transition to established pathways of procurement, distribution, and payment—was expected to occur in the fall of 2023.[90]

Supply

The early 2000s saw unprecedented shortages in the supply of many routinely used vaccines.[91] The impact of these shortages included frequent and sometimes confusing changes in the recommended immunization schedule, temporary revision of state school entry requirements, parental frustration, and a burden placed on providers to track interrupted schedules and recall patients when vaccine supplies returned to sufficiency.

Shortages result from a convergence of factors, including the following:

- *Few manufacturers*—Vaccines are low-profit products compared with other pharmaceuticals. The costs of development are high, the timeline from preclinical testing to market may be long, and the risks are substantial—a licensed vaccine may or may not be recommended for use by large numbers of people. Moreover, the risk of failure persists for some time after marketing, since rare adverse events may not show up until millions of doses have been distributed. Four companies—GSK, Merck, Pfizer, and Sanofi—control 90% of the global vaccine market.[92] With so few manufacturers, disruptions at one company can have a major effect on supply; that effect is magnified for single-source products.
- *Business decisions*—Companies may choose to pull products from the market rather than invest in costly changes prompted by new GMPs or recommendations. An example of the latter was the 1999 recommendation to remove thimerosal from childhood vaccines (see *Chapter 7: Addressing Concerns About Vaccines—Autism*), which led some companies to pull out rather than retool their manufacturing and packaging processes and demonstrate equivalency of the reformulated products in clinical trials.
- *Production problems*—Production problems may have a biologic basis. For example, the influenza A(H3N2) strain used for the 2000-2001 vaccine grew slowly in culture, delaying vaccine production. Similarly, a low yield of vaccine strain VZV in culture led to shortages of MMRV. Production problems can also result from routine physical plant maintenance activities.
- *Underestimated demand*—Greater-than-expected demand for PCV7, MenACWY-D and RZV contributed to shortages after each of those vaccines was licensed.

Lists of vaccines that are currently in short supply can be found on the CDC (https://www.cdc.gov/vaccines/hcp/clinical-resources/shortages.html) and FDA (https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages) Web sites (accessed July 10, 2023). When deferral of doses is recommended during shortages, providers should keep lists of patients who will need to be recalled once supplies improve.

The CDC maintains stockpiles of vaccines that can be used in case of shortages. These might be more accurately termed *storage and rotation contracts* or *dynamic strategic inventories*—some portion of vaccine production lots enters the stockpile, and older vaccine with respectable shelf-life left is released into the market. The goal is to stockpile 6 months' worth of each routine childhood vaccine (except for influenza vaccine, which changes in composition from year to year).

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Standards, Principles, and Regulations

Healthy People

The Healthy People initiative is an attempt to systematically identify the most significant preventable public health threats and focus public and private efforts to address those threats. Reports have been published every 10 years since 1979; each one—the work of many federal and state agencies, scientists, professional organizations, and members of the public—sets out a comprehensive set of health objectives for the subsequent decade. Each of the objectives outlined in the reports has a reliable data source, a baseline measure, and a specific target for improvement.

Vaccination-related goals of Healthy People 2030, which was published in 2020, include increasing uptake of the HPV series in adolescents; increasing yearly influenza vaccinations; increasing Tdap administration during pregnancy; reducing the proportion of children who are unimmunized; and increasing the proportion of people with vaccination records in an immunization information system (IIS).[1]

Standards for Immunization Practices

Standards for both pediatric and adult immunization practices have been developed, representing the most desirable practices that health care professionals should strive to achieve.

Standards for Child and Adolescent Immunization Practices

In 1992, a working group convened by the National Vaccine Advisory Committee (NVAC) developed a set of standards for pediatric immunization practices, largely in response to the measles resurgence in the late 1980s. These standards were revised and updated in 2003 and have been endorsed by most professional organizations that deal with pediatric immunization.[2]

Key elements of each standard are listed below.

- *Standard 1—Vaccination services are readily available.* Routinely recommended vaccines should always be part of primary care. Vaccination status should be assessed at all

points of contact with the health care system, including subspecialty practices, schools, and specialty clinics. If vaccines cannot be offered at these sites, patients should be referred elsewhere. Primary care providers should be notified about vaccines given outside the medical home.

- *Standard 2—Vaccinations are coordinated with other health care services and provided in a medical home when possible*. Vaccinations should be coordinated with routine well-child visits or other visits. Patients who receive vaccines outside the medical home should be encouraged to receive subsequent vaccines from their primary care provider. Those who do not have a primary care provider should receive assistance in finding one.
- *Standard 3—Barriers to vaccination are identified and minimized*. Vaccine visits should be scheduled promptly and, if necessary, independently of visits for other well-child services. Long waiting periods in the office should be avoided and culturally and age-appropriate educational materials should be available. A physical examination is not required for immunization—screening and observation are sufficient. Providers should ask parents and patients how they could make vaccinations more accessible.
- *Standard 4—Patient costs are minimized.* Money should not be a barrier to vaccination. Free vaccines are available through public programs like the Vaccines for Children Program, Public Health Service Section 317 grants to states, and state and local programs. Providers utilizing these resources should make it clear that even though the patient may be charged for administration of the vaccines, they will not be denied vaccination because of inability to pay. Health and insurance plans should cover all routinely recommended vaccines and reimbursement to providers should be enough to cover all expenses associated with delivering vaccines in practice.
- *Standard 5—Health care professionals review the vaccination and health status of patients at every encounter to determine which vaccines are indicated.* Any and all health care visits are an opportunity to review vaccination status and minimize missed opportunities. This might include, for example, emergency room visits, hospitalizations, and appointments with specialists. Undervaccination should be documented in the patient's chart. Providers who do not give vaccines should refer patients to a primary care provider who does.
- *Standard 6—Health care professionals assess for and follow only medically accepted contraindications.* There are very few true contraindications to vaccination. Decisions to withhold vaccination should be supported by published guidelines and should be documented in the medical record.
- *Standard 7—Parents/guardians and patients are educated about the benefits and risks of vaccination in a culturally appropriate manner and in easy-to-understand language.* Sufficient time should be allowed to discuss the benefits of vaccines, the diseases they prevent, and the known risks. The schedule should be reviewed and the importance of bringing the hand-held vaccination record should be emphasized. Parents should be told how to report adverse events. Vaccine Information Statements (VISs) should be provided and supplemented by oral or visual explanations when appropriate, and the parent's questions and concerns should be addressed. Reporting of adverse events should be encouraged.
- *Standard 8—Health care professionals follow appropriate procedures for vaccine storage and handling.* This is critical to maintaining potency and effectiveness.
- *Standard 9—Up-to-date, written vaccination protocols are accessible at all locations where vaccines are administered.* Protocols should detail vaccine storage and handling; the recommended schedule; contraindications; administration technique; treatment and reporting of adverse events; risk-benefit communication; and record maintenance and accessibility.
- *Standard 10—People who administer vaccines and staff who manage or support vaccine administration are knowledgeable and receive ongoing education.* Vaccine recommendations change frequently, and all personnel involved in the process of vaccine delivery should remain abreast of these changes. Many resources are available for this purpose, including free e-mail listservs and distance-based training opportunities through the Centers for Disease Control and Prevention (CDC).
- *Standard 11—Health care professionals simultaneously administer as many indicated vaccine doses as possible.* There are very few routine vaccines that cannot be administered at the same time at separate sites. When vaccines are not given simultaneously, arrangements should be made for the patient's earliest return to receive the needed vaccines. Although not specifically mentioned in the standard, combination vaccines allow delivery of multiple antigens with fewer shots and are generally preferred to separately administered components.
- *Standard 12—Vaccination records for patients are accurate, complete, and easily accessible.* This standard goes beyond the record keeping mandated by law. It calls for a permanent record that the parents carry with them, and verification of vaccines received from other providers. All vaccinations should be reported to state or local IISs. Vaccine refusal also should be documented.
- *Standard 13—Health care professionals report adverse events after vaccination promptly and accurately to the Vaccine Adverse Event Reporting System (VAERS) and are aware of a separate program, the National Vaccine Injury Compensation Program (VICP).* These programs are described below. The law requires reporting of cer-

tain events, and reporting of all significant events is encouraged, even if causality is not established. Health care professionals should be aware that parents and patients could report adverse events to VAERS on their own.

- *Standard 14—All personnel who have contact with patients are appropriately vaccinated.* Offices and clinics should have policies to review and maintain the vaccination status of their staff.
- *Standard 15—Systems are used to remind parents/guardians, patients, and health care professionals when vaccinations are due and to recall those who are overdue.* Computerized or manual tracking, recall, and reminder systems should be in place.
- *Standard 16—Office- or clinic-based patient record reviews and vaccination coverage assessments are performed annually.* A simple random survey of patient records can yield information about coverage rates, missed opportunities, and record quality; in general, physicians will find that they overestimate the proportion of their patients who are appropriately immunized. Systematic assessments should be conducted. Feedback and incentives are important elements of quality improvement.
- *Standard 17—Health care professionals practice community-based approaches.* Providers should be responsive to the needs of their patients, but it should be recognized that high coverage rates protect the entire community. Partnering with other service providers, such as the US Department of Agriculture's Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), advocacy groups, schools, and service organizations, should be encouraged.

Before 2005, vaccinations during adolescence were for catch-up, except for the Td booster. Since then, new vaccines (MenACWY, MenB, Tdap, HPV, and seasonal influenza) have been recommended for adolescents. From 2007 through 2012, to highlight the *adolescent platform* (see *Chapter 8: Routine Schedules*), the routine schedule was separated into one chart for young children and one for older children and adolescents; the two have since been recombined. While there are no adolescent standards per se, it is worth emphasizing that optimally immunizing adolescents represents a special set of challenges, not the least of which is the fact that adolescents make infrequent visits for preventive health services.[3,4] In addition, young adolescents are very different from older ones in terms of their cognitive style and the issues that are important to them, so the approach to immunization must take these differences into account. The question of whether adolescents should be allowed to independently consent to vaccination is unresolved[5] (it is noteworthy that HPV series initiation rates are higher in states that allow this[6]).

Standards for Adult Immunization Practices

The National Coalition for Adult Immunization first offered standards for adult immunization practices in 1990. Revised standards were issued by NVAC in 2003[7] and in 2014 (**Table 3.1**). The standards emphasize, among other things, the role of *all* providers (not just primary care physicians) in assessing immunization status and recommending needed vaccines; the importance of community vaccinators (eg, pharmacists) in achieving higher adult coverage rates; the use of electronic health records and incentives to enter information into IISs; and the fact that health care reform is moving in the direction of payment for better outcomes of care (including disease prevention through vaccination).

Annual mortality from vaccine-preventable diseases among adults reaches into the tens of thousands and hospitalizations into the hundreds of thousands. Moreover, vaccine-preventable diseases among adults cost billions of dollars each year, and adult vaccination is cost-effective.[8,9] Historically, adult immunization rates have lagged behind childhood rates, and a particular problem has been completion of multidose series.[10] In 2007, the Infectious Diseases Society of America (IDSA) published a set of principles—billed as a "call to action"—designed to call attention to all of this.[11] In 2008, the IDSA and the American College of Physicians released a joint statement, endorsed by many other professional organizations, encouraging subspecialty physicians to take a more active role in keeping adults up-to-date.[12] Barriers to implementing the Adult Standards include perceived limitations in scope of practice; inadequate reimbursement; staffing issues; lack of equipment; and difficulty uploading data into IISs.[13,14]

In 2016, the National Adult Immunization Plan[15] was adopted to address the challenge of improving adult immunization rates. The goals are to 1) strengthen the adult immunization infrastructure; 2) improve access to adult vaccines; 3) increase community demand for adult immunizations; and 4) foster innovation in adult vaccine development and vaccination-related technologies.

National Vaccine Injury Compensation Program (VICP)

In response to public concern about vaccine safety and industry concern about litigation, which threatened vaccine supply, Congress passed the National Childhood Vaccine Injury Act of 1986 (NCVIA). The NCVIA established the VICP, a no-fault alternative to the tort system for resolving claims that result from adverse reactions to mandated childhood vaccines.[16] It is administered jointly by the Health Resources and Services Administration (HRSA), the US Court of Federal Claims (the Court), and the Department of Justice (DOJ), and is funded by an excise tax levied on every dose of vaccine that is purchased.

TABLE 3.1 — Standards for Adult Immunization Practices

All Providers

- Incorporate immunization needs assessment into every encounter
- Strongly recommend needed vaccines and administer or refer for administration
- Remain up to date on recommendations and educate patients about them
- Implement systems to incorporate vaccine assessment into routine care
- Understand how to access IISs

Non-immunizing Providers

- Routinely assess immunization status, recommend needed vaccines, and refer for administration
- Establish referral relationships with immunizing providers
- Confirm that patients receive recommended vaccines

Immunizing Providers

- Ensure professional competency in immunization
- Assess immunization status during every patient encounter and strongly recommend needed vaccines
- Ensure that vaccinations are documented in the medical record and appropriate IIS

Professional Organizations, Associations, and Health Care Systems

- Provide immunization education and training for members (including trainees)
- Provide resources and assistance to implement systems to accomplish needs assessment, vaccination, or referral
- Encourage members to be up to date on their own immunizations
- Assist members in staying up to date on immunization information and recommendations
- Partner with other immunization stakeholders to educate the public
- Seek out collaboration with other immunization stakeholders
- Collect and share best practices for immunization
- Advocate policies that support adult immunization standards
- Payers and the like should assure that their networks provide timely access and have adequate providers

Continued

TABLE 3.1 — *Continued*

Public Health Departments

- Determine community needs, vaccination capacity, and barriers
- Provide access to recommended vaccines for insured and uninsured adults and work toward becoming in-network providers
- Partner with other stakeholders and support measures that improve awareness, increase vaccination rates, and reduce barriers
- Ensure professional competencies in immunization
- Collect, analyze, and disseminate immunization data
- Provide outreach and education to providers and the public
- Work to decrease disparities in coverage and access
- Increase IIS access and use by providers
- Develop capacity to bill for immunization of injured people
- Ensure preparedness for outbreaks of vaccine-preventable diseases
- Promote adherence to applicable laws, regulations, and standards among stakeholders

IIS, immunization information system

Adapted from Poland GA, et al. *Am J Prev Med.* 2003;25:144-150.

Anyone who seeks remedy for injury by a covered vaccine must first go through the VICP. To receive compensation, petitioners must show that any one of the following occurred: 1) they incurred an injury found in the Vaccine Injury Table (VIT)[17]; 2) the vaccine caused the injury; or 3) the vaccine significantly aggravated a pre-existing condition. The VIT, which lists specific injuries or conditions and the timeframes in which they must have occurred, serves as a basis for presumption of causation. Some conditions listed on the VIT, such as vaccine-strain measles disease in an immunodeficient recipient, are straightforward. Others, like encephalopathy after pertussis vaccine, have remained on the Table despite the evidence against causation (see *Chapter 7: Addressing Concerns About Vaccines—Encephalopathy*). Shoulder injury and syncope were added in 2017, but the Department of Health and Human Services (HHS) ruled in 2021 that these be removed because they are related to the *vaccination process* rather than the *vaccine itself* (these events were still listed on the VIT as of July 2023).[18] Individuals can file claims for injuries not listed in the VIT, but there must be *proof of causation*. In recent years, the standard for proof seems to have shifted from a *preponderance of the evidence* to *biologic plausibility*.[19]

For a claim to be filed, the injury must have lasted for at least 6 months following vaccination, resulted in hospitalization and

surgery, or resulted in death. To be compensated, the petitioners must prove that a) they received a vaccine listed on the VIT, and b) the first signs of injury occurred within the specified time frame, or the vaccine caused the injury or caused an existing illness to get worse (it must also be determined that the injury or death did not have another cause). When a claim is filed, HHS reviews the medical aspects and makes recommendations to a DOJ lawyer representing the Secretary of HHS, who reviews the legal aspects of the case. The HHS and DOJ reviews are then forwarded to the Court, where a Special Master (a lawyer appointed by the Court) decides if the claim will be paid and how much money will be offered. If the medical case is straightforward—for example, an individual develops chronic arthritis (not otherwise explained) within 7 to 42 days after receiving a rubella-containing vaccine—HHS may concede the case, acknowledging that the injury fits the VIT definition (this is often referred to as a *Table injury*). In this instance, the Special Masters will usually pay the claim. If it is not a Table injury and HHS contests the claim, hearings may be held. The decision of the Special Masters can be appealed by either party (HHS or the petitioner) to a judge of the Court, then to the US Court of Appeals for the Federal Circuit, and ultimately to the US Supreme Court.

Vaccines recommended by the Advisory Committee on Immunization Practices (ACIP) for routine use in children or pregnant women are automatically covered under the VICP (note that when a recommended vaccine is given to a pregnant woman, both the woman and the baby in utero are considered to have been vaccinated). Advice regarding the VICP and recommended changes to the VIT comes from the Advisory Commission on Childhood Vaccines.[20] Covered vaccines as of July 2023 are listed in *Footnote f* in **Table 3.2.**

Important points about the VICP:

- Claims can be filed by individuals, parents, legal guardians, trustees, legal representatives of the estate of deceased persons, non-US citizens, and, under certain conditions, individuals vaccinated outside of the US. Claims may be filed on behalf of live-born children who were in-utero at the time a woman received a covered vaccine.
- Adults are covered under the program if they receive one of the covered vaccines.
- A settlement under the VICP is not an admission by the government that the vaccine caused the injury; rather, it should be seen as an agreement between the government and the petitioner to resolve the issue quickly and efficiently.
- Petitioners are free to reject the decision of the Court and pursue civil litigation.
- Compensation is available for past and future non-reimbursable medical, custodial, and rehabilitation costs and lost earnings. There are no limits on compensation for attorney's fees; petitioners representing themselves can only recover legal costs, not fees. Compensation for pain and suffering, and compensation to the estate in the case of death, is capped at $250,000.

Over the first 30 years of the program, >21,000 petitions were received; >18,300 were adjudicated with approximately 6900 being deemed compensable.[21] A total of $4.3 billion was paid out. It was estimated that compensation for vaccine injury occurred approximately 1 out of every 1 million doses.

Many people had not heard of the vaccine court or the VICP until 2009 and 2010, when landmark decisions regarding vaccines and autism were handed down (see *Chapter 7: Addressing Concerns About Vaccines—Autism*). In addition to this, the Supreme Court found in 2011 (Bruesewitz vs Wyeth[22]) that the NCVIA preempts all vaccine design defect claims where plaintiffs seek compensation for injury or death caused by a vaccine's adverse effects. This ruling acknowledges Congress' intent to set vaccines aside from other consumer goods, for which manufacturers can be held liable if harms result from design defects, regardless of how much care was exercised in their production and sale.[23] Vaccines may have unavoidable side effects that relate to how they function—for example, they may cause fever, which results from the immune response that ultimately protects the person from disease. Fever, then, in a sense, is not a "design defect," and if it results in damage, the vaccine manufacturer cannot be held liable—as long as the vaccine was properly manufactured and was accompanied by proper directions and warnings.

Vaccine Adverse Event Reporting System (VAERS)

The NCVIA also established VAERS, a passive surveillance program in operation since 1990 that collects and analyzes post-marketing information about adverse events after vaccination.[24] Any event following vaccination can be reported, with no restriction on the interval between vaccination and the onset of illness and no requirement for medical care having been rendered (reports can be submitted at https://vaers.hhs.gov/esub/index.jsp; accessed July 10, 2023). Anyone can submit a report, including health care professionals, pharmaceutical companies, lawyers, parents, and patients. However, health care providers are *required* to report events that are listed by the manufacturer as a contraindication to subsequent doses, as well as events listed in the Reportable Events Table (**Table 3.3**). VAERS data are available to the public for analysis, although caveats regarding interpretation are offered (see *Chapter 2: Vaccine Infrastructure in the United States—Vaccine Adverse Event Reporting System).*

TABLE 3.2 — Federal Requirements Regarding Routine Vaccination[a]

Requirement	Details
Give a VIS	Give a current copy of the relevant VIS before *each* dose of *each* vaccine[b]
	Children: give to the parent or legal representative[c]
	Adults: give to the patient or legal representative[d]
	Use the VIS published by the CDC[e]
	Mandatory for vaccines covered under the VICP[f]
	Mandatory for any vaccines purchased under a federal (CDC) contract
	Encouraged for all other vaccines
	Provide VIS for each component of a combination vaccine if there is no VIS for the combination
	Use translations if necessary[g]
Document in the permanent medical record or office log	Name of the VIS, edition date, and date it was given to the recipient[h]
	Name, office address and title of the individual who administered the vaccine
	Date of administration
	Manufacturer
	Lot number
Report to VAERS	Any event listed in the Reportable Events Table (**Table 3.3**) that occurs within the specified time period after vaccination

CDC, Centers for Disease Control and Prevention; VAERS, Vaccine Adverse Event Reporting System; VICP, National Vaccine Injury Compensation Program; VFC, Vaccines for Children Program; VIS, Vaccine Information Statement

[a] For requirements related to COVID-19 vaccines, see CDC COVID-19 Vaccination Program Provider Requirements and Support. CDC Web site. https://www.cdc.gov/vaccines/covid-19/vaccination-provider-support.html. Accessed July 11, 2023.

[b] Initially, federal law was interpreted as requiring that a physical, take-home copy of the VIS be given. While this is still commonly done, other options are considered acceptable, including: providing a permanent, laminated copy, which may be read in the office; allowing patients to view the VIS on a computer monitor or video display; and downloading the VIS to the patient's smart device to be read at his or her convenience. VISs may be read before the immunization visit, but patients must still be offered a take-home copy (which can be electronic) at the immunization visit (they may choose not to take it home with them). The VIS should be supplemented as needed with oral discussions, videotapes,

Continued

TABLE 3.2 — *Continued*

other printed material, and whatever else is needed for the parent or patient to gain understanding. The information on the VIS must still be conveyed to the vaccinee even if he or she is blind, deaf, or cannot read.

[c] If immunizations are to be given when the parent is not present (eg, during a school-based program) the following options can be exercised:

Consent prior to administration of each dose of a series. The VIS is mailed to the family or sent home with the student prior to each dose. A consent form is signed and returned before vaccination, and the form is placed in the medical record.

Single signature for series. Some states permit the parents to sign a single consent form for the entire vaccine series. They first receive a copy of the VIS and sign a statement acknowledging receipt of the VIS and authorizing the complete series. A VIS is still sent home prior to each dose in the series.

[d] For incompetent adults living in long-term care facilities, all relevant VISs may be provided at the time of admission or at the time of consent if later than admission.

[e] Available from Vaccine Information Statements. CDC Web site. http://www.cdc.gov/vaccines/hcp/vis/current-vis.html. Accessed July 11, 2023. Providers may not alter a VIS or make their own version of a VIS, but they can add the practice's name, address, and phone number. A multiple-vaccines-VIS is available that covers all the vaccines in the first 6 mo of life. Providers do not need to withhold a vaccine if a VIS for it does not yet exist. In this situation, the package insert, or a homemade information sheet can be used until the official VIS is available (at that point, the VIS should be used). When a new VIS is released, CDC provides guidance as to whether providers may use up their stock of the old VIS (it depends how much the information in the VIS has changed).

[f] As of July 2023, the following vaccines were included: DT, DTaP, DTP, HepA, HepB, Hib, HPV9, seasonal influenza (any form), IPV, MenB-FHbp, MenB-4C, MenACWY, MMR, MMRV, OPV, PCV, RV1, RV5, Td, Tdap, TT, VAR, and any component or combination of these. Nirsevimab is not covered under the VICP, but an Immunization Information Statement, which is similar to the VIS, is available and must be given to parents by VFC providers.

[g] VIS translations are considered de facto equivalents of the English versions and are available from the Immunize.org Web site (Vaccine information statements. http://www.immunize.org/vis. Accessed July 11, 2023).

[h] The name of the VIS and the edition date are contained on 2-dimensional bar codes at the bottom of the last page; scanning this information into the record is an option. The patient's signature is not required, and the VIS should not be construed as informed consent, which may be required in certain states.

Adapted from Instructions for using VISs. CDC Web site. http://www.cdc.gov/vaccines/hcp/vis/about/required-use-instructions.html. Accessed July 11, 2023; Document the Vaccination(s). CDC Web site. https://www.cdc.gov/vaccines/hcp/admin/document-vaccines.html. Accessed July 11, 2023.

TABLE 3.3 — Reportable Events Table (Effective March 21, 2017)

Vaccine[a]	Event[b]	Interval From Vaccination To When Event Occurs
Note: For all vaccines, events listed in the package insert as contraindications to additional doses are considered reportable events, even if they are not listed here. Reporting of any clinically significant or unexpected event for any vaccine is encouraged. Manufacturers are required to report all adverse events made known to them for any vaccine. Any acute complications or sequelae of the listed events, including death, are also reportable, with no applicable interval from the date of vaccination.		
Tetanus	Anaphylaxis or anaphylactic shock	7 d
	Brachial neuritis	28 d
	Shoulder injury related to vaccine administration	7 d
	Vasovagal syncope	7 d
Pertussis	Anaphylaxis or anaphylactic shock	7 d
	Encephalopathy or encephalitis	7 d
	Shoulder injury related to vaccine administration	7 d
	Vasovagal syncope	7 d
MMR	Anaphylaxis or anaphylactic shock	7 d
	Encephalopathy or encephalitis	15 d
	Shoulder injury related to vaccine administration	7 d
	Vasovagal syncope	7 d
Rubella	Chronic arthritis	42 d
Measles	Thrombocytopenic purpura	7-30 d
	Measles virus infection in an immunodeficient recipient, vaccine strain identified	Unlimited
	Measles virus infection in an immunodeficient recipient, strain determination not done or laboratory testing inconclusive	12 mo

Continued

TABLE 3.3 — *Continued*

Vaccine[a]	Event[b]	Interval From Vaccination To When Event Occurs
OPV[c]	Paralytic polio or vaccine-strain poliovirus infection	Immunocompetent: 30 d
		Immunocompromised: 6 mo
		Community case: unlimited
IPV	Anaphylaxis or anaphylactic shock	7 d
	Shoulder injury related to vaccine administration	7 d
	Vasovagal syncope	7 d
HepB	Anaphylaxis or anaphylactic shock	7 d
	Shoulder injury related to vaccine administration	7 d
	Vasovagal syncope	7 d
Hib	Shoulder injury related to vaccine administration	7 d
	Vasovagal syncope	7 d
VAR	Disseminated varicella, vaccine strain identified	Unlimited
	Disseminated varicella, strain determination not done or laboratory testing inconclusive	42 d
	Varicella vaccine strain reactivation	Unlimited
	Shoulder injury related to vaccine administration	7 d
	Vasovagal syncope	7 d
RV	Intussusception	21 d
PCV	Shoulder injury related to vaccine administration	7 d
	Vasovagal syncope	7 d

Continued

TABLE 3.3 — *Continued*

Vaccine[a]	Event[b]	Interval From Vaccination To When Event Occurs
HepA	Shoulder injury related to vaccine administration	7 d
	Vasovagal syncope	7 d
IIV, LAIV	Guillain-Barré syndrome	42 d
	Shoulder injury related to vaccine administration	7 d
	Vasovagal syncope	7 d
MenACWY, MenB, MPSV4[c]	Shoulder injury related to vaccine administration	7 d
	Vasovagal syncope	7 d
HPV	Shoulder injury related to vaccine administration	7 d
	Vasovagal syncope	7 d
Any new vaccine routinely recommended for children	Shoulder injury related to vaccine administration	7 d
	Vasovagal syncope	7 d

[a] Listed vaccines are also covered when they are part of combinations.
[b] See reference below for event definitions.
[c] No longer available in the US.

Adapted from VAERS Table of Reportable Events Following Vaccination. Vaccine Adverse Event Reporting System Web site. https://vaers.hhs.gov/docs/VAERS_Table_of_Reportable_Events_Following_Vaccination.pdf. Accessed July 11, 2023.

Vaccine Information Statements (VISs)

The NCVIA mandated that providers give vaccine recipients a VIS—a concise description of the risks and benefits of a given vaccine, written for lay people, and published by the CDC—for each vaccine received. Most parents who read VISs feel they contain useful information.[25] **Table 3.2** summarizes the use of VISs and lists other obligations that are binding on vaccine providers. Keep in mind that there may be state laws that supplement national requirements.

Public Readiness and Emergency Preparedness (PREP) Act

Just as the NCVIA protects manufacturers of routinely recommended vaccines, the PREP Act, enacted in 2005, provides legal immunity to manufacturers of pandemic vaccines.[26] It also protects those who distribute and administer pandemic vaccines and other *covered countermeasures* (the only exception is willful misconduct). The PREP Act is invoked when the Secretary of HHS declares a public health emergency (see *Chapter 2: Vaccine Infrastructure in the United States—Emergency Preparedness and Response)*. In cases where the public health emergency expires but a credible risk of future public health emergencies still exists, the Secretary may extend the liability protections; this happened with COVID-19, for which the public health emergency declaration expired on May 11, 2023.

Persons claiming to have been injured by a covered countermeasure may seek compensation from the Countermeasures Injury Compensation Program, which is administered by HRSA.[27] There are important differences between this program and the VICP.[28] For example, compensation is only available for the most serious injuries; moreover, there is a high burden of proof; a statute of limitations, a limit on awards for damages, and no reimbursement of attorneys' fees. Finally, there are no provisions for judicial review or civil litigation if claims are denied.

Occupational Safety and Health Administration (OSHA)

Because most vaccines are injected percutaneously, vaccine providers and their employees are at risk for needlestick injuries. As such, all facilities where vaccinations are given fall under OSHA regulations designed to minimize occupational exposure to bloodborne pathogens. Some states may have OSHA plans that exceed the federal requirements discussed below, but those plans cannot be less stringent.

Basic elements of the Bloodborne Pathogens Standard (created in 1991 and revised in 2001[29]) are listed below. With respect to vaccinations, the most important elements are the use of engineered sharps protections on needles and the proper disposal of sharps. However, most physicians' offices perform other procedures, such as phlebotomy, wound cleansing, and suturing, necessitating attention to many other aspects of the standard.

- *Exposure-control plan*—A *written* plan needs to be in place that details all the elements listed below. In addition, the procedures and job classifications where exposure to blood might occur should be delineated. An annual review and update must be conducted that considers innovations in medical procedures and new technological developments that reduce the risk of exposure.

- *Sharps-injury log*—Employers must maintain a log of percutaneous injuries from contaminated sharps. It must include, at a minimum, the type and brand of device, department or work area where the incident occurred, and an explanation of how the incident occurred. In addition, it must protect the confidentiality of the injured employee. The log should serve as a tool to identify high-risk areas and evaluate devices.
- *Engineered sharps protections*—Devices with built-in safety features or mechanisms that effectively reduce the risk of exposure must be used for procedures that will involve contact with blood. Such features should be an integral part of the device, allow the worker's hands to remain behind the needle at all times, remain in effect after the procedure and during disposal, and be as simple as possible. Documentation must be provided in the exposure-control plan that appropriate, commercially available, engineered devices are evaluated each year, and justification must be provided for selecting a particular device (*not* selecting an engineered device is not an option). In addition, it must be documented that front-line employees with direct patient care responsibilities had input into the selection. Since sheaths and the like are considered temporary measures, even sharps with engineered protections must be disposed of in an approved container.
- *Universal precautions*—All blood and body fluids must be treated as if infectious for hepatitis B, hepatitis C, and HIV, even if they are from low-risk individuals. Facilities for handwashing and personal protective equipment (eg, gloves, gowns, masks, mouthpieces, and resuscitation bags) must be available at no cost to employees. Employers must launder lab coats and scrubs, if used as protective equipment, at no cost to employees (home laundering is not permitted). Gloves (hypoallergenic if necessary) must be available and hand washing is required after use. However, use of gloves is not required when administering injections if bleeding is not anticipated.
- *Procedures*—Detailed protocols must be given for all procedures with risk, including decontamination of equipment, handling of sharps-disposal containers and other regulated waste, broken glassware, and laundry. Routine cleaning of work sites should be described.
- *Sharps handling*—The exposure control plan must contain a protocol for handling of sharps. Recapping contaminated needles is prohibited but this should not be an issue since needles will have engineered controls. If recapping is necessary for uncontaminated needles, such as those used to draw vaccine from a vial into a syringe, the cap should be scooped up from a flat surface using the hand that is holding the syringe and needle. Disposal containers should be closable, puncture resistant, leak proof, labeled appropriately, and located where procedures are performed. The protocol should specify how the containers are handled once they are filled.
- *Warning labels*—Orange or orange-red biohazard labels must be affixed to containers of regulated waste and refrigerators and freezers containing blood or infectious materials (labeled bags may also be used).
- *HepB vaccination*—Vaccination should be available at no cost to all employees with potential blood contact. The employee's health insurance cannot be used to pay this expense unless the employer routinely pays the entire premium. Employees must sign a declination form if they choose to opt out.
- *Postexposure evaluation*—Specific procedures should be outlined for the handling of exposures. Baseline and follow-up laboratory tests should be done after consent is obtained and must be provided free of charge. Provisions for confidential medical follow-up must be made. Postexposure HIV prophylaxis should be offered if indicated in accord with current guidelines. The source individual's blood should be tested for blood-borne pathogens after consent is obtained; if consent is not given, this needs to be documented. Medical records on employees must be kept for the duration of employment plus 30 years.
- *Training*—Training that includes background information and the exposure-control plan must be provided upon assignment and annually thereafter. Documentation of training sessions, including the dates, content, trainer, and attendees must be maintained.

Mandates and Exemptions

There are no federal laws specifying which people, short of those in military service and immigrants, must receive which vaccines (except for COV; *see below*)—in this sense, all vaccine mandates are local. Some states, employers, and institutions require certain vaccines or proof of immunity for selected individuals. Examples include influenza vaccine, COV, MMR, VAR, Tdap, and HepB for health care personnel (HCP); influenza, COV, and pneumococcal vaccines for residents and employees of long-term care facilities; vaccines for laboratory workers who work with specific pathogens; and RAB for animal handlers. In addition, states have laws specifying which vaccines must be received before attendance is allowed at day care, preschool, school, or college. Mandates work—a systematic review of studies that spanned a variety of vaccine mandates in diverse geographies showed increases in coverage rates and decreases in disease incidence.[30]

Day Care Centers and Schools

Day care and school requirements have been instrumental in the eradication or near-eradication of many diseases.[31] The courts have repeatedly upheld the legal basis for these statutes, which rests on three concepts: 1) *beneficence,* or doing the right thing (protecting individuals and society from the harm of vaccine-preventable diseases; 2) *nonmaleficence*, or not doing harm (vaccines are among the safest medical products in use); and 3) *justice*, or equally protecting the rights of all people (including the right of children to be protected despite their parents' actions or inactions, the right of children who cannot be vaccinated to be protected, and the right of all people to benefit from herd immunity).[32] The case for mandates that prevent the spread of highly contagious diseases (such as measles) in schools is relatively straightforward. Even seasonal influenza has been successfully impacted by mandates.[33] The situation becomes complicated when considering infections such as human papillomavirus, which is not spread in schools, can largely be prevented by avoidance of high-risk behaviors, and which represents a complex political and ethical situation[34]; nevertheless, arguments in favor of school HPV mandates have been made.[35]

In interpreting the validity of an immunization record (see *Chapter 4: Vaccine Practice—Improving Delivery*), the CDC recommends a 4-day grace period for specific minimum age and interval requirements. For counting purposes, "Day 1" is the day before the day that marks the minimum age or interval. Thus, a child who receives MMR 3 days before his first birthday (the minimum age) is considered effectively immunized; one who receives MMR a week before his first birthday is not. Similarly, Dose 3 of DTaP is considered valid if given 26 days after Dose 2, even though the minimum interval is 28 days. One exception to the grace period is the minimum interval between certain live vaccines, which is 28 days (see *Chapter 5: General Recommendations—Ten Simple Rules by Which to Vaccinate*). Thus, a dose of VAR given 26 days after MMR is considered invalid. Other exceptions include the RAB series, which must be given exactly according to schedule, and the first 3 doses of the accelerated HepA-HepB series.

The grace period should be used for interpreting a person's immunization history, not for scheduling future vaccinations. Some local school districts may not accept the 4-day grace period, so the best advice is to give vaccines at the recommended ages. Practitioners may have to balance the idea of giving a vaccine before the specified age with the risk that the patient may not return to be vaccinated at the appropriate time.

All states allow exemption from school immunization requirements for medical reasons. As of 2023, 6 states—California, Connecticut, Maine, Mississippi, New York, and West Virginia—do not allow exemptions for religious or personal beliefs.[36] Laws requiring counseling and the signature of a licensed health care provider in order to obtain an exemption appear to be effective at reducing exemption rates.[37] Major professional medical organizations—including the American Academy of Pediatrics (AAP),[38] the American Academy of Family Physicians,[39] and the American Medical Association[40]—have called for the elimination of nonmedical exemptions from immunization mandates, although there has been a parallel call for transparency regarding anticipated outcomes and strategies to minimize unintended consequences.[41] Overall, nonmedical exemption rates have increased in the last 2 decades,[42] and medical exemption rates are higher in states with more stringent nonmedical exemption criteria, suggesting that parents seek (and receive) medical exemptions when it is difficult to receive religious or personal belief exemptions.[43] In fact, after personal belief exemptions were banned in California in 2015, other forms of exemption—including medical—increased.[44] Importantly, exemptors tend to aggregate geographically, leading to local increases in vaccine-preventable diseases.[45,46]

There is a need for sensitivity and flexibility in dealing with parents' religious beliefs.[47,48] At the same time, constitutional guarantees of religious freedom do not permit children to be harmed through religious practices. All the world's major religions espouse themes of preservation of life, caring for others, and duty to community—themes that arguably resonate with the intent of immunization programs.[49] By and large, objections to vaccination that might be considered "properly theological" have been dismissed. For example, some vaccines contain gelatin derived from pigs, which, ostensibly, might prohibit observant Muslims and Jews from taking them (because of their respective dietary doctrines). However, Jewish authorities recognize a difference between oral consumption of pork products and their injection, and even oral consumption of pork derivatives in the context of medicines is acceptable because of the scriptural imperative to protect life.[50] Muslim authorities have determined that gelatin derived from the transformation of tissues from an impure animal is, in fact, pure.[51] See *Chapter 7: Addressing Concerns About Vaccines—Fetal Tissue* and *Chapter 12: COVID-19* for discussion of religious objections based on the use of fetal cell lines to produce and/or test vaccines.

Personal belief exemptions are problematic because the level of proof can be minimal (as it may be for religious exemptions as well), amounting simply to parents being "opposed to immunization." In some cases, parents request personal belief exemptions as a matter of convenience when their children's immunizations are not up to date.

Exemption from immunization requirements places others in harm's way, and society has a mandate to prevent this. As John Stuart Mill (1806-1873) wrote in 1859, "The only purpose for which power can be rightfully exercised over any member of a

civilized community, against his will, is to prevent harm to others." Put another way by Zechariah Chafee (1885-1957) in 1919, "Your right to swing your arms ends just where the other man's nose begins." The argument against exemption from school mandates was nicely summed up by the Mississippi Supreme Court in 1979: "The relationship of parent and child is one in which the law concerns itself more with parental duties than with parental rights. The relationship carries with it a duty resting upon the parent to provide the child with food, clothing, and shelter and to protect the child from preventable exposure to danger, disease, and immorality."[52]

Physicians, public health providers, and school officials should not grant exemptions out of convenience, and in general should work toward the repeal of nonmedical exemption laws. Encouragingly, while about half of the 175 vaccine bills put forward by state legislators between 2011 and 2017 aimed to expand exemptions, 12 of the 13 that were signed into law actually restricted exemptions.[53] At the same time, lawmakers should consider policies that educate parents as to the risks and benefits of vaccines, facilitate respectful dialogue, and promote public discussion regarding the balance between protecting public health and preserving individual choice.[54]

Hospitals and Other Institutions

The term "HCP" includes all paid and unpaid people working in a health care setting who have the potential for exposure to patients and/or to infectious materials, including body substances, contaminated medical supplies and equipment, contaminated environmental surfaces, and contaminated air.[55] Nationally, only 80% of HCP received influenza vaccine during the 2021-2022 season (92% in the hospital setting, 81% in ambulatory care, and 66% in long-term care facilities or home healthcare).[56] In 2007, the Joint Commission approved a standard that requires accredited organizations to offer influenza vaccination to staff and volunteers with close patient contact. Since then, many professional organizations, state and local health departments, and individual institutions and practices have adopted mandates.[57] In fact, in 2013 the IDSA, the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society released a statement calling for policies that require documentation of immunity or receipt of ACIP-recommended vaccinations as a condition of HCP employment, unpaid service, and granting of professional privileges.[58] In 2020, SHEA reinforced its position that vaccination should be a condition of employment or functioning at a healthcare facility.[59]

The legal framework for mandatory HCP immunization has been delineated,[60] and recent court cases have focused on such fine points as what exactly constitutes a "religion" and how hospitals should enforce their policies.[61] The moral argument can be summed up in four basic principles: 1) the professional obligations to put the patients' interests before one's own; 2) to do no harm; 3) to protect those who are vulnerable; and 4) to set a good example for the public.[62] HCP may be leery of mandates because of misperceptions about vaccine safety and their risk of acquiring influenza at work.[63] In fact, when HCP do get vaccinated, many do so for their own benefit and not for the benefit of their patients.[64] Immunization rates may depend on how the issue is raised; for example, uptake is higher using opt-out rather than opt-in strategies.[65]

Influenza vaccine coverage rates among HCP should be followed as an integral part of all patient safety programs. Immunize.org (formerly the Immunization Action Coalition) maintains the *Influenza Vaccination Honor Roll*, which lists health care organizations and institutions that require influenza vaccination for employees and have measures (eg, mask requirements, reassignment, or dismissal) in place to prevent transmission from unvaccinated workers to patients. As of 2023, there were >1300 organizations on the list.[66]

COVID-19 Vaccination Mandates

The COVID-19 pandemic brought to the forefront legal and ethical issues surrounding vaccination mandates.[67] Early on, there was debate as to whether vaccines approved under EUA *could* be mandated, centering on language in the statute regarding "the option to accept or refuse administration of the product" and the possibility of consequences of refusal.[68] In July 2021, the Justice Department's Office of Legal Counsel issued an opinion that mandates for vaccines under EUA were, in fact, legal[69]; by that time more than half of private employers already indicated that they had or would require employees to be vaccinated.[70] Whereas the right of private employers to mandate vaccination has largely been upheld, in January 2022 the Supreme Court blocked the Biden Administration's mandate for private companies with more than 100 employees to require weekly COVID-19 tests for unvaccinated employees.[71] On the other hand, the Court refused to block a vaccination requirement for workers and contractors at Medicare- and Medicaid-certified facilities, which was in place from November 2021 to June 2023. Around the same time, federal judges blocked the Administration's vaccination mandate for federal employees and employees of federal contractors (the mandate was in place until May of 2023, although a standing injunction prohibited its enforcement). During the pandemic, many states had some form of COVID-19 vaccination mandate in place, applying as it were to various state employees and contractors; school personnel and students; attendees at large public events; employees of long-term care facilities; health care personnel; childcare workers; and transportation workers. On the other hand, some states *prohibited* vaccination mandates.

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Vaccine Practice

Handling, Storage, and Transport

Mishandling of vaccines can reduce potency and leave vaccinated people susceptible to disease. Here are some general guidelines for proper vaccine management[1]:

- *Basics*
  - Designate one person (and a backup) to be in charge, but educate all staff about vaccine storage, handling, and inventory. Responsibilities of the immunization coordinator are listed in **Table 4.1**.
  - Maintain up-to-date written standard operating procedures that include general information (eg, critical contact information, job descriptions, training requirements); all aspects of inventory management, from ordering to disposal; and emergency procedures.
  - Make sure deliveries are scheduled when the facility is open and knowledgeable staff are present, keeping in mind holidays, vacations, and changes in hours of operation.
  - Anticipate seasonal changes in vaccine needs (eg, influenza season and back-to-school time).
  - Know the demographics of the clinical population to anticipate vaccine needs, keeping in mind that each vaccine has unique age indications, formulations, and presentations.
- *Inventory*
  - Maintain an inventory log, including product name, manufacturer, lot number, doses received, date received, condition on arrival, and expiration date.
  - Inspect products on delivery, including the integrity of containers and cold chain monitoring devices.
  - Store vaccines immediately under appropriate conditions.
  - If there are questions about a vaccine's condition at delivery, store the vaccine under the recommended conditions, label it "DO NOT USE," and contact the manufacturer's quality-control office or the state immunization program.
  - Discard mishandled and expired vaccines (when the expiration date is a month and year, the vaccine can be

TABLE 4.1 — Responsibilities of the Immunization Coordinator

- Order vaccines
- Oversee receipt and storage
- Document and manage vaccine inventory
- Organize refrigerator and freezer
- Set up temperature monitoring devices
- Monitor and record storage unit temperatures daily
- Download and review temperature data weekly
- Inspect refrigerator and freezer daily
- Make sure storage unit doors are closed
- Rotate stock at least weekly
- Remove expired vaccine
- Respond to temperature excursions
- Oversee vaccine transport
- Prepare for emergencies
- Maintain storage and handling documentation
- Maintain storage equipment and corresponding records
- Maintain VFC documentation
- Ensure training of designated staff
- Maintain open lines of communication with providers
- Keep up with new recommendations
- Prepare talking points to address concerns
- Look for ways to improve coverage and timeliness
- Champion immunization

VFC, Vaccines for Children Program

Adapted from Vaccine storage and handling toolkit: January 2023. CDC Web site. https://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf. Accessed July 12, 2023.

used until the last day of the month; when a date is included, the vaccine can be used through the end of that day).

– Rotate stock so that the vaccine with the shortest expiration date is up front.
– Keep vaccines purchased through the Vaccines for Children Program (VFC) separate from privately purchased vaccines.
– Keep vaccines in original boxes until ready for use.
– Inspect stock every day.
– Designate an alternate site where vaccines can be safely stored.
– Discourage "brown bagging," where patients pick up their vaccines at a pharmacy and bring them to the provider for administration.

• *Administration*
– Consider as invalid any doses that were inadvertently given with mishandled or expired vaccine.
– Do not open more than one multidose vial at a time.
– Be aware that for some multidose vials, there is a limited shelf life after the vial is first entered.
– Only withdraw the recommended number of doses from a multidose vial, even if there is enough residual in the vial to constitute additional doses.
– Prefilling syringes with vaccines that are supplied in vials is discouraged (this increases the risk of administration error and raises stability and storage issues).
– Never intentionally give partial or fractional doses of a vaccine.
– Use only the diluent supplied by the manufacturer to reconstitute lyophilized vaccines.
– Dispose of all vaccine materials using medical waste disposal procedures, including sharps/biohazard containers.

• *Storage*
– **Tables 4.2, 4.3**, and **4.4** give storage conditions for vaccines licensed in the US.
– Separate, dedicated refrigerator and freezer units are ideal. If the office has a household-style combination refrigerator/freezer, it can only be used for refrigerated vaccines (frozen vaccines must be stored in a separate unit). Dormitory style units that have a freezer compartment within the refrigerator should never be used.
– Keep a logbook for each piece of equipment, including serial number, date of installation, maintenance and repair dates, and service contact information.
– Position the units ≥4 inches from any wall to ensure good air circulation.
– Use a duster to keep the coils clean.
– Do not store food in the vaccine refrigerator or freezer.
– Do not store vaccines on shelves in the refrigerator door.
– Vaccines that need to be refrigerated should be placed in the middle of the refrigerator, at least 2 to 3 inches from the walls and away from cold air vents.
– Use clearly labeled, color-coded, breathable plastic mesh trays for each product and include separate compartments for unopened and opened vials (record the date of opening or reconstitution directly on the label). For refrigerated vaccines that require reconstitution, the corresponding diluents should be stored with the vaccines (diluents should never be frozen).

TABLE 4.2 — Vaccines Stored in the Refrigerator[a]

Vaccine	Trade Name	Comments or Special Instructions
Adenovirus	—	Store type 4 and type 7 vaccine together
		Keep bottles tightly closed
		Do not remove desiccant and protect from moisture
AVA	BioThrax	—
Cholera	Vaxchora	Store buffer and active component packets together
		Packages may be stored at room temperature for ≤5 d before reconstitution
		Protect from light and moisture
COV-aPS (Novavax)	—	Discard vial within 12 h of first puncture
		Protect from light
Dengue	Dengvaxia	Store lyophilized dengue vaccine and diluent together
		May store reconstituted vaccine in refrigerator for ≤30 min
		Protect from light
DT	Diphtheria and Tetanus Toxoids Adsorbed	—
DTaP	Daptacel	—
	Infanrix	—
DTaP-HepB-IPV	Pediarix	—
DTaP-IPV	Kinrix	—
DTaP-IPV	Quadracel	—
DTaP-IPV/Hib	Pentacel	Store lyophilized Hib-T and DTaP-IPV diluent together
DTaP-IPV-Hib-HepB	Vaxelis	Protect from light
HepA	Havrix	Do not dilute to administer
	Vaqta	—
HepA-HepB	Twinrix	—

Continued

TABLE 4.2 — *Continued*

Vaccine	Trade Name	Comments or Special Instructions
HepB	Engerix-B	Do not dilute to administer
	Heplisav-B	—
	PreHevbrio	Protect from light
	Recombivax HB	Protect from light
Hib-OMP	PedvaxHIB	—
Hib-T	ActHIB	Store lyophilized Hib-T and diluent together
		May store reconstituted vaccine in refrigerator for ≤24 h
	Hiberix	Store lyophilized Hib-T and diluent together
		May store reconstituted vaccine in refrigerator for ≤24 h
		Protect from light
HPV9	Gardasil 9	May be administered if total time at room temperature is ≤72 h before administration
		Protect from light
IIV	See **Table 20.1**	Protect Afluria, Fluarix, Flublok, Flucelvax, Flulaval, and Fluvirin from light
IPV	IPOL	Protect from light
JE-VC	Ixiaro	During storage, a clear liquid with a white precipitate can be observed
		Protect from light
LAIV	Flumist	A single temperature excursion up to 77°F (25°C) for 12 h has no adverse impact on the vaccine—in the event of such an exposure, return vaccine to recommended storage temperature and use as soon as possible (discard if there is more than one exposure)
		Protect from light

Continued

TABLE 4.2 — *Continued*

Vaccine	Trade Name	Comments or Special Instructions
MenACWY-CRM	Menveo (2-vial presentation)	Store lyophilized MenA and MenCWY diluent together
		May store reconstituted vaccine at room temperature or in refrigerator for ≤8 h
		Protect from light
	Menveo (1-vial presentation)	Protect from light
MenACWY-D	Menactra	—
MenACWY-T	MenQuadfi	—
MenB-4C	Bexsero	Protect from light
MenB-FHbp	Trumenba	Store syringes flat on the shelf to minimize the re-dispersion time
MMR (GSK)	Priorix	Store lyophilized MMR and diluent together
		May store reconstituted vaccine in refrigerator for ≤8 h
		Protect from light
PCV13	Prevnar 13	—
PCV15	Vaxneuvance	Protect from light
PCV20	Prevnar 20	Store horizontally to minimize resuspension time
		May be administered if total time at room temperature is ≤96 h and if total time at 0°C to 2°C is ≤72 h
PPSV23	Pneumovax 23	—
RAB-HDC	Imovax Rabies	Store lyophilized RAB and diluent together
RAB-PCEC	RabAvert	Store lyophilized RAB and diluent together
		Protect from light
RSV	Abrysvo	Store lyophilized RSV and diluent together
		May store reconstituted vaccine at room temperature for ≤4 h (do not store reconstituted vaccine in refrigerator or freezer)

Continued

TABLE 4.2 — *Continued*

Vaccine	Trade Name	Comments or Special Instructions
RSV (*continued*)	Arexvy	Store lyophilized RSV and diluent together
		May store reconstituted vaccine at room temperature for ≤4 h
		Protect from light
RV1	Rotarix (oral dosing applicator only presentation)[b]	Protect from light
RV5	RotaTeq	Protect from light
RZV	Shingrix	Store lyophilized RZV and diluent together
		May store reconstituted vaccine in refrigerator for ≤6 h
		Protect from light
TBE vaccine	Ticovac	Protect from light
Td	Tenivac	—
	TdVax	—
Tdap	Adacel	—
	Boostrix	—
TVIPSV	Typhim Vi	—
Ty21a	Vivotif	—
YFV	YF-Vax	Store lyophilized YFV and diluent together

[a] Refrigerator temperature should be maintained at 36°F to 46°F (2°C to 8°C). Refrigerated vaccines and diluents should never be frozen (MMR [Merck] is an exception since the lyophilized vaccine can be stored in the refrigerator or freezer). Room temperature is generally considered to be 68°F to 77°F (20°C to 25°C).

[b] The vial and oral dosing applicator (lyophilized) presentation was no longer being distributed as of June 2023.

Adapted from the respective package inserts and vaccine storage and handling toolkit: January 2023. CDC Web site. https://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf. Accessed June 12, 2023.

TABLE 4.3 — Vaccines Stored in the Freezer[a]

Vaccine	Trade Name	Comments or Special Instructions
COV-mRNA (Moderna)	Spikevax	May store thawed vaccine in refrigerator for ≤30 d
		May store thawed vaccine at room temperature for ≤24 h
		Thawed vaccine can be handled in room light
		Discard vial within 12 h of first puncture
		Prefilled syringes may be stored in refrigerator for ≤30 d and at room temperature for ≤24 h
		Protect from light
MMR (Merck)	M-M-R_{II}	Store diluent in refrigerator or at room temperature
		Before reconstitution, store lyophilized vaccine in refrigerator
		May store reconstituted vaccine in refrigerator for ≤8 h
		Protect from light
MMRV	ProQuad	Store diluent at room temperature or in refrigerator
		May store vaccine in refrigerator for ≤72 h before reconstitution
		May store reconstituted vaccine at room temperature for ≤30 min
		Protect from light

Continued

TABLE 4.3 — *Continued*

Vaccine	Trade Name	Comments or Special Instructions
Smallpox	ACAM2000	Store diluent at room temperature
		May store reconstituted vaccine at room temperature for 6-8 h
		May store reconstituted vaccine in refrigerator for ≤30 d
	Jynneos	Store in original package to protect from light
		May store thawed vaccine in refrigerator for 4 wk
VAR	Varivax	Store diluent at room temperature or in refrigerator
		May store vaccine in refrigerator for ≤72 h before reconstitution
		May store reconstituted vaccine at room temperature for ≤30 min
		Protect from light

[a] Freezer temperature should be maintained at -58°F to 5°F (-50°C to -15°C). Room temperature is generally considered to be 68°F to 77°F (20°C to 25°C). In general, vaccines should not be refrozen once thawed or reconstituted.

Adapted from the respective package inserts and storage and handling toolkit: January 2023. CDC Web site. https://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf. Accessed July 12, 2023.

TABLE 4.4 — Vaccines Stored in the Ultra-Low Temperature Freezer[a]

Vaccine	Trade Name	Comments or Special Instructions
COV-mRNA (Pfizer-BioNTech)	Cominarty	Store diluent at room temperature
		May store vaccine in freezer[b] for ≤2 wk
		May thaw undiluted vials and store in refrigerator for ≤1 mo
		Thaw vial at room temperature for 30 min before dilution (thawed vial may be handled in room light and may be stored at room temperature for ≤2 h)
		May store diluted vial in refrigerator or at room temperature for ≤6 h
		Protect from light
Ebola vaccine	Ervebo	Thaw vaccine at room temperature and use immediately
		May store thawed vaccine in refrigerator for ≤2 wk or at room temperature for ≤4 h
		Protect from light

[a] Ultra-low temperature freezer should be maintained at -112°F to -76°F (-80°C to -60°C); the temperature indicated on the Comirnaty package insert is -130°F to -76°F (-90°C to -60°C). Refrigerator temperature should be maintained at 36°F to 46°F (2°C to 8°C). Freezer temperature should be maintained at -58°F to 5°F (-50°C to -15°C). Room temperature is generally considered to be 68°F to 77°F (20°C to 25°C). In general, vaccines should not be refrozen once thawed or reconstituted.

[b] Freezer temperature indicated on the package insert is -13°F to 5°F (-25°C to -15°C). Vials may be returned one time to the ultra-low temperature freezer.

Adapted from the respective package inserts and storage and handling toolkit: January 2023. CDC Web site. https://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf. Accessed July 12, 2023.

Be aware that vaccines can only be used for a limited time after reconstitution.

– Arrange vaccines by age group (pediatric, adolescent, adult).
– Post a sign that specifies which vaccines are stored in the refrigerator and which are stored in the freezer.
– The refrigerator and freezer should have a buffered temperature probe with a digital data logger that is set to record temperatures at least every 30 minutes. The device should have a display for current, minimum, and maximum temperatures; a low-battery indicator; an out-of-range alarm; and a valid *Certificate of Calibration Testing* (also known as a *Report of Calibration*; this certifies calibration *after* manufacturing). Calibration should be performed every 1 to 2 years. The minimum and maximum temperatures should be recorded on a log when the office opens in the morning (these logs should be kept for ≥3 years). *Appropriate ranges are 36°F to 46°F (2°C to 8°C) for the refrigerator and -58°F to 5°F (-50°C to -15°C) for the freezer.* The importance of proper storage temperature was highlighted in a 2012 report by the Office of the Inspector General, which found that vaccines had been exposed to inappropriate temperatures at 76% of 45 practices.[2]
– Keep water bottles (label "DO NOT DRINK") on the top shelf, floor, and door shelves of the refrigerator. Place ice packs in the freezer. These measures help maintain a steady temperature and provide some stability in the event of a power outage.
– Place a "DO NOT UNPLUG" sign near the outlet for the refrigerator and freezer units. Mark other points along the circuit (eg, fuses or circuit breakers) in a similar fashion.
– Do not use an outlet with a ground fault circuit interrupter (ie, one with test and reset buttons) or one connected to a wall switch.
– Use plug guards to prevent accidental dislodging.
– If possible, use an outlet connected to an auxiliary power source.
– **Table 4.5** gives some suggestions for managing vaccine inventory in the event of a power failure or weather emergency.

• *Off-site transportation*

– The total time that vaccines are off-site, including transportation and the clinic workday, should not exceed 8 hours.
– US Food and Drug Administration regulations require that multidose vials be used only by the provider's office where they were first opened (partially used vials may be moved to other sites operated by the same provider if the cold chain is maintained).
– The following may be used to transport vaccines at 36°F to 46°F (2°C to 8°C): original shipping containers, hard-sided plastic insulated containers, and Styrofoam coolers with walls that are at least 2 inches thick (do not use the thin-walled coolers typically found in grocery stores).
– It is best not to transport VAR-containing vaccines. However, if this is absolutely necessary, they may be transported at 36°F to 46°F (2°C to 8°C) as above but must be used within 72 hours and should not be refrozen.

TABLE 4.5 — Storage and Handling During Emergencies

Written Standard Operating Procedures

- Prioritized key contact notification system
- Emergency phone numbers for power company, equipment repair, alarm monitoring companies, backup storage facility, dry ice vendor, generator repair company, and vaccine manufacturers
- Working agreements with hospitals, health departments, or other facilities to serve as emergency vaccine storage facilities
- Procedures for entering facilities and storage areas during emergency or after hours, including floor plan with location of emergency equipment and packing materials
- Record of storage unit specifications, backup power sources, and packing and transport supplies
- Procedures for packaging vaccines, including inventory documentation and cold-chain monitoring
- Procedures for transporting vaccines, including preferred and alternative routes
- Priority list for vaccine rescue, aiming to minimize dollar loss but ensure ability to deliver the routine schedule in the short term

Power Outages

- Have emergency contact information posted on electrical box
- Do not open refrigerators and freezers until power is restored
- Record temperature after power is restored and note duration of outage (do not open to monitor temperature during outage)
- Transfer to alternate storage with reliable power source if possible, maintaining cold chain and monitoring temperature
- Contact state or local public health authorities or the vaccine manufacturer if there is any question about the potential potency of exposed vaccine
- Label exposed vaccine and keep it separated from new stock

Weather Emergencies

- Track inclement weather conditions, especially thunderstorms, tornadoes, hurricanes, ice storms and snowstorms
- Suspend vaccination and implement emergency procedures in advance of the event
- Ensure prior availability of staff to package and transport vaccine

Adapted from Vaccine Storage and Handling Toolkit: January 2023. CDC Web site. https://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf. Accessed July 12, 2023.

- Use refrigerated or frozen gel packs, not loose or bagged ice (use enough of these to maintain the proper temperature and validate a stable temperature before using the cooler for vaccines).
- Keep the vaccines in their original boxes.
- Place bubble wrap or Styrofoam peanuts around the vaccines to prevent direct contact with the refrigerated or frozen gel packs; include a thermometer next to the vaccines.
- Diluents should always travel with their corresponding vaccines. They can stay at room temperature. If packed inside coolers, they should be refrigerated ahead of time and should not come in direct contact with the refrigerated or frozen gel packs.

Improving Delivery

A large evidence base exists on strategies to improve immunization delivery. Many of the following strategies are emphasized in *Chapter 3: Standards, Principles, and Regulations—Standards for Child and Adolescent Immunization Practices* and *Standards for Adult Immunization Practices*. The starting point is always documenting which vaccines have been given and when. The Advisory Committee on Immunization Practices (ACIP) holds that "written" documentation is required; the only exceptions are influenza vaccine and PPSV23, for which self-reported doses are considered valid (the rationale for influenza vaccine is that it is given yearly, which makes accurate recall more likely; for PPSV23, the rationale is to avoid overvaccination, which can lead to increased reactogenicity). The following guidance applies to documentation of vaccinations received:

- A physical written record from a medical provider is considered proof of vaccination.
- A screenshot, photo, scan, or photocopy of a written record from a medical provider is acceptable.
- Doses recorded in an electronic health record (EHR) or immunization information system (IIS) are valid.
- Records kept by a parent (as in a "Baby Book") can be considered valid if the provider is sure that the entries reflect reality. In other words, providers have discretion to interpret the Baby Book entries as "valid" (reliable parent, appropriate dates and times, variations in handwriting or writing instrument) or "not valid" (untrusted parent, all entries look like they were made at the same time).

Reminder, Recall, and Tracking Systems

Reminders are messages that immunizations are due. They may be directed at parents in the form of telephone calls (by humans or computers) or mailings (simple postcards or letters), or they may

be directed at physicians, nurses, or other staff members in the form of chart or EHR flags. Text messaging is an option—one large randomized controlled trial in an urban, low-income population showed improved influenza immunization rates in children whose families were assigned to a text messaging intervention[3]; another study set in both private and safety-net pediatric practices showed that bidirectional text messaging (where a short message from the provider prompts a response from the parent) can result in improved immunization rates at modest cost.[4] Interestingly, in a study of text reminders for influenza vaccination, the most effective text message was one that said, "We have a shot reserved for you", as opposed to simple reminders or other messages.[5] In a large Danish study of "electronic nudges" in persons ≥65 years of age, one of the most effective messages was one highlighting potential cardiovascular benefits, especially among those who had not received influenza vaccine in the previous season.[6]

Recall messages are notices to parents that vaccinations are overdue. Tracking systems, which can be manual or computerized, allow each child's immunization status to be followed precisely. Studies have consistently shown improvements in immunization rates for children and adults if tracking and messaging systems are used, in both public and private settings.[7,8] However, reminder and recall systems are particularly difficult to implement in practices with high patient turnover or in populations that frequently change residence or phone numbers. In some areas, bilingual reminders may be necessary.

Missed Opportunities

Providers should utilize all clinical encounters, including acute care visits, to assess immunization status and administer all vaccines for which a person is eligible, as long as true contraindications do not exist. The idea is to prevent contacts with the health care system from becoming missed opportunities for vaccination.[9,10] In order to minimize missed opportunities, providers must be able to accurately determine immunization status "on the fly"—EHRs and IISs can facilitate this, as can attentive office staff. Erroneous contraindications (**Table 5.6**) must not stand in the way. Additional barriers may exist in emergency departments and other acute care facilities, including time constraints, concerns about insurance reimbursement, and the perception that by giving routine immunizations, the patient's relationship with his primary care provider will be disrupted.

Medical Home and Immunization Neighborhood

The medical home—a place for primary care that is patient-centered, comprehensive, team-based, coordinated, accessible, and focused on quality and safety[11]—is the preferred place for vaccination. After-hours or weekend clinics may help boost coverage rates by making it more convenient for parents to bring their children in or for adults to stop by after work. In addition, access to vaccination once a patient enters the office can be facilitated using "vaccination express lanes" and drop-in clinics. With proper vaccine storage and handling, there is no reason why home visits could not be used to vaccinate those persons who are receiving home health services for other reasons.

Children make fewer and fewer visits for preventive health care as they get older, and many adolescents and adults simply do not go to the doctor. Given this, it seems prudent to expand the vaccination home into an *immunization neighborhood*, opening access points where people can get immunized. Pharmacists, for example, have had an expanding role in vaccine administration.[12] In recent years, the number of adults who are immunized in pharmacies has dramatically increased, and there is good evidence that involving pharmacists in the immunization process—as educators, facilitators, or administrators—improves immunization rates.[13] In response to lower routine childhood vaccination rates seen during the COVID-19 pandemic (*see below*), the federal government authorized certain state-licensed pharmacists to order and administer COVID-19 vaccines, as well as ACIP-recommended routine vaccines, to children 3 to 18 years of age.[14] The authorities for COVID-19 and influenza vaccination have been continued until at least December 2024, but the authorities for routine immunization ended in May 2023 with the end of the public health emergency declaration.[15] States differ in terms of which vaccines they can administer, who they can vaccinate, and whether a prescription is needed.[16]

Expanding access for adults, which serves to protect them as well as their infant contacts, requires thinking outside the box in terms of where immunization could occur. For example, postpartum women (who have not already received Tdap) and other household members could receive Tdap in the hospital before the mother and baby go home. This idea was successfully implemented at a hospital in Houston—over 90% of postpartum women, and many other family members who anticipated contact with the infant, were immunized.[17] Unfortunately, this notion of "cocooning"—surrounding infants with immune contacts to erect a barrier to disease transmission—does not seem to work that well. One reason for this is the difficulty identifying and immunizing *all* adults who may come into contact with infants, and doing so early enough for them to develop immunity *before* they will be around the infant.[18,19] In fact, a study from Canada (where, admittedly, the incidence of infant pertussis is lower than in the US) demonstrated that at least 1 million parents would need to be given Tdap in order to prevent 1 infant death from pertussis.[20] And it is not just about immunizing adults in the environment: in recent years, there has been a shift in the source of pertussis in infants from parents and other adults to siblings.[21]

This is in large part why the emphasis for prevention of infant pertussis has shifted to immunization of pregnant women (see *Chapter 14: Diphtheria, Tetanus, and Pertussis*). Having said that, it

is hard to imagine that giving vaccines that are due wherever and whenever adults can be "captured" is a bad thing. This is part of the idea behind New York State Public Health Law §2805-H, which requires hospitals to offer influenza vaccine to the parents and caregivers of infants admitted to the Neonatal Intensive Care Unit, and mandates all hospitals with newborn nurseries or obstetric services to offer Tdap to parents and caregivers of newborns.

Likewise, parents of infants who are hospitalized could be immunized when they visit the hospital; this takes the concept one step further, since those parents, unlike postpartum women, are not themselves patients. Nevertheless, the strategy has been successfully employed for both influenza[22] and pertussis[23] immunization. One added value to this approach is that immunization rates among health care personnel (HCP) tend to increase.

The pediatric office is also fair game as a venue for adult immunization.[24]

Immunization During the COVID-19 Pandemic

Routine immunizations across the age spectrum declined sharply in the early months of the COVID-19 pandemic as the result of stay-at-home orders and concerns that the virus could be transmitted in offices and clinics (in truth, there is little evidence that COVID-19 is commonly acquired in medical offices). Wellness visits largely recovered by 2021, but recovery in immunization rates was not as robust, especially for HPV vaccination in adolescents, HepA in persons 19 to 49 years of age, and pneumococcal vaccination in persons ≥65 years of age.[25] Potential explanations for this discrepancy include increased pandemic-related vaccine hesitancy, provider workforce issues, and prioritization of COVID-19 vaccination over routine vaccination, among others.

Standing Orders

Standing orders enable nonphysician personnel, such as nurses and pharmacists, to prescribe or deliver vaccinations by protocol at the time of an encounter; direct physician involvement is not required. This is one of the most effective interventions for increasing adult immunization rates, and studies show that the entire process can be computerized—that is, patients can be screened for eligibility electronically and the orders can be generated automatically, without investment of personnel time. Employing standing orders in nursing homes, hospitals, clinics, pharmacies, physicians' offices, and other institutional settings can significantly increase coverage rates and is strongly endorsed.[26] Barriers to adoption in pediatric practice include concern that patients may mistakenly receive the wrong vaccine and the belief that parents prefer the direct involvement of physicians.[27] Immunize.org maintains a catalog of standing order templates at https://www.immunize.org/standing-orders/ (accessed July 12, 2023) that can be adopted to individual practice situations.

School-Located Vaccination (SLV)

Schools are attractive sites for vaccination when one considers that, well, that is where the kids are. In addition, schools are integral to communities, and school nurses are trusted health care professionals. Providers generally support SLV, although they may have concerns about record-keeping, the potential for negative financial impact on their practices, and their ability to maintain a relationship with the patient.[28,29] Parents (and even students) may be favorably inclined to SLV[30,31]; barriers include negative perceptions about equipment sterility, low trust in the competency of school personnel to administer vaccines, a perceived lack of organization and ability to address medical issues, and concerns about confidentiality.[32]

The paradigm for SLV has been established by seasonal influenza vaccination programs, which in some cases succeed in immunizing the majority of students in school districts or larger communities.[33] Demonstrated benefits include decreased rates of influenza and improved school attendance,[34] and the net cost per dose delivered might actually be less than that in private practice, at least when you include the parental costs averted (ie, with SLV, parents do not have to take their kids to the doctor's office).[35] However, there are many reasons why broadening SLV to include other vaccines may be difficult. For one, influenza campaigns are temporally focused, employ one vaccine, and target all children every year. In contrast, programs designed to address other childhood vaccines would require year-round implementation, would likely target only children who are behind or have no medical home, and would be highly dependent on accurate IISs. Successful programs require extensive lead time for clinic planning; partnerships between school personnel, school governance, parent-teacher associations, providers, and local health departments; communication with parents, children, administrators, teachers, medical providers, and the community at large; and successful education through local media, school events, and mailings.[36] In addition, clinic operations need to be well-defined, including how informed consent will be obtained (consent via Internet is one option[37]); organizational structure, roles, and accountability; staffing; training; supplies; vaccine storage and handling; team communication; and data management.[38] Other issues that must be addressed include screening for VFC eligibility and obtaining reimbursement.

Immunization Information Systems

IISs, formerly known as *registries*, are confidential, population-based, centralized computerized systems that maintain information about immunizations. The ideal IIS contains all persons in a geographic area and receives vaccination data from all regional providers. The need for IISs is easy to see—an increasingly complex vaccine schedule must be administered to children who frequently relocate and change health care providers, and the number of vac-

cines being recommended for adults is increasing. For children and adults, vaccination histories are often incomplete and fragmented, leading to both missed opportunities and unnecessary duplication. As of 2021, 98% of children <6 years of age and 86% of adolescents had ≥2 immunizations in an IIS; 98% of adults had ≥1 immunization recorded.[39] The potential benefits and challenges of IISs are summarized in **Table 4.6**.

Immunization Coalitions

Immunization coalitions bring people together, combining resources and talents to increase immunization rates. They involve health departments, hospitals, insurers, health maintenance organizations, providers, nonprofit organizations, vaccine manufacturers, and individuals. About a third of coalitions are organized at the county level and another third at the regional or state level; most focus on all vaccines and all age groups.[40] Activities include education, advocacy, and lobbying.

Other Strategies

Community education regarding the importance of immunizations plays a role in improving coverage rates by increasing demand. Physician and staff education is also important, and the immunization coordinator can facilitate this (**Table 4.1**). Regular, systematic assessment and feedback can identify problem areas and evaluate the effectiveness of new interventions. To this end, the CDC offers a program called IQIP (Immunization Quality Improvement for Providers) that promotes and supports implementation of provider-level strategies to increase on-time vaccination of children and adolescents (IQIP replaced AFIX [Assessment, Feedback, Incentives, eXchange] in July 2019]).[41] A software application called CoCASA, for Comprehensive Clinic Assessment Software Application, is available from the CDC to assess immunization practices in clinics, private practices, or other sites where immunizations are given.[42]

Comprehensive strategies can make a difference in immunization rates. For example, Denver Health, an integrated urban safety net healthcare system in Colorado, was able to achieve adolescent immunization rates well above national averages by implementing the strategies shown in **Table 4.7**. Similarly, the *4 Pillars Practice Transformation Program*, summarized in **Table 4.8**, has been successful in improving adult[43] and adolescent[44] immunization rates.

Screening

Screening patients for contraindications, precautions, and other problems before every dose of a vaccine is an important part of preventing adverse events and ensuring vaccine "take." This can be effectively accomplished by asking the simple questions shown in **Table 4.9**, which are applicable to both children and adults. The issues addressed by these questions are also indicated in the table. Standardized forms for screening can be downloaded from Immunize.org (formerly the Immunization Action Coalition) at http://www.immunize.org/clinic/screening-contraindications.asp (accessed July 12, 2023).

Administration

General Issues

During well child visits, vaccines should be brought to the examination room rather than moving the patient to a designated shot area. Reconstitution, if needed, should be done for each individual patient rather than in batches to reduce the risk of confusion and wastage. Young infants do better if held on the parent's lap, while older children may prefer to sit on the edge of the examining table and hug the parent. Adolescents who are at risk for syncope should sit or lie down. HCP should wash their hands or use antiseptic hand gel before each patient encounter.

Here are some additional administration pearls:

- A physical exam is not required for vaccination of healthy persons.
- There is no limit to the number of vaccines that can be given at a single visit.
- Gloves are not routinely needed to administer injected vaccines but should be worn if the vaccinator may come in contact with body fluids or has open lesions on the hands.
- The rubber stopper on vaccine vials is not sterile and should be cleaned with a *sterile* alcohol pad (yes, there are *nonsterile* alcohol pads!) after the protective cap is removed.
- It is not necessary to change the needle after withdrawing vaccine from the vial; this only increases the risk of sharps injury and bacterial contamination.
- Air bubbles in manufacturer-filled syringes do not need to be expelled before injection (the amount of air is small, and the air will usually rise to the top when the syringe is inverted for delivery). However, air that enters a syringe when the user withdraws vaccine from a vial *should be* expelled, because the amount is likely to be larger.
- The contents of one syringe should never be transferred into another syringe, and residuals from multiple vials should never be combined to constitute a full dose.
- The injection site should be swabbed with a sterile alcohol pad (a different one than was used to clean the vial cap) and allowed to dry.

TABLE 4.6 — Immunization Information Systems

Society-Level Benefits

- Improved immunization rates[a]
- Response to outbreaks and public health emergencies[b]
- Adverse event surveillance
- Identification of coverage gaps and disparities
- Improved vaccine distribution
- Quality assurance initiatives

Patient- and Practice-Level Benefits

- Synthesized, consolidated immunization history from various sources
- Timely vaccination after changes in provider
- Enhanced patient reminder and recall
- Data on usage and coverage rates
- Improved inventory management
- Reduced vaccine wastage, duplicated vaccinations and invalid doses[c]
- Reduced costs associated with missed opportunities
- Direct sharing of immunization records with schools[d]
- Patient access to their immunization records
- Improved HEDIS scores and increased pay-for-performance

Challenges

- User learning curve
- Integration into existing business practices
- Fidelity of communication between the practice and the IIS
- Need for individualized communication interfaces with new and evolving EHRs[e]
- Lack of full interoperability between various IISs[f]
- State regulation barriers to effective information exchange
- Reporting consistency and varying state requirements
- Costs associated with algorithm and immunization schedule updates in the EHR[g]
- Heterogeneity of data quality[h]
- Heterogeneity in funding sources
- Concerns about confidentiality
- Perception of minimum value-added for participation

EHR, electronic health record; HEDIS, Healthcare Effectiveness Data and Information Set; IIS, immunization information system

[a] Groom H, et al. *J Public Health Manag Pract*. 2015;21:227-248.

[b] Examples include the response to Hurricane Katrina (Urquhart GA, et al. *J Public Health Manag Pract*. 2007;13:481-485); the A(H1N1) pandemic (CDC. *MMWR*. 2010;59:363-368); and COVID-19 (Preparing ISSs for COVID-19 response. CDC Web site. https://www.cdc.gov/vaccines/covid-19/reporting/downloads/Master-Awardee-Work-Plan.pdf; accessed July 12, 2023).

Continued

TABLE 4.6 — *Continued*

[c] IISs may have more robust and timely logic than that deployed in EHRs.

[d] This may vary from state to state.

[e] "Meaningful use" criteria require the ability to communicate with an IIS in a standard current format (currently HL7 2.5.1).

[f] The CDC's Immunization Gateway transmits requests for data from one IIS to another and transmits the responses to those requests, all without storing any of the data (The Immunization Gateway. CDC Web site. https://www.cdc.gov/vaccines/programs/iis/iz-gateway/overview.html. Accessed July 12, 2023).

[g] These costs are accounted for in the relative value units value of the Current Procedural Terminology codes for vaccine administration. However, this value has recently been reduced, and Medicaid does not recognize or pay for individual vaccine component counseling and administration.

[h] Two-dimensional barcodes on vaccine products that specify lot number, manufacturer, and other information can facilitate the accuracy and completeness of data in IISs (Vaccine two-dimensional [2D] barcodes. CDC Web site. https://www.cdc.gov/vaccines/programs/iis/2d-barcodes/index.html. Accessed July 12, 2023).

Adapted from Hackell JM, et al. *Pediatrics*. 2022;150:e2022059281; American Immunization Registry Association Web site. https://www.immregistries.org (accessed July 12, 2023).

TABLE 4.7 — Strategies for Successful Adolescent Vaccine Delivery

- A robust registry is used for recording vaccine history, recommending needed vaccines at every visit, and other functions
- Medical assistants check the registry for recommended vaccines at every visit
- Routine immunizations are given by standing order
- Vaccines are given early in the visit
- Providers are educated to present Tdap, MenACWY and HPV as a "bundle"
- Providers receive "report cards" with adolescent vaccination coverage rates
- Vaccination drives are held at school-based health centers

The table shows successful measures implemented at Denver Health, an integrated urban safety net healthcare system in Colorado that serves about 40% of the city's children, between 2004 and 2014.

Adapted from Farmar ALM, et al. *Pediatrics*. 2016;138:e20152653.

TABLE 4.8 — Increasing Adult Immunization Rates—The 4 Pillars Practice Transformation Program

Pillar 1—Convenient Vaccination Services

- Use every patient visit as an opportunity to vaccinate
- Offer open access/walk-in vaccination during office hours
- Hold express vaccination clinics outside of normal office hours
- Create a dedicated vaccination station

Pillar 2—Communication With Patients About the Importance of Vaccination and the Availability of Vaccines

- Train staff to discuss vaccines during routine processes (such as taking vital signs)
- Discuss the serious nature of vaccine-preventable diseases
- Promote vaccination of staff to set a good example
- Use telephone on-hold messages that advertise vaccine availability and promote vaccination
- Promote vaccination through posters, fliers, electronic message boards, websites, and social media
- Conduct outreach by email, phone, text, mail, health portal, and the like

Pillar 3—Enhanced Office Systems to Facilitate Vaccination

- Assess vaccination eligibility for every scheduled patient at the beginning of the day and discuss in daily huddles
- Assess immunizations as part of the vital signs when a patient is roomed and record outside vaccinations in the electronic health record
- Incorporate electronic health record prompts for vaccination into the workflow
- Incorporate standing orders for vaccination by nurses and/or medical assistants into the workflow
- Ensure sufficient vaccine inventory to accommodate increased immunizations
- Promote simultaneous vaccination (for example, offer other vaccines at the time influenza vaccine is being given)

Pillar 4—Motivation Through an Office Immunization Champion

- Set improvement goals and chart progress regularly, displaying results in a prominent location
- Provide ongoing feedback to staff using email, posted notices, announcements, or a combination of these (encourage, nudge, and cheer to keep the momentum going)

Continued

TABLE 4.8 — *Continued*

Pillar 4—Motivation Through an Office Immunization Champion (*Continued*)

- Report on progress at staff meetings or huddles; facilitate discussion to identify strategies that are working (or not working) and changes that need to be made
- Create a competition among the staff for the most vaccinations given
- Provide rewards for success, creating a fun-spirited environment that promotes vaccination across the practice

Adapted from Nowalk MP, et al. *Vaccine*. 2016;34:5026-5033.

- Aspirating back on the syringe after insertion and before injection is discouraged.[45]
- The best technique involves a direct, rapid plunge of the needle through the skin, followed by a rapid withdrawal after delivering the vaccine (the British call vaccine injections "jabs").
- Multiple vaccines can be given in the same limb but should be separated by 1 to 2 inches. Simultaneous administration by different personnel may minimize anticipatory anxiety.
- If there is movement or pulling away during an injection such that some of the vaccine does not make it into the patient (or is not retained), the dose should be considered invalid. In addition, the needle should be considered contaminated and should be discarded along with the syringe. For non-live vaccines, a new (full) dose should be given on the same day or as soon as possible thereafter; one exception is RZV, for which if a new full dose cannot be given on the same day, the new dose should be given ≥4 weeks after the invalid dose to avoid exceeding the standard dose of the adjuvant in the vaccine (see **Table 5.5** for recommendations regarding incomplete doses of COV). For live vaccines, a new (full) dose should be given on the same day or ≥28 days later to avoid interference (see *Chapter 5: General Recommendations—Rule 2*). If the infant spits or regurgitates a dose of RV, the dose is still considered valid. If a person sneezes after receiving LAIV, or if some of the liquid runs out of the nose, the dose is considered valid.

Routes

For *intramuscular* administration (**Figure 4.1**), the needle enters the skin at a 90° angle, penetrating deep enough to hit the muscle. Traction can be applied to the skin and subcutaneous tissue before injection and released after injection. Preferred sites, which differ by age, are the vastus lateralis muscle in the anterolateral aspect

TABLE 4.9— Screening Questions

Question	Example of Issues Addressed
Is the patient sick today?	Moderate or severe illness is a precaution for all vaccines
Does the patient have severe allergies to drugs, foods, vaccine components, or latex?	Severe allergy to a vaccine component is a contraindication for that vaccine
	Severe allergy to eggs is a contraindication for YFV
	Severe allergy to drugs (eg, neomycin) or food ingredients (eg, gelatin or baker's yeast) is a contraindication for certain vaccines (note that celiac disease is not a contraindication for yeast-containing vaccines)
	Severe allergy to latex is a contraindication for vaccines whose vials or syringes contain latex
	Severe allergy to polyethylene glycol or polysorbate-80 is a contraindication for certain COVID-19 vaccines
Has the patient had serious reactions to previous vaccinations?	Various contraindications and precautions for further doses
Is the patient on long-term aspirin or salicylate therapy?	Aspirin and salicylate therapy are contraindications for LAIV and precautions for VAR (theoretical risk of Reye syndrome)
Has the patient or a close family member had seizures or a brain or neurologic problem?	Evolving neurologic disorder is a precaution for pertussis-containing vaccines
	Person who is susceptible to seizures might be at risk for seizures associated with fever after vaccination
	Guillain-Barré syndrome within 6 wk of a previous dose of influenza vaccine or tetanus-containing vaccine is a precaution for further doses
Does the patient have a history of bowel obstruction?	History of intussusception is a contraindication for RV

Continued

TABLE 4.9 — *Continued*

Question	Example of Issues Addressed
Does the patient have asthma or another chronic medical condition (eg, lung, heart, kidney, or metabolic)?	Some chronic medical conditions are precautions for LAIV
	Special vaccines may be indicated
If the patient is a child between 2-4 y, has a health care provider diagnosed wheezing or asthma in the past year?	Asthma and wheezing are contraindications for LAIV in children 2-4 y
Does the patient have cancer, leukemia, a blood disorder, HIV infection, AIDS, tuberculosis, or any problem with the immune system?	Live vaccines are generally contraindicated in patients with immune impairment
	Special vaccines may be indicated
	History of thrombocytopenia or thrombocytopenic purpura is a precaution for MMR
	Active, untreated tuberculosis is a precaution for MMR and VAR
In the last 3 mo, has the patient received any treatment that might weaken his or her immune system, such as steroids, cancer chemotherapy, or radiation?	Live vaccines are generally contraindicated in patients with immune impairment
	Person may respond poorly to vaccination
Are there any family members who have problems with their immune system?	Person may be at risk for a heritable immune deficiency that would be a contraindication for live vaccines

Continued

TABLE 4.9 — *Continued*

Question	Example of Issues Addressed
Has the patient received blood transfusions or immune globulin in the past year?	Antibody-containing blood products can interfere with response to vaccination
	Person may have an undisclosed serious underlying illness
Is the patient pregnant or is there a chance she could become pregnant in the next 3 mo?	Pregnancy is generally a contraindication for live vaccines
	Pregnancy is an indication for influenza vaccine, RSV vaccine, and Tdap, and pregnant people should be up to date on COVID-19 vaccination
Has the patient received any other vaccines in the last 4 wk?	Certain live vaccines not given on the same day need to be separated by ≥4 wk
	MenACWY-D and PCV13 need to be separated by ≥4 wk in functionally and anatomically asplenic children
	MenACWY-D should not be given within 4 wk of DTaP in children at increased risk of invasive meningococcal disease
	Violating minimum intervals may invalidate doses

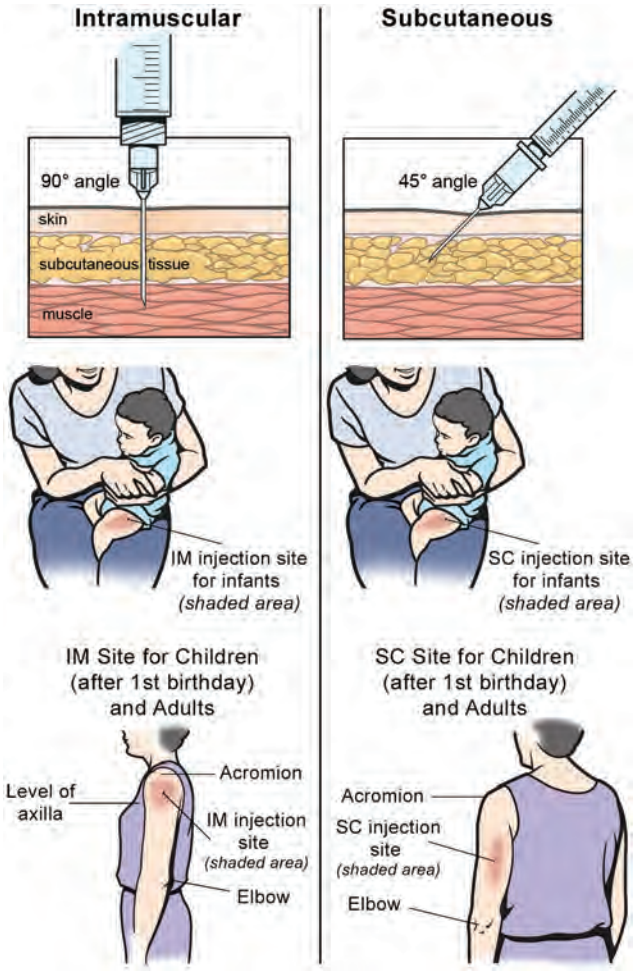
Adapted from Screening for vaccine contraindications and precautions. Immunize.org Web site. https://www.immunize.org/clinic/screening-contraindications.asp. Accessed July 12, 2023.

of the upper thigh and the deltoid muscle, in the upper, outer part of the arm above the armpit and below the acromion (the upper third of the arm should be avoided to reduce the risk of injecting the bursa and causing *shoulder injury related to vaccine administration*[46,47]). The required needle length varies by patient age (**Table 4.10**). The buttocks should not be used because the fat layer is too thick and damage to the sciatic nerve is possible.

For *subcutaneous* injections (**Figure 4.1**), the skin and subcutaneous tissue are pinched-up, and the needle is directed at a 45° angle. The preferred sites and needle length again vary with age (**Table 4.10**).

For infants, *oral* administration (**Figure 4.2**) of RV is best accomplished with the child lying in the feeding position in the parent's arms. The tip of the applicator is placed in the infant's mouth toward the inner cheek and slowly emptied until all the liquid is dispensed.

FIGURE 4.1 — Injection Technique



Adapted from Administering vaccines. Immunize.org Web site. https://www.immunize.org/clinic/administering-vaccines.asp. Accessed July 12, 2023.

TABLE 4.10 — Needle Type and Injection Site

	Intramuscular[a] (22- to 25-gauge)		Subcutaneous[b] (23- to 25-gauge)	
Age	Site	Needle (inch)	Site	Needle (inch)
0-28 d[c]	Anterolateral upper thigh	⅝	—	—
1-12 mo	Anterolateral upper thigh	1	Anterolateral upper thigh	⅝
1-2 y	Anterolateral upper thigh[d]	1 to 1¼	Anterolateral upper thigh or upper outer triceps	⅝
	Deltoid	⅝ to 1		
3-18 y	Deltoid[d]	⅝ to 1	Anterolateral upper thigh or upper outer triceps	⅝
	Anterolateral upper thigh	1 to 1¼		
≥19 y	Deltoid	Female or male <130 lbs (<60 kg): ⅝ to 1	Anterolateral upper thigh or upper outer triceps	⅝
		Female or male 130-152 lbs (60-69 kg): 1		
		Female 153-200 lbs (70-91 kg) or male 153-260 lbs (70-118 kg): 1 to 1½		
		Female >200 lbs (91 kg) or male >260 lbs (118 kg): 1½		

[a] The needle is inserted at a 90° angle. When using a ⅝-inch needle, the skin should be stretched tight to ensure that the muscle is reached.
[b] Skin and fatty subcutaneous tissue are bunched up and the needle is inserted at a 45° angle.
[c] Includes premature infants.
[d] Preferred site.

Adapted from Vaccine administration. CDC Web site. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/administration.html. Accessed July 12, 2023.

LAIV is supplied in a syringe-like sprayer for *intranasal* administration (**Figure 4.2**). The recipient should be in the upright position. The tip of the sprayer is inserted just inside the nose and the plunger is rapidly depressed until the dose-divider clip stops the plunger. The clip is then removed, and the remainder of the dose is given in the other nostril.

Two vaccines are approved for *intradermal* administration. idIIV, which was discontinued in 2017, was given using a micro-

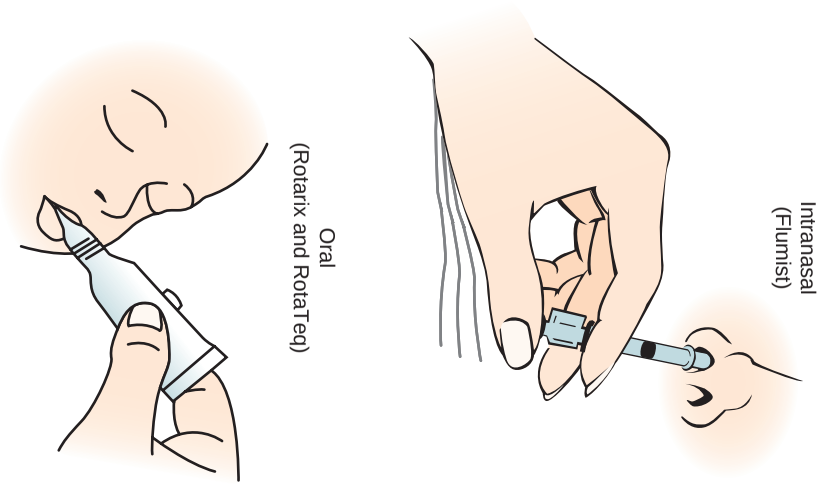


FIGURE 4.2 — Other Administration Techniques

Adapted from Administering vaccines. Immunize.org Web site. https://www.immunize.org/clinic/administering-vaccines.asp. Accessed July 12, 2023.

injection system supplied with the product. One type of smallpox vaccine (ACAM2000) is given with a bifurcated needle that is used to puncture the skin, drawing a small amount of blood. Gloves should be worn, and the site should be covered with gauze and a semipermeable dressing. Skin preparation is not required unless there is gross contamination, in which case soap and water should be used for cleansing. If alcohol is used, the skin must dry thoroughly before inoculation to prevent inactivation of the vaccine virus.

Jet injectors produce a narrow stream of liquid under high pressure, penetrating the epidermis and delivering vaccines into the subcutaneous tissue or muscle. They eliminate the threat of needlestick injury and are particularly amenable to mass vaccination campaigns. The only vaccine that is licensed in the US to be delivered in this fashion is Afluria (a brand of IIV, delivered by the PharmaJet Stratis Needle-Free Injection System).

Anxiety, Pain, and Fever

For infants, pain can be reduced by oral sucrose solution (50%) given directly into the mouth with a small syringe or administered on a pacifier. The "5 S's"—swaddling, side/stomach position, shushing, swinging, and sucking—also seem to work well.[48] For older children, stress and anxiety can be ameliorated by truthfully informing them what to expect before the visit occurs and by parental endorsement of vaccination as being valuable.[49] Parents should be allowed to comfort young children (rather than assist in restraining them) and should try to distract them by telling stories, playing music, or having them blow into pinwheels or imaginary candles. Technique is important: a quick "jab" into and out of the muscle is less painful than a slow injection with aspiration.[50] Stroking the adjacent skin before and during the injection may help, as may pressure applied to the site after withdrawal. For sequential injections, the least painful one should be given first. Topical anesthetics, such as eutectic mixture of local anesthetic (EMLA cream) or vapocoolant sprays, should be considered for patients who are phobic or extremely anxious about the injection.[51]

Acetaminophen may be considered as needed for analgesia or fever control after immunization, but prophylactic use is not recommended, even in children with a history of febrile seizures.[52] There is evidence that prophylactic acetaminophen, as well as ibuprofen, can interfere with antibody responses,[53,54] although priming does not appear to be affected and there is no evidence of decreased protection.[55,56] Fortunately, high fevers and medical attention for fever or other symptoms after vaccination are rare.

Emergencies

Acute emergencies after routine vaccine administration are rare. A Vaccine Safety Datalink study from 2009 to 2011 identified only 33 cases of anaphylaxis (and no related deaths) that occurred after 25,173,965 vaccine doses, for a rate of 1.3 per million.[57] The AAP recommends that children be observed in the office for 15 minutes after vaccination to monitor for reactions. Both the AAP and ACIP suggest that providers consider monitoring adolescents for syncope for 15 minutes after routine vaccination. The benefits of rapid, mass vaccination programs, such as "drive-by" influenza vaccine clinics, probably far outweigh the risks of curtailing any medical observation period. The ACIP recommends that all vaccine providers be certified in cardiopulmonary resuscitation and that offices have an emergency plan in place.

Standing orders for the medical management of vaccine reactions, including anaphylaxis, in children and adults should be available in the office. Exemplary standing orders and equipment lists for children (http://www.immunize.org/catg.d/p3082a.pdf) and adults (http://www.immunize.org/catg.d/p3082.pdf) are available from Immunize.org (accessed July 12, 2023).

Syncope

Vasovagal reactions are most common in adolescents and young adults, particularly females. About 60% occur within 5 minutes of vaccination and approximately 90% occur within 15 minutes; a minority of cases result in hospitalization, although there have been reports of serious injury such as skull fracture. After the advent of the adolescent vaccine platform—Tdap and MenACWY in 2005 and HPV in 2006—there was a sharp increase in reported syncopal episodes related to vaccination,[58] and clusters of syncope and other anxiety-related events have been reported following administration of COV.[59] However, the absolute number of reported episodes of syncope after any vaccination remains low—only 32,000 reports in VAERS from 1990 to 2023, a period when hundreds of millions of vaccine doses were given.[60] HCP should be aware of predisposing conditions (eg, needle and pain phobia) and presyncopal symptoms (eg, light-headedness, dizziness, pallor, diaphoresis, cold extremities, nausea, weakness, visual disturbance). At-risk individuals should be encouraged to sit or lie down; a cool, damp cloth to the face and neck may help. If syncope does occur, the patient should be protected as much as possible from fall injury and should be placed supine with the legs raised until symptoms abate.

Anaphylaxis

Anaphylaxis is a medical emergency that usually occurs within minutes when the patient is still likely to be within reach of medical personnel. Signs and symptoms include:

- Flushing, warmth, urticaria, erythema, soft tissue edema, pruritus
- Dry mouth, swelling of the lips, tongue and throat, sneezing, congestion, rhinorrhea

- Hoarseness, stridor, cough, dyspnea, chest tightness, wheezing, cyanosis
- Tachycardia, hypotension, weak pulse, dizziness, shock, cardiovascular collapse
- Crampy abdominal pain, nausea, vomiting, diarrhea

For patients with signs of anaphylaxis, the emergency medical system should be activated. Vital signs should be monitored. If the blood pressure is low, elevate the legs; if breathing is difficult, elevate the head and monitor the airway. Administer epinephrine IM in the lateral thigh at a dose of 0.01 mg/kg; the solution is supplied at a concentration of 1 mg/mL (formerly labeled "1:1000"), so the dose is 0.01 mL/kg (maximum 0.3 mL in children, 0.5 mL in adolescents and adults). A dose can be repeated every 5 to 15 minutes if necessary for up to 3 total doses. In addition, an antihistamine such as diphenhydramine can be given at a dose of 1-2 mg/kg (maximum 50 mg) PO, IM, or IV. Patients should be observed for several hours and may require intensive care, including airway maintenance, oxygen, and blood pressure support with isotonic intravenous fluids and vasopressors. Biphasic reactions may account for up to 50% of fatal cases. Asymptomatic intervals vary widely and can be as long as 24 hours. All patients with mild or severe anaphylaxis should be referred to an allergist prior to future vaccinations and should carry an epinephrine autoinjector.

Coding, Billing, and Costs

Billing for immunization services is complex. Providers should be aware that there are 3 basic systems in use:

- *Current Procedural Terminology (CPT) Codes*—These codes describe the *procedures* or *services* performed during a visit. The *visit itself* usually falls under evaluation and management codes for preventive medicine services performed in the outpatient setting, provided the immunization occurs in the context of a comprehensive "checkup." There are corresponding codes for the *vaccines themselves*. There are also codes for the *administration* of the vaccines, which are based on the components of the vaccine, defined as all antigens that prevent disease caused by one organism. The code for the first or only component for patients through 18 years of age, by any route, and with counseling is 90460; additional components are reported with 90461. If a visit is *only* for immunization (eg, before travel), most offices bill only for the vaccine and the administration, using the vaccine product CPT codes and the administration codes. If evaluation and management services unrelated to vaccination are performed during the vaccine visit, those services receive separate codes.
- *International Classification of Diseases (ICD) Codes*—These codes describe the *reason* for the service (for simplicity, the suffix "-Clinical Modification", as in "ICD-9-CM", is not used here). The Ninth Edition, ICD-9, was used in the US from 1979 to 2015, when providers were required to switch to the Tenth Edition (ICD-10). ICD-9 codes for vaccination were very specific. For example, the code that accompanied the vaccine Hib-T was V03.81, or "need for prophylactic vaccination and inoculation against *H influenzae* type b." In ICD-10, the code Z23 is reported as the reason for *all vaccine related encounters* for *all vaccines given*. In ICD-9, the *visit itself* usually fell under V20.2 (routine infant or child health check beyond the first month of life); in ICD-10, the code is Z00.129 (encounter for routine child health examination without abnormal findings).
- *National Drug Codes (NDCs)*—Many payers are now requiring that National Drug Codes (NDCs) for vaccines be submitted along with CPT and ICD codes. The NDC is a unique 10-digit, 3-segment number. The first segment identifies the company that makes, repacks, or distributes the product. The second segment identifies the product, strength, dosage form, and formulation. The third segment identifies the package size and type. Sometimes an asterisk appears as a placeholder. NDCs can easily be found by searching the National Drug Code Directory[61] by proprietary name, active ingredient, or company name. It is also found on the package insert in the "How Supplied" section.

All components of all services should be clearly documented in the medical record. If the practice receives vaccines free-of-charge through VFC, it cannot bill for the *vaccine itself*, but it can bill for *administration of the vaccine* and for the *visit itself* (if it is a "checkup").

Providers can purchase vaccines from the manufacturer, a third-party distributor, or a vaccine purchasing group (VPG). VPGs establish agreements with manufacturers that exchange product loyalty for discounts; members benefit from discounted prices as well as cost offsets from the distribution of administration fees paid by the manufacturer.[62] This can be particularly helpful for small practices, since the price paid to the VPG is not based on volume.

The vaccine tables in *Section B: Diseases and Vaccines* contain information on the purchase price for commonly used vaccines. The public sector cost is the contracted price between the CDC and the manufacturer, which changes from year to year.[63] The estimated private sector cost is most useful for highlighting relative differences between products. However, these data can be misleading. In a study conducted in 2007, 76 private practices in five states supplied data on their purchase price for vaccines for privately insured children.[64] Significant variation was seen—for example, some practices paid

$8.77 per dose for Infanrix while others paid $21.60. Variables associated with the price paid included the size of the practice, its location, use of purchasing cooperatives or buying groups, and the availability of discounts and rebates. Large variation was also seen in reimbursement—for example, some practices were reimbursed $45.32 per dose of ActHIB, others $15.33. Reimbursement for first-dose vaccine administration ranged from $0 to $26.55. In negotiating contract prices with private payers, physicians must consider all the costs involved in providing vaccines.[65]

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General Recommendations

Ten Simple Rules by Which to Vaccinate

The following general rules, derived from the Centers for Disease Control and Prevention's General Best Practice Guidelines for Immunization,[1] are offered as advice for day-to-day practice. See *Chapter 12: COVID-19* for additional information about COVID-19 vaccines.

Rule 1—Any Vaccines Can Be Given on The Same Day

Exceptions

- VAR and live, attenuated, smallpox vaccine (ACAM-2000) should not be given at the same time.
- Use of non-live, viral, non-replicating smallpox vaccine (Jynneos) should be prioritized over ACAM-2000 when co-administering COV and an orthopox virus vaccine.
- PCV and PPSV23 should not be given at the same time.
- MenACWY-D and PCV13 should not be given at the same time in persons with anatomic or functional asplenia and/or HIV infection (this rule does not apply to persons with complement deficiency).

Simultaneous administration of all vaccines for which a person is eligible at a given visit is encouraged to achieve optimal protection without delay and to increase the likelihood that all recommended vaccine series will be completed. There are no vaccines that cannot be given at the same time, considering both reactogenicity and immunogenicity, with the above exceptions. The concern with ACAM-2000 and VAR is the possibility of increased complications from the smallpox vaccine; for ACAM-2000 and COV it is the potential risk of myocarditis and pericarditis. People, particularly adolescent or young adult males, who are recommended to receive both COV and orthopox virus vaccine should consider separating them by 4 weeks; however, if the risk of mpox or severe COVID-19 is increased, administration of both vaccines should not be delayed. For simultaneous administration of MenACWY-D and PCV13, the concern is reduced response to *S pneumoniae.* For this reason, MenACWY-D should not routinely be given to asplenic children 9 to 23 months of age. For asplenic persons ≥2 years of age who

are to receive both PCV13 and MenACWY-D, all recommended doses of PCV13 should be given first and MenACWY-D should be given ≥4 weeks later.

Vaccines administered on the same day must be given at separate sites and should never be mixed in the same syringe unless the products are specifically labeled for that purpose. Combination vaccines can reduce the high number of shots that are now unavoidable at certain visits during childhood.

There is an increased risk of febrile seizures when IIV and PCV13 are given on the same day to children <5 years of age (see *Chapter 7: Addressing Concerns About Vaccines—Febrile Seizures*).[2] The magnitude of the risk is <1 per 1000 children vaccinated, and the Advisory Committee on Immunization Practices (ACIP) considers simultaneous administration acceptable.[3]

Rule 2—Live Vaccines Not Given on the Same Day Should Be Separated by ≥28 Days

Exceptions

- YFV may be given at any time after single-antigen measles vaccine.
- Live oral vaccines (RV, Ty21a, cholera, and adenovirus) may be given at any time in relation to any other live vaccines (cholera vaccine should be given ≥8 hours before Ty21a).

Different live vaccines may be given on the same day, with the exception noted in *Rule 1*. The live oral cholera and typhoid vaccines (Ty21a) are given ≥8 hours apart to minimize the risk that the cholera vaccine buffer will interfere with Ty21a. If, for some reason, 2 or more injectable live vaccines cannot be given on the same day, they should be separated by ≥28 days (the concern here is that replication of the first vaccine will interfere with replication of the second); for YFV, the minimum interval is 30 days, and travel should be postponed if this minimal interval cannot be established. Live vaccines given at mucosal surfaces are exempt from this requirement; thus, for example, Ty21a may be given at any time after MMR. The only exception is LAIV—if not given on the same day as an injectable live vaccine, administration of these 2 vaccines should be separated by ≥28 days.

The 4-day grace period (see *Chapter 3: Standards, Principles, and Regulations—Mandates and Exemptions*) does *not* apply to minimum intervals between live vaccines.

Rule 3—Different Non-Live Vaccines May Be Given at Any Time With Respect to Each Other

Exceptions

- MenACWY-D should not be given within 4 weeks of DTaP in children at risk for invasive meningococcal disease.

- See *Rule 1* regarding simultaneous administration.

Simultaneous administration, or, better yet, the use of combination vaccines, is preferred because of improved compliance. However, there is no evidence that sequential administration of different non-live vaccines, or live and non-live vaccines, at any time interval interferes with immunogenicity or increases reactogenicity. The problem with sequential use of MenACWY-D after DTaP is that meningococcal responses are impaired.

Rule 4—Doses of the Same Vaccine Must Be Separated by Minimum Intervals

Exceptions

- There is a 4-day grace period for non-live vaccines.
- Some situations call for early or accelerated schedules.

Proper spacing of doses within a given vaccine series is essential for optimal immune responses. For this reason, doses of the same vaccine administered sooner than the specified minimum interval are considered invalid. The 4-day grace period (see *Chapter 3: Standards, Principles, and Regulations—Mandates and Exemptions*) applies to non-live vaccines (except RAB) but does not apply to most live vaccines (see *Rule 2*). Doses that are invalid because they violated the minimum interval should be repeated, but the minimum interval should elapse between the invalid dose and the repeat dose to insure a proper immune response. There are somewhat confusing recommendations along these lines for HepA. If the second dose in the series is given <6 months after the first dose, the second dose is invalid and a valid second dose should be given ≥6 months after the invalid second dose. However, if a third dose has already been given ≥6 months after the first dose (regardless of when the invalid second dose was given), the series is considered complete. This illustrates the difference between *how long you should wait before giving the next dose* and *how you should interpret doses that have already been given.*

There are circumstances where early or accelerated schedules can be used, such as for catch-up immunization or impending international travel. However, even here the minimum intervals should be followed. **Table 5.1** shows the recommended minimum intervals for routinely used vaccines.

One caveat: *a minimum interval is a minimum interval except when it is not.* Here are some examples:

- The minimum interval between doses 3 and 4 of DTaP is 6 months. However, if Dose 4 is given ≥4 months after Dose 3, it is considered valid. This is a "special grace period" of 2 months that is applied when retrospectively assessing immunization status. In other words, if you are *retrospectively* assessing the status of a 15-month-old who received DTaP at 2, 4, 6, and 10 months of age, he would be considered up to date. In fact, the

TABLE 5.1 — Minimum Ages and Intervals for Routine Vaccines[a]

Vaccine	Dose Number	Age		Interval to Next Dose	
		Recommended	Minimum	Recommended	Minimum
Dengue	1	9-16 y	9 y	6 mo	5 mo after age at Dose 1
	2	9-16 y	9 y 5 mo	6 mo	5 mo after age at Dose 2
	3	9-16 y	9 y 10 mo	—	
DTaP	1	2 mo	6 wk	8 wk	4 wk
	2	4 mo	10 wk	8 wk	4 wk
	3	6 mo	14 wk	6-12 mo	6 mo[b]
	4	15-18 mo	15 mo	3 y	6 mo
	5	4-6 y	4 y	—	—
HepA	1	12-23 mo	12 mo	6-18 mo	6 mo[c]
	2	≥18 mo	18 mo	—	—
HepB[d]	1	Birth	Birth[e]	4 wk-4 mo	4 wk
	2	1-2 mo	4 wk	8 wk-17 mo	8 wk[f]
	3	6-18 mo	24 wk	—	—
Hib	1[g]	2 mo	6 wk	8 wk	4 wk
	2	4 mo	10 wk	8 wk	4 wk
	(3)[h]	6 mo	14 wk	6-9 mo	8 wk
	4	12-15 mo	12 mo	—	—
HPV9 (2-dose)[i]	1	11-12 y	9 y	6-12 mo	5 mo
	2	11-12 y (plus 5 mo)	9 y 5 mo	—	—
HPV9 (3-dose)	1	11-12 y	9 y	8 wk	4 wk
	2	11-12 y (plus 2 mo)	9 y 1 mo	4 mo	12 wk[j]
	3	11-12 y (plus 6 mo)	9 y 5 mo	—	—
IIV	1[k]	≥6 mo (annual)	6 mo[l]	4 wk	4 wk
IPV	1	2 mo	6 wk[m]	8 wk	4 wk[m]
	2	4 mo	10 wk	8 wk-14 mo	4 wk
	3	6-18 mo	14 wk	3-5 y	6 mo
	4[n]	4-6 y	4 y	—	(6 mo)[n]
LAIV	1[k]	2-49 y (annual)	2 y[o]	4 wk	4 wk
MenB-4C[p]	1	16-18 y	10 y	4 wk	4 wk
	2	16-18 y (plus 1 mo)	10 y 1 mo	—	—

Continued

TABLE 5.1 — *Continued*

Vaccine	Dose Number	Age		Interval to Next Dose	
		Recommended	Minimum	Recommended	Minimum
MenB-FHbp (2-dose)[p,q]	1	16-18 y	10 y	6 mo	6 mo
	2	16-18 y (plus 6 mo)	10 y 6 mo	—	—
MenB-FHbp (3-dose)[p]	1	16-18 y	10 y	1-2 mo	4 wk
	2	16-18 y (plus 1 mo)	10 y 1 mo	4-5 mo	4 mo[r]
	3	16-18 y (plus 6 mo)	10 y 6 mo	—	—
MenACWY[s]	1	11-12 y	2 mo[l,t]	4-5 y	8 wk
	2	16 y	11 y 2 mo	—	—
MMR	1	12-15 mo	12 mo	3-5 y	4 wk[u]
	2	4-6 y	13 mo	—	—
PCV13, PCV15, or PCV20[v]	1[g]	2 mo	6 wk	8 wk	4 wk[w]
	2	4 mo	10 wk	8 wk	4 wk[w]
	3	6 mo	14 wk	6 mo	8 wk[w]
	4	12-15 mo	12 mo	—	(8 wk)[v]
PPSV23[v]	1	—	2 y	5 y	5 y
	2	—	7 y	—	—
RV1 and RV5[x]	1	2 mo	6 wk	8 wk	4 wk
	2	4 mo	10 wk	(8 wk)	(4 wk)
	(3)	6 mo	14 wk	—	—
RSV[y]	1	≥60 y[z]	60 y[z]	—	—
RZV	1	≥50 y[A]	50 y	2-6 mo	4 wk
Td	1	11-12 y[B]	7 y	10 y	5 y
Tdap	1	≥11 y	7 y[C]	—	—
VAR	1	12-15 mo	12 mo	3-5 y	12 wk[t,D]
	2	4-6 y	15 mo	—	—

ACIP, Advisory Committee on Immunization Practices

[a] Age means that the individual has passed one mark in time but has not yet reached the next relevant mark (see *Front Matter—Conventions Used in This Book*). For example, "2 mo" (2 months of age) means at or beyond the 2-mo birthday but not yet at the 3-mo birthday. Age intervals are indicated by a hyphen; thus, "4-6 y" means from the *4th birthday until the day before the 7th birthday*, and "4 wk-4 mo" means *from the 29th day of life until the day before the 5-mo birthday*. *Weeks* are 7 d. Under 4 mo, *months* are 28 days; at 4 mo and beyond, *months* are *calendar months*, in which case the interval is to the same date in the appropriate month. For example, for an infant vaccinated on January 6, an interval of 6 mo would be on July 6. See *Chapter 6: Vaccination in Special Circumstances* for recommendations in non-routine situations.

[b] Dose 4 does not need to be repeated if given ≥4 mo after Dose 3 (see *Rule 4*).

[c] See text regarding HepA.

Continued

TABLE 5.1 — *Continued*

[d] Infants who receive a birth dose of HepB and then 3 doses of a HepB-containing combination vaccine may receive 4 total doses of HepB. In this situation, Dose 4 of HepB must be given at ≥24 wk and ≥16 wk after Dose 1, but there is no specified minimum interval between Doses 3 and 4.

[e] Combination products cannot be used for the birth dose.

[f] Dose 3 should be given ≥16 wk after Dose 1. A 2-dose schedule (1 mL at 0 and 4-6 mo) of Recombivax HB is available for persons 11-15 y, and Heplisav-B is given as a 2-dose schedule (0.5 mL at 0 and 1 mo) to persons ≥18 y.

[g] Children receiving Dose 1 after 6 mo require fewer doses.

[h] A dose at 6 mo is not necessary if Hib-OMP is used for Doses 1 and 2.

[i] A 2-dose schedule of HPV9 is recommended for healthy persons 9-14 y (immunocompromised persons and those 15-45 y should receive the 3-dose schedule). If 2 doses are given <5 mo apart, a third dose should be given ≥4 mo after the second dose. The 2-dose recommendation is "retroactive", meaning that a healthy person 9-14 y who received 2 doses of HPV9 separated by ≥5 mo is considered complete, even if the doses were given before the 2016 recommendations were released. Also, the 2-dose regimen may be used if the first dose was given at 9-14 y.

[j] Dose 3 should be given ≥5 mo after Dose 1.

[k] Two doses separated by ≥4 wk are required for children <9 y who are being immunized for the first time (if a child turns 9 y before the second dose is given, that dose becomes unnecessary).

[l] The minimum age differs by product.

[m] Minimum age and minimum intervals during the first 6 mo of life should only be used if the child is at risk of imminent exposure to poliovirus.

[n] Dose 4 is not necessary if Dose 3 was given at ≥4 y and ≥6 mo after the previous dose. A fifth dose is needed if all previous doses were given before 4 y (the final dose of IPV should be given at ≥4 y regardless of the number of previous doses). This would apply, for example, if a child received 4 doses of IPV as DTaP-IPV/Hib by 18 mo.

[o] If LAIV is given to a child 6 mo to 2 y in error, the dose is considered valid.

[p] MenB may be given based on shared clinical decision-making.

[q] A 2-dose schedule of MenB-FHbp may be used in persons who are not at high risk for invasive meningococcal disease. If Dose 2 is given <6 mo after Dose 1, a third dose should be given ≥6 mo after Dose 1.

[r] Dose 3 should be given ≥6 mo after Dose 1.

[s] Routine (one-time) revaccination is recommended at 16 y for adolescents who received Dose 1 at 11-12 y and at 16-18 y for those who received Dose 1 at 13-15 y. MenACWY is not routinely recommended for unvaccinated persons 19-21 but may be administered as a catch-up vaccination.

[t] MenACWY-CRM is licensed for use in infants as young as 2 mo and MenACWY-D as young as 9 mo. MenACWY-T is not licensed under 2 y.

[u] The minimum interval is 12 wk if MMRV is used.

[v] See **Figure 6.1** for use of pneumococcal vaccines in high-risk persons.

[w] At <12 mo, the minimum interval between doses of PCV is 4 wk. At ≥12 mo, the minimum interval is 8 wk.

[x] RV1 is given as a 2-dose and RV5 as a 3-dose series. The labeled schedules differ from the ACIP recommendations (ACIP recommendations are usually followed in practice). According to the RV1 package insert (November 2022), Dose 1 may be given at 6-20 wk, and no dose should be given beyond 24 wk. According to the RV5 package insert (April 2023), Dose 1 should be given at 6-12 wk, and no dose should be given beyond 32 wk. ACIP recommends that Dose 1 of either vaccine be given at 6 wk-14 wk 6 d and all doses be given by 8 mo 0 d. If any dose in the series is RV5 or unknown, a total of 3 doses should be given.

[y] RSV vaccine may be given to older adults based on shared clinical decision-making.

[z] RSV (Pfizer) may be given to pregnant women at any age.

[A] If Dose 1 of RZV is given at 18-49 y, it is considered valid, but Dose 2 should be given at ≥50 y.

[B] Tdap should be used routinely at 11-12 y rather than Td.

[C] The minimum labeled age for Adacel and Boostrix is 10 y, but either product may be used beginning at 7 y for children whose pertussis immunization is incomplete (use of either product at 7-9 y is off-label). Children who receive a dose at 7-9 y should receive a second dose at 11-12 y, as per the routine schedule. Administration of >2 doses of either product is off-label.

[D] If the second dose is given ≥28 d after the first dose, this should be considered valid and should not be repeated. The minimum interval is 4 wk if the series is initiated ≥13 y. For immunocompromised persons such as those with HIV infection, doses given <12 wk apart are considered invalid.

Adapted from General best practice guidelines for immunization. CDC Web site. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html. Accessed July 14, 2023.

4-day grace period also applies in this situation; in other words, he would be considered up-to-date even if Dose 4 was given 4 days before he turned 10 months of age. The "special grace period" of 2 months cannot be used *prospectively* to schedule vaccinations. In other words, if you are seeing a 10-month-old who received DTaP at 2, 4, and 6 months of age, you cannot give him Dose 4 now—you have to wait until he is at least 12 months of age.

- Under 13 years of age, the minimum interval between doses of VAR is 12 weeks, but if Dose 2 is given ≥28 days after Dose 1, it is considered valid (unless the person is immunocompromised).

The minimum interval between doses of combination vaccines is determined by the component antigen with the longest minimum interval.

Rule 5—All Vaccines Have a Minimum Age

Exception

- There is no minimum age for HepB and RAB.

Live parenteral vaccines can be inactivated by maternal antibody, which can persist for as long as a year. Maternal antibody can also interfere with responses to non-live vaccines.[4,5] Live oral vaccines such as RV have not been studied in children <6 weeks of age. For Hib, the issue is that administration in the first 6 weeks of life might induce immunologic tolerance. HepB may be given at birth. During measles outbreaks when cases are occurring in infants <1 year of age, and for impending travel outside the US, measles vaccine can be given as early as 6 months of age. Similarly, HepA may be given to infants as young as 6 months of age who are traveling to endemic areas. For both MMR and HepA, the minimum age is 12 months, so doses given between 6 and 12 months of age do not count as part of the routine series. BCG may be given at birth, but this vaccine is not used in the US.

The 4-day grace period applies to the minimum age for both live and non-live vaccines. The minimum age for combination vaccines is determined by the component antigen with the oldest minimum age. **Table 5.1** shows the recommended minimum age for routinely used vaccines.

Rule 6—Do Not Restart a Vaccine Series if the Recommended Dosing Interval Is Exceeded

Exception

- The Ty21a series may need to be repeated if not completed in 3 weeks.

If there is a lapse in the administration of sequential doses of a given series, simply begin where the series was suspended, keeping in mind the minimum intervals between doses. The only exception to this rule is Ty21a, for which some experts recommend repeating the series if all 4 doses are not given within 3 weeks.

Rule 7—Similar Vaccines Made by Different Manufacturers Are Generally Interchangeable

Exceptions

- The same MenACWY product is preferred for all doses in the series for high-risk infants 2 to 23 months of age (MenACWY-CRM should be used for all 4 doses in an infant with asplenia).
- The same MenB product should be used for all doses in the series.
- Authorization to use different COV products interchangeably varies by history, age, and product.

Sufficient data exist to consider many of the vaccines made by different manufacturers interchangeable in a given series. In mixing and matching vaccine brands in a series, the brand with the highest number of doses wins; thus, for example, if Hib-T (ActHIB or Hiberix) is used as Dose 1 or Dose 2 in the infant primary series, 3 total Hib doses should be given (an all-Hib-OMP [PedvaxHIB] schedule requires only 2 doses for the primary series). For RV, if any one of the doses in the series was RV5 or unknown, 3 total RV doses should be given (an all-RV1 schedule requires only 2 doses). If 2 doses of IIV are being given in the same season (as, for example, in the case of a 2-year-old being immunized for the first time), the available brands are considered interchangeable, provided they are used within their respective labels. For some vaccines (DTaP is an example), there is a preference for the same product for the entire series; however, vaccination should not be deferred if the same product is not available or if the previous products are not known.

Keep in mind that different vaccines for the same disease are not strictly interchangeable. For example, the two available vaccines against *N meningitidis* serogroup B—MenB-4C and MenB-FHbp—differ in composition; in fact, mixed schedules are considered invalid (doses of the same product should be given at appropriate times to complete the series for that product). Likewise, DTaP and Tdap may contain the same antigens (in differing amounts) but are used for different purposes (respectively, primary and booster immunization against pertussis).

The rules for COV as of October 2023 are best understood by referring to **Figures 12.6** and **12.7**.

Rule 8—There Is No Harm in Vaccinating a Person Who Has Already Had the Disease or the Vaccine

Exceptions

- AVA is more reactogenic in persons who have had anthrax disease.
- Administering too many doses of PPSV23, tetanus toxoid, or diphtheria toxoid can cause increased reactogenicity.

For some diseases, vaccination is *indicated* even if the person has had the disease. For example, infants <2 years of age who had invasive *H influenzae* type b infection should still be vaccinated because infection at that age does not confer immunity. Zoster vaccine is specifically designed to be given to people who have had VZV infection and should be given to people who have had zoster. For *S pneumoniae*, the vaccine protects against multiple serotypes, so prior infection with a particular serotype does not obviate the need for vaccination. Along similar lines, HPV should be given to women who have had cervical dysplasia or other evidence of human papillomavirus infection, not to alter the course of infection (which it does not do) but to protect against other serotypes. Influenza vaccine must be given each year whether or not the person has had influenza in the past. Some experts recommend pertussis vaccine for children who have had well-documented pertussis (culture positive or epidemiologically linked to a culture-positive case) because the duration of natural immunity is not known. Clinicians often wonder if a child with a questionable history of chickenpox or varicella vaccination should receive the vaccine. The motto here is—*when in doubt, vaccinate*! With chickenpox, as with most other diseases, there is no evidence of harm if a person who has had the disease receives a dose of the corresponding vaccine. Likewise, excess vaccine doses are not associated with any unexpected adverse health events.[6]

Rule 9—Some Vaccines Should be Deferred After Administration of Antibody-Containing Products

Exceptions

- MMR and VAR should not be deferred in postpartum women who received antibody-containing blood products during pregnancy, including anti-Rho(D) globulin.

Antibodies contained in blood products can inactivate injectable live vaccines and reduce effectiveness or "take." Several factors play into whether deferral is recommended and how long to wait before giving a vaccine. One factor is the product itself—immune globulin is likely to contain more antibody than packed red cells, necessitating a longer delay. Another factor is the specific antibody content of the product; for example, blood products in the US are unlikely to contain antibodies to yellow fever virus, so this vaccine (as well as the dengue vaccine, which is based on the yellow fever vaccine) can be given at any time with respect to blood products. Finally, passively transferred antibodies are unlikely to inactivate vaccines delivered at mucosal surfaces, such as LAIV, RV, adenovirus, Ty21a, and cholera vaccine.

Table 5.2 shows the recommended intervals between blood product administration and MMR, VAR, and MMRV. Here are a few other things to know:

- If a child has already received MMR, VAR, or MMRV, 14 days should elapse before an antibody-containing blood product is given, because the vaccine viruses must still replicate to induce immunity. If an antibody-containing blood product is given during the 14-day window, the vaccine dose is considered invalid and should be repeated at the appropriate minimum interval (**Table 5.1**).
- An infant's first dose of RV should not be deferred if the mother received a blood product while pregnant.
- Monoclonal antibody products such as palivizumab (Synagis) and nirsevimab (Beyfortus), which are directed against respiratory syncytial virus, do not interfere with live vaccines.
- Serological testing and administration of dengue vaccine should be delayed 12 months after receipt of antibody-containing blood products (proof of previous dengue infection is mandatory before vaccination, and passively acquired immune globulin can cause false-positive serological results).

While there is some evidence that passive antibody can interfere with the immunogenicity of non-live vaccines, there is no reason to defer administration of most non-live vaccines after administration of antibody-containing products. People who previously received anti–SARS-CoV-2 monoclonal antibodies or convalescent plasma may receive COV at any time.

Rule 10—Live Vaccines May Be Used in Households With Pregnant and Immunocompromised Persons

Exceptions

- Live, attenuated, smallpox vaccine (ACAM-2000) should not be given to close contacts of pregnant or immunocompromised persons.
- LAIV should not be given to close contacts of profoundly immunosuppressed persons.

There is no evidence that MMR or YFV can be transmitted from a vaccinee to another person. VAR can be transmitted, but only if the vaccinee develops skin lesions after vaccination (in this case, direct contact with immunocompromised persons should be avoided until the skin lesions resolve). While transmission of RV, adenovirus, Ty21a, and cholera vaccine by the fecal-oral route is a

TABLE 5.2 — Interval Between Receipt of Antibody-Containing Products and Administration of MMR, VAR, or MMRV[a]

Product (Route)	Indication	Usual Dose	Duration of Deferral
Monoclonal antibody			
Palivizumab (IM)	Prevention of RSV disease	15 mg/kg	None[b]
Nirsevimab (IM)	Prevention of RSV disease	Neonates and infants <5 kg: 50 mg ≥5 kg: 100 mg Vulnerable children through their second RSV season: 200 mg	None[b]
Immune globulin			
Immune globulin (IM)	Hepatitis A prophylaxis, postexposure and short-term travel	0.1 mL/kg	6 mo
	Hepatitis A prophylaxis, long-term travel	0.2 mL/kg	6 mo
	Postexposure prophylaxis for measles, not pregnant or immunocompromised	0.5 mL/kg	6 mo
Immune globulin (IV)[c]	Replacement therapy for immune deficiency[d]	400 mg/kg	8 mo
	Postexposure prophylaxis for varicella[d]	400 mg/kg	8 mo
	Postexposure prophylaxis for measles[d]	400 mg/kg	8 mo
	Immune thrombocytopenia	400 mg/kg	8 mo
		1 g/kg	10 mo
	Kawasaki disease[e]	2 g/kg	11 mo
Hyperimmune globulin			
CMV immune globulin (IV)	Prevention of CMV disease in transplant patients[d]	150 mg/kg (maximum)	6 mo
HBIG (IM)	Postexposure prophylaxis for hepatitis B	0.06 mL/kg	3 mo
HRIG (IM and intrawound)	Postexposure prophylaxis for rabies	20 IU/kg	4 mo
RhoGAM (IM)	Prevention of maternal Rh isoimmunization	300 mcg	None[f]
TIG (IM)	Postexposure prophylaxis for tetanus	250 units	3 mo
VariZIG (IM)	Postexposure prophylaxis for varicella	125 IU/10 kg (max 625 IU)	5 mo
BabyBIG (IV)	Treatment of infant botulism	1 mL/kg	6 mo
Other blood products			
Red blood cells, washed	Transfusion (IV)	10 mL/kg	None
Red blood cells, adenine-saline added	Transfusion (IV)	10 mL/kg	3 mo
Red blood cells, packed	Transfusion (IV)	10 mL/kg[g]	6 mo
Whole blood	Transfusion (IV)	10 mL/kg	6 mo
Plasma or platelet products	Transfusion (IV)	10 mL/kg	7 mo

Continued

TABLE 5.2 — *Continued*

CMV, cytomegalovirus; HBIG, hepatitis B immune globulin; HRIG, human rabies immune globulin; IM, intramuscular; IV, intravenous; RSV, respiratory syncytial virus; TIG, tetanus immune globulin

[a] Other live vaccines (LAIV, RV, adenovirus, Ty21a, and YFV) do not need to be deferred after receipt of antibody-containing blood products (no data are available on use of cholera vaccine after receipt of blood products, but interference would be unlikely). Passively acquired antibodies would be unlikely to inactivate vaccines given at mucosal surfaces, such as RV, adenovirus, LAIV, and Ty21a. In addition, blood products in the US are unlikely to contain substantial amounts of antibody to *S typhi* and yellow fever virus, and blood products would be unlikely to have antibodies to circulating influenza strains. Testing for dengue antibodies, which is required before dengue vaccination (the vaccine is only indicated in people with prior DENV infection), should be delayed for 12 mo after receipt of antibody-containing products (risk of detecting passively-acquired antibodies and erroneously concluding that the person has had prior DENV infection).

[b] These are monoclonal products that do not contain antibody to childhood vaccine viruses.

[c] Patients who receive immune globulin subcutaneous (IGSC) at regular (eg, 1-4 week) intervals should not be vaccinated while on therapy. If IGSC therapy is discontinued and vaccination is not otherwise contraindicated, vaccination may occur ≥8 months later.

[d] Live viral vaccines may be contraindicated in patients who are immune deficient or qualify for postexposure prophylaxis for other reasons.

[e] Multisystem inflammatory syndrome in children resulting from COVID-19 is similar to Kawasaki disease in some respects and is often treated with immune globulin (IV) at similar doses; in such cases, the same deferral period would apply.

[f] Administration of live vaccines, if indicated, to postpartum women should not be delayed if antibody-containing products were given during the last trimester (this includes RhoGAM). Likewise, the infant's immunization with RV should not be delayed.

[g] Assumes a hematocrit of 65% and serum IgG concentration of 16 mg/mL. The American Academy of Pediatrics recommends an interval of 5 months because it accounts for the possibility of a lower range of IgG concentration in the transfused product.

Adapted from General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). CDC Web site. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html. Accessed July 14, 2023.

theoretical possibility, it is considered safe to use these vaccines in homes with immunocompromised persons, as long as good hand hygiene is practiced. Whereas LAIV may be given if the household contact has mild or moderate immunosuppression, it should not be used in the home, for example, of a hematopoietic cell transplant (HCT) patient who is in a special protective environment (some guidelines include any HCT patient in the first 2 months after transplant or with graft versus host disease, as well as patients with severe combined immunodeficiency[7]). The story with nonemergency use of ACAM-2000 is different: the vaccine should not be given if there is a pregnant or immunosuppressed person in the home.

Administration Errors

Sometimes mistakes are made in vaccine administration. **Table 5.3** lists some of the most common error categories and **Table 5.4** gives recommendations to remedy specific errors for routine vaccines. **Table 5.5** lists common errors and deviations for COV.

The Institute for Safe Medication Practices, in partnership with the California Department of Public Health, operates the National Vaccine Errors Reporting Program (VERP), whereby healthcare professionals may confidentially report administration errors and near misses.[8] For the years 2017 and 2018, the most commonly reported vaccination errors (N=1143) were administration of the wrong vaccine (24%), vaccine given at the wrong age (17%), extra dose given (11%), and use of expired vaccine (8%).[9] Confusion over brand and generic names contributes to errors—a good example would be the mistaken use of PedvaxHIB (generic name Haemophilus b Conjugate Vaccine [Meningococcal Protein Conjugate]) instead of MenACWY (the meningococcal protein in PedvaxHIB is used as the conjugate for the Hib polysaccharide and does not provide protection against *N meningitidis).*

Testing for Immunity

Testing for varicella antibodies before vaccination might be cost-effective in adults who do not have a personal history of chickenpox. However, in most other circumstances vaccines should be given without testing for immunity (this might include internationally adopted children with a questionable vaccination history—see *Chapter 6: Vaccination in Special Circumstances—International Adoptees, Refugees, Immigrants and Others Vaccinated Outside the United States*). Testing for antibodies against SARS-CoV-2 is not recommended to assess the need for COV, nor to evaluate the response to vaccination outside of research studies.

Immunity is presumed to result from appropriate vaccine schedules and doses. With measles, for example, immunity is presumed if the person received 2 valid doses of MMR at the right ages

TABLE 5.3 — Vaccination Errors Reported to VAERS, 2000–2013

Error Type	Percent[a]
Inappropriate schedule[b]	27
Storage and dispensing[c]	23
Wrong vaccine[d]	15
General error	12
Incorrect dose[e]	9
Administration error[f]	9
Others	5

VAERS, Vaccine Adverse Event Reporting System

[a] *N* = 21,843 errors reported.
[b] Includes administration to a patient of inappropriate age.
[c] Includes use of expired product and inappropriate reconstitution.
[d] Includes administration of vaccine to the wrong patient.
[e] Includes administration of extra dose.
[f] Includes administration at inappropriate site, use of incorrect dosage form or route, and wrong technique.

Adapted from Hibbs BF, et al. *Vaccine*. 2015;33:3171-3178.

and with appropriate minimum intervals—even if serological results are negative and even for health care personnel (HCP). Testing for seroconversion is indicated only rarely, such as in high-risk HCP or dialysis patients given HepB, laboratory workers receiving pre-exposure RAB, HIV-infected persons after the HepA series, and in some cases where individuals received invalid doses. In fact, testing for antibody may give you information you did not want in the first place! For example, healthy persons who receive a full series of HepB are presumed to be immune, and serological testing is not recommended except in high-risk groups. What should be done about a (usual-risk) person who is (for some reason) tested and found to be negative for hepatitis B surface antibody (HBsAb), despite a complete series of HepB at appropriate ages and intervals? Options include 1) do nothing and assume protection based on adequate immunization history (antibody may have waned, but the person is probably still protected), and 2) give a dose of HepB and look for an anamnestic response in 4 to 6 weeks. If there is a robust anamnestic response, the person likely responded to the initial series, was protected all along, and remains protected after boosting. If there is no response, make sure the person is negative for hepatitis B surface antigen (chronic carriage can lead to low levels of HBsAb), then complete a second HepB series. If the person remains negative after this, they are a non-responder and should be managed accordingly if there is an exposure to hepatitis B.

Contraindications and Precautions

A *contraindication* is a condition that *increases the likelihood of a serious adverse event*; when present, the vaccine in question should not be given. The only permanent contraindication for all routine vaccines is severe allergy or anaphylaxis to the vaccine or any of its components. Severe allergy is IgE-mediated, occurs in minutes to hours, and requires medical attention. Examples include generalized urticaria, facial swelling, airway obstruction, wheezing, anaphylaxis, hypotension, and shock. Delayed-type hypersensitivity occurs by a different mechanism and is generally not a contraindication to vaccination. Most vaccines contain buffers as well as excipients, which are defined as substances other than the vaccine that are included in the manufacturing process or added to the final product (excipients are listed in the relevant vaccine tables in *Section B: Diseases and Vaccines*, and the more common relevant allergies are listed as contraindications). In addition, there may be contaminating substances that carry over from early steps in processing, and some vial stoppers and syringes contain latex, which can cause reactions in the patient. Both excipients and contaminants can be triggers for allergic reactions in sensitized patients.

Acute encephalopathy within 7 days of receipt of a pertussis-containing vaccine is a permanent contraindication for DTaP and Tdap, although there is no evidence that pertussis vaccine causes or exacerbates encephalopathy (see *Chapter 7: Addressing Concerns About Vaccines—Pertussis Vaccine and Brain Damage*). Pregnancy is a contraindication for live vaccines based on theoretical risks to the fetus and the possibility that naturally occurring birth defects might be attributed to the vaccine (see *Chapter 6: Vaccination in Special Circumstances—Pregnancy, Postpartum, and Breast-Feeding*). However, there is no definitive evidence of fetal damage from any live vaccine except live, attenuated, smallpox vaccine (ACAM-2000). In addition, in some circumstances, the benefits may outweigh the risks; for example, YFV can be considered for pregnant women traveling to high-risk areas. Although live vaccines are generally contraindicated in immunocompromised persons, there may be situations where the benefits outweigh the risks. For example, natural varicella probably represents a greater risk to a partial DiGeorge syndrome patient with mildly impaired cellular immunity than does the live attenuated vaccine. Severe combined immunodeficiency and a history of intussusception are contraindications for use of RV.

A *precaution* is a condition that might *increase the risk of a serious adverse event, compromise the immunogenicity of the vaccine, or result in diagnostic confusion*. Moderate or severe acute illness with or without fever is a precaution for all vaccines because of the difficulty distinguishing natural illnesses from vaccine reactions (progression of the natural illness could mistakenly be attributed to the vaccine). Vaccination of patients with acute COVID-19 should be delayed

TABLE 5.4 — Common Administration Errors and Corrective Actions

Vaccine Involved[a]	Administration Error	Why This Is Incorrect	Validity of Dose(s)	Corrective Action
Any	Expired or damaged non-live vaccine given	Expired or damaged vaccines should not be used	Invalid	Give proper dose as soon as error is discovered
	Expired or damaged live vaccine given	Expired or damaged vaccines should not be used	Invalid	Give proper dose on same day or ≥28 d later
	Less-than-full dose of non-live vaccine given	Correct dose should be used	Invalid	Give correct dose as soon as error is discovered[b]
	Less-than-full dose of live vaccine given[c]	Correct dose should be used	Invalid	Give correct dose on same day or ≥28 d later
	More-than-full dose of vaccine given	Correct dose should be used	Valid	None
VAR, MMR, MMRV, YFV	Dose given intramuscularly	Should be given subcutaneously	Valid	None
DTaP	Dose given to adolescent or adult	Tdap should be used	Valid for routine Tdap booster	None
	Dose given to fully-vaccinated child at 7-9 y	Not indicated at ≥7 y	Invalid as routine Tdap booster	Give Tdap at 11-12 y
	Dose given to child at 10 y	Not indicated at ≥7 y	Valid for routine Tdap booster	None
DTaP-IPV (Kinrix, Quadracel)	Dose given to child 15-18 mo as Dose 4 of DTaP	Only indicated for Dose 5 of DTaP in children 4-6 y	Valid for DTaP dose	None
DTaP-IPV (liquid component of Pentacel)	Dose given to child as any dose of DTaP or IPV	Should only be used as part of Pentacel (after reconstitution of lyophilized Hib-T component)[d]	Valid for DTaP and IPV doses	None
DTaP-IPV-Hib-HepB (Vaxelis)	Dose given as Dose 4 or Dose 5 of DTaP, Dose 4 of Hib, or Dose 4 of IPV	Should only be used for the infant series	Valid for DTaP, IPV, Hib, and HepB doses	None
HepA	Dose given subcutaneously	Should be given intramuscularly	Valid	None

Continued

TABLE 5.4 — *Continued*

Vaccine Involved[a]	Administration Error	Why This Is Incorrect	Validity of Dose(s)	Corrective Action
HepB	Dose given subcutaneously	Should be given intramuscularly	Invalid	Give dose intramuscularly as soon as error is discovered
	Dose given to an adult in gluteal muscle	Should be given in deltoid muscle	Invalid	Give dose in deltoid muscle as soon as error is discovered
Hib-T (ActHIB, Hiberix)	One vaccine reconstituted with the diluent from the other	Should be reconstituted with the proper diluent	Invalid	Give either vaccine reconstituted with appropriate diluent as soon as error is discovered
HPV9	Dose given subcutaneously	Should be given intramuscularly	Invalid	Give dose intramuscularly as soon as error is discovered
IIV (FluLaval or Fluarix)	0.25 mL dose given to a child 6-35 mo	Correct dose is 0.5 mL	Invalid	Give an additional 0.25 mL of FluLaval or Fluarix on the same day; otherwise, give a full dose of any IIV labeled for children 6-35 mo (including FluLaval and Fluarix) on a subsequent day
LAIV	Dose given to person 6-23 mo	Only labeled for persons 2-49 y	Valid	None
	Dose given to person receiving influenza antivirals within 48 h before dose	Antivirals can inhibit immune response	Invalid	Give IIV as soon as error is discovered, or give LAIV ≥28 d later (if person is not on antivirals at that time)
	Dose given 1 d to <4 wk after dose of MMR, VAR, or MMRV	Replication of first vaccine viruses could interfere with immune response to LAIV	Invalid	Give IIV as soon as error is discovered, or give LAIV ≥28 d later
MenACWY-D, MenACWY-CRM or MenACWY-T	Dose given subcutaneously	Should be given intramuscularly	Valid	None
MenACWY-CRM	Liquid component (serogroups C, W, Y) given alone	Only licensed as a 4-valent vaccine where liquid component is used to reconstitute lyophilized serogroup A component	Valid if recipient does not plan to travel outside US (not protected against serogroup A) Invalid if travel outside the US is planned	Discard remaining vial of lyophilized vaccine If travel planned, give MenACWY-D, MenACWY-T, or correctly reconstituted MenACWY-CRM as soon as error is discovered Discard remaining vial of lyophilized vaccine

Continued

TABLE 5.4 — *Continued*

Vaccine Involved[a]	Administration Error	Why This Is Incorrect	Validity of Dose(s)	Corrective Action
MenACWY-D	Dose given <4 wk after DTaP	Response to MenACWY-D is diminished	Valid	None
MenB	Mixed schedule of MenB-4C and MenB-FHbp given	Same product should be used for all doses in the series	Invalid	Complete series of one product using appropriate dosing interval
MMRV	Dose given to person >12 y	Only labeled for persons 12 mo-12 y	Valid	None
PPSV23	Dose given to child <2 y	PCV13, PCV15, or PCV20 should be used	Invalid	Give PCV13, PCV15, or PCV20 as soon as error is discovered
	Dose given concomitantly with PCV	PPSV23 and PCV should not be given together	Both doses valid	None
RAB	Dose given in gluteal muscle	Should be given in anterolateral thigh (infant) or deltoid (older child and adult)	Invalid	Give dose in appropriate muscle as soon as error is discovered
	Dose given subcutaneously	Should be given intramuscularly	Invalid	Give dose in the appropriate muscle as soon as error is discovered
RV	Dose 1 given after 15 wk	Dose 1 should be given between 6 wk and 14 wk 6 d	Valid	Give remaining doses in the series at the recommended intervals, but no doses should be given after 8 mo 0 d
RZV	Dose given to a child for prevention of varicella	VAR should be used	Invalid	Give VAR as soon as error is discovered
Tdap	Dose given to infant or child as part of primary series	DTaP should be used	Invalid	Give DTaP as soon as error is discovered
	Dose given to infant or child as Dose 4 or 5 in series	DTaP should be used	Valid	None
VAR	Dose given to adult ≥50 y for prevention of shingles	RZV should be used	Invalid	Give RZV ≥2 mo later

[a] See **Table 5.5** for COVID-19 vaccines.
[b] For RZV, give a correct dose 4 wk after the partial dose was given (the interval is intended to minimize reactions from the adjuvant).
[c] Exceptions: sneezing or blowing nose after LAIV administration, and vomiting, spitting up, or regurgitating after RV administration.
[d] The remaining lyophilized Hib-T component of Pentacel can only be used if reconstituted with the DTaP-IPV liquid component of Pentacel or the 0.4% saline diluent for ActHIB.

TABLE 5.5 — COVID-19 Vaccine Administration Errors and Deviations[a]

Type	Error or Deviation	Why This Is Incorrect	Validity of Dose(s)	Corrective Action
Site/route	Vaccine given at site other than the deltoid or vastus lateralis muscle	Deltoid or vastus lateralis muscle should be used	Valid	If dose given subcutaneously, inform recipient of potential for local and systemic adverse events
Age	Dose given to infant <6 mo	Vaccines only authorized for ≥6 mo	Valid	Administer subsequent doses of the series when the person becomes age-eligible
Product and dosage	Higher-than-authorized dose given (includes instances when too little or no diluent was used to prepare a dose)	Appropriate dilution and dose should be used	Valid	Consider delaying the next dose if unexpected adverse events occurred
	Lower-than-authorized dose given (includes instances when too much diluent was used to prepare a dose)	Appropriate dilution and dose should be used	Invalid	Give an appropriate dose as soon as error is discovered[b]
	Only diluent given	Vaccine should be mixed with correct amount of appropriate diluent	Invalid	Give an appropriate dose as soon as error is discovered
	Incorrect diluent used	Vaccine should be mixed with correct amount of appropriate diluent	Invalid, unless manufacturer can confirm stability of vaccine	Give appropriate dose as soon as error is discovered, unless dose is validated by manufacturer
	Diluent used for "do not dilute" vaccine	Vaccine should be used without dilution	Invalid, unless manufacturer can confirm stability of vaccine	Give appropriate dose as soon as error is discovered, unless dose is validated by manufacturer
	Single-use vial of diluent used to mix multiple vials of vaccine	Vial should only be entered one time	Valid	Inform patient of potential for bacterial contamination
Intervals	Any vaccine dose given before the minimum interval	Each vaccine has specified minimum intervals between doses	Invalid, unless within the 4-day grace period[d]	Give a repeat dose at the appropriate minimum interval from the dose given in error, unless it was given within 4 d of the minimum interval
	Any vaccine dose given after the recommended interval	Each vaccine has recommended intervals between doses	Valid	None[e]
Interchangeability	See *Chapter 5: General Rules—Rule 7—Similar Vaccines Made by Different Manufacturers Are Generally Interchangeable* and **Figures 12.6** and **12.7** for information on mixed schedules			

Continued

TABLE 5.5 — *Continued*

IIS, immunization information system; VAERS, Vaccine Adverse Event Reporting System

[a] Providers are required to report COVID-19 vaccine administration errors (even those not associated with an adverse event) to VAERS and should consult with the state immunization program and/or IIS to determine how erroneous doses should be entered into the IIS. Data current as of July 2023.

[b] If a half-volume dose was given, a second half-volume dose can be given on the same day (together these count as 1 full dose).

[c] If dose given in error was Dose 1, the repeat dose should be given ≥4 wk later; for other doses, follow the usual minimum intervals.

[d] See *Chapter 3: Standards, Principles, and Regulations—Mandates and Exemptions*.

[e] Reporting to VAERS is not necessary.

Adapted from Appendix C. Vaccine administration errors and deviations. CDC Web site. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us-appendix.html#appendix-c. Accessed July 13, 2023.

until their period of isolation is over, so as not to expose others to COVID-19.

The moderate or severe illness precaution should not be construed as prohibiting vaccination during hospitalization; in fact, vaccination should be possible during most elective admissions, as well as during acute care admissions once the patient is recovering. Understanding what to do when a precaution is noted is sometimes difficult. In general, vaccination should be deferred. However, the risks of deferral (susceptibility to disease) must be weighed against the risks of vaccination (largely theoretical). In making these judgments, the provider must consider the prevailing epidemiology of the disease, the patient's personal circumstances, and the possibility that an opportunity for vaccination will be missed.

Sometimes it is difficult to know when a condition is a "contraindication" or a "precaution" (package inserts also contain "warnings," but it is not clear how these differ from "precautions"). For example, pregnancy is not listed as a *contraindication* or *precaution* for HPV9 administration in Table 4-1 (Contraindications and Precautions to Commonly Used Vaccines) of the *General Best Practice Guidelines*; however, there is a footnote stating that the vaccine is not recommended during pregnancy, which, for all intents and purposes, sounds like a *contraindication.*[10] On the other hand, the HPV9 package insert (April 2023)—while containing data showing no association between vaccination and birth defects or miscarriage in pregnant animals and humans—does not caution against vaccination during pregnancy. Instead, it states simply that safety and effectiveness in pregnant women have not been established.

In *Section B: Diseases and Vaccines*, each vaccine table lists contraindications and precautions, to be interpreted, respectively, as "do not vaccinate in these situations" and "defer vaccination in these situations, unless the benefits outweigh the risks."

Misconceptions about vaccine contraindications can result in missed opportunities. **Table 5.6** lists some erroneous contraindications; vaccines can and should be given in these circumstances.

TABLE 5.6 — Erroneous Contraindications and Precautions to Vaccination

- Mild acute illness, with or without fever[a]
- Mild respiratory illness (including most cases of otitis media)
- Mild gastroenteritis
- Antibiotic or antiviral therapy[b]
- Low-grade or moderate fever and/or local redness, pain, and swelling after a previous dose
- Prematurity[c]
- Pregnant or immunosuppressed household contact[d]
- Unimmunized household contact
- Breast-feeding[d]
- Current, recent, or upcoming anesthesia, surgery, or hospitalization
- Convalescent phase of illness
- Exposure to an infectious disease
- Positive TST without active disease[e]
- Simultaneous TST or IGRA[f]
- Allergy to penicillin, duck meat or feathers, or environmental allergens
- Fainting after a previous dose
- Seizures, sudden infant death syndrome, allergies, or vaccine adverse events in family members
- Malnutrition
- Lack of previous physical examination in a well-appearing individual
- Stable neurologic condition (eg, cerebral palsy, well-controlled seizure disorder, developmental delay)
- Allergy shots
- Extensive limb swelling after DTwP, DTaP, or Td that is not an Arthus-type reaction[g]
- Brachial neuritis after previous dose of tetanus toxoid-containing vaccine
- Autoimmune disease (not on immunosuppressive medication)
- Having had the disease that the vaccine is designed to prevent[h]

HBsAg, hepatitis B surface antigen; IGRA, interferon-gamma release assay; TST, tuberculin skin test

[a] People with symptomatic acute COVID-19 should delay vaccinations until their isolation period is over (to avoid spreading COVID-19 to others).

[b] Antibiotics could interfere with live bacterial vaccines (eg, Ty21a), and antivirals could interfere with live viral vaccines (eg, VAR).

[c] The birth dose of HepB should be delayed (because of poor immunogenicity) in infants weighing <2000 g whose mothers are HBsAg-negative.

[d] Pre-event use of live, attenuated, smallpox vaccine is an exception.

Continued

TABLE 5.6 — *Continued*

[e] Active, untreated tuberculosis is a precaution for MMR and VAR.

[f] Live attenuated vaccines, including MMR, VAR, and ACAM2000 can temporarily suppress the response to a TST and may cause false negative IGRA results. If testing for tuberculosis is warranted, the preferred option is to place a TST or perform an IGRA on the same day as vaccination. Otherwise, the tuberculosis test should be delayed ≥4 wk.

[g] An Arthus reaction is a local vasculitis caused by deposition of immune complexes and activation of complement. It occurs when there is a high concentration of antigen and antibody, as might be the case when a person who already has high antibody titers to a particular antigen receives a homologous vaccine. Characteristics include severe pain, swelling, induration, edema, and hemorrhage; local necrosis can occur. Symptoms usually develop within 4-12 h of vaccination.

[h] Immunity from natural infection may wane with time, as in the case of pertussis. Alternatively, the vaccine (eg, HPV, MenACWY, PCV, RV) might protect against serotypes to which the individual has not been previously exposed. Anthrax is an exception.

Adapted from General best practice guidelines for immunization, Table 4-2. Best practices guidance of the advisory committee on immunization practices (ACIP). CDC Web site. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html. Accessed July 14, 2023. More details can be found for individual vaccines in *Section B: Diseases and Vaccines*.

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Vaccination in Special Circumstances

Special vaccination circumstances arise from host factors, such as immune deficiency states and chronic medical conditions, as well as environmental factors, such as the potential for exposures at work or during travel. Issues range from safety concerns—for example, the potential for live vaccines to cause disease in immunocompromised persons—to the need for non-routine vaccines—for example, YFV for travelers to certain parts of Africa and South America. Navigating these special circumstances should be viewed as a shared responsibility between all providers who care for the patient.[1]

Immune Deficiency States

Vaccination of patients with impaired immunity requires special consideration.

- *The balance between risks and benefits is complex*—Immunocompromised persons are at greater risk for complications and death from vaccine-preventable diseases. They may also be at increased risk for complications from live vaccines and poor responses to non-live vaccines. Decisions regarding vaccination must consider the prevalence of disease, probability of exposure, nature and degree of immunodeficiency, type of vaccine, likelihood of adverse events, vaccine efficacy when immunity is impaired, and the confounding effects of other interventions.
- *Immunocompromised states differ qualitatively*—Qualitative differences dictate which vaccines are indicated and which are contraindicated. Primary immunodeficiencies may affect humoral immunity, cell-mediated immunity, phagocyte function, or complement function in different and interconnected ways. Humoral immune defects place patients at higher risk for invasive infection with encapsulated bacteria, warranting special consideration for vaccination against *H influenzae* type b, *S pneumoniae*, and *N meningitidis*. Whereas isolated humoral defects do not increase the risk of serious varicella per se, they may predispose the patient to bacterial complications. Therefore, VAR is indicated in patients with isolated humoral defects—as long as they are not receiving immune globulin, in which case the vaccine

is unlikely to be effective because donor-derived antibodies in the immune globulin product will inactivate the vaccine virus. Similarly, phagocyte dysfunction per se does not substantially weaken defenses against influenza virus, but it *does* increase the risk of bacterial superinfection. Thus, patients with chronic granulomatous disease (CGD), whose neutrophils fail to undergo oxidative burst, should be high priority for influenza vaccination in order to prevent secondary bacterial pneumonia. Complement deficiencies, and complement inhibitor use, put patients at risk for bacterial infections but carry no implications for the safety of live or non-live vaccines. Secondary immune deficiency states, such as those resulting from immunosuppressive medications, nephrotic syndrome, malnutrition, splenectomy, cancer chemotherapy, or hematopoietic cell transplantation (HCT) also differ qualitatively from primary immunodeficiencies and from one another.

- *Immunocompromised states differ quantitatively*—In general, patients with cell-mediated immune defects should not receive live vaccines because of the risk of disease caused by the vaccine. However, cellular defects may range from mild to profound, and these differences affect the risk-benefit assessment. For example, whereas VAR *should be avoided* in an HIV-infected person with very low CD4 count, poor T-cell function, and a history of opportunistic infections, it *should be given* to a mildly symptomatic HIV-infected child whose CD4 percentage is consistently ≥15%. In the former situation, the risk of vaccination is too great; in the latter, the risk of vaccination is small and is outweighed by the potential consequences of natural disease. Similarly, MMR may be given to HIV-infected children without severe immunosuppression. DiGeorge syndrome, a quantitative T-cell deficiency resulting from thymic dysplasia, is variable in expression—whereas those patients with low T-cell numbers and function should not receive live vaccines, live vaccines are probably safe in those patients with normal T-cell studies.
- *Immune responses may be suboptimal*—Some patients with immune deficiencies are not expected to respond at all to vaccination. Patients with X-linked agammaglobulinemia (XLA), for example, do not make antibody, so administration of non-live vaccines would seem to be futile. Live vaccines such as MMR and VAR would theoretically be useful in XLA patients because these vaccines stimulate T-cell responses, of which XLA patients are fully capable—were it not for the fact that XLA patients receive immune globulin infusions that would inactivate the vaccines. Fortunately, the very same antibodies in immune globulin that prevent the "take" of MMR and VAR also protect XLA patients from natural measles, mumps, rubella, and varicella. An outstanding question is whether there might be enough of a T-cell response to some non-live vaccines—IIV, for example—to justify their use in these patients. Patients with common variable immunodeficiency (CVID) may or may not respond to vaccination, so in general it is worth a try. Some patients who have normal concentrations of immune globulin may still not respond appropriately to certain vaccines. In fact, this constitutes an operational definition of *antibody deficiency with normal immunoglobulins* or *antibody dysfunction syndrome*, often diagnosed by failure to respond to PPSV23. In some immune deficient patients, more intensive immunization regimens are necessary to achieve protective immunity; a good example of this is the 2-dose primary series of MenACWY that is recommended for immunocompromised adolescents (healthy adolescents are primed with one dose).
- *Immunization of close contacts is important*—Immunocompromised patients can be protected by ensuring that close contacts, especially other household members, are appropriately immunized. For example, AIDS patients may not respond well to influenza vaccine but can be protected from influenza by immunizing family members. Likewise, HepA should be given to contacts of immunosuppressed persons if the family resides in a high-prevalence area. Live vaccines carry the theoretical risk of transmission from vaccinees to immunocompromised contacts, in which they could cause disease (see *Chapter 5: General Recommendations—Ten Simple Rules By Which To Vaccinate*). However, the risk of transmission varies by vaccine, and some live vaccines, including MMR, carry no risk of transmission. Likewise, the consequences of transmission range from serious (eg, live, attenuated smallpox vaccine) to theoretical (eg, RV).
- *Official recommendations may differ from product labels*—Some package inserts list immunodeficiency states as contraindications. Recommendations may be discordant with the product label because of the availability of new data or reasoned re-evaluations of the pertinent risks and benefits. For example, the VAR package insert (March 2023) lists immunodeficiency and immunosuppression as contraindications to vaccination. The official recommendations, however, allow for vaccination of certain persons with these conditions.
- *Passive immunoprophylaxis or antibiotic prophylaxis may be indicated*—Persons who receive immune globulin intravenous (IGIV) on a monthly basis are probably protected against measles and varicella; in the case of exposure, consideration should be given to shortening the interval to the next IGIV dose by 1 or 2 weeks (patients who receive weekly immune globulin subcutaneous are probably continuously protected). Recommendations for passive immunoprophylaxis against hepatitis A, hepatitis B, measles, rabies, tetanus, and varicella are given in the respective chapters in *Section B: Diseases and*

Vaccines. Some patients with asplenia may qualify for antibiotic prophylaxis against *S pneumoniae*.

Tables 6.1, **6.2**, and **6.3** provide guidance for immunization of persons with altered immunity.

Chronic Medical Conditions

Persons with chronic underlying conditions may be unusually susceptible to infectious diseases, whether or not they have defined immunodeficiency. As a general rule, all routine vaccines should be given unless they are specifically contraindicated. Most of these patients are high priority for yearly IIV; LAIV should not be used in patients with conditions that predispose them to complications of influenza, including those with chronic cardiac (eg, congenital heart disease), respiratory (eg, cystic fibrosis), allergic (eg, asthma), hematologic (eg, sickle cell disease), metabolic (eg, type 1 and type 2, but not gestational, diabetes), neuromuscular (eg, muscular dystrophy), hepatic (eg, cirrhosis), and renal (eg, chronic renal failure) disorders. HepB, which is routinely recommended for persons <60 years of age, is also recommended for persons ≥60 years of age with certain risk factors, including diabetes.[2] Patients with chronic liver disease (chronic hepatitis B or C; cirrhosis; fatty liver disease; alcoholic liver disease; autoimmune hepatitis; transaminases more than twice the upper limit of normal) are at risk for severe hepatitis and should receive HepA and HepB (patients with chronic hepatitis B do not need HepB).[3] Obesity poses the risk of complicated influenza and poor response to vaccines.[4] It is also one of the most important risk factors for serious COVID-19, along with hypertension; diabetes; cardiovascular disease; chronic lung, liver and kidney disease; malignancy; and underlying medical complexity like that associated with developmental delay and/or genetic abnormalities (see *Chapter 12: COVID-19* for information about COVID-19 vaccines).[5-7]

Some conditions place patients at particular risk for invasive *S pneumoniae* infection (**Figure 6.1**).[8] For example, patients with nephrotic syndrome are susceptible, due in part to loss of IgG and complement components in the urine (in this sense they are considered immunocompromised). Nephrotics have been successfully immunized with PPSV23 at disease onset and despite steroid therapy,[9] and PCV7 has been given without exacerbation of the underlying disease[10]; this suggests that optimizing immunity to *S pneumoniae* can be started as soon as the diagnosis of nephrotic syndrome is made. Diabetes, chronic heart disease, and chronic lung disease also place patients at higher risk. Asthma and cigarette smoking are considered risk factors for adults, and moderate to severe persistent asthma is a risk factor for children.[11] Patients with CSF leaks and cochlear implants are at increased risk for pneumococcal meningitis because the bacterium can spread to the central nervous system from contiguous spaces that are colonized.

Pregnancy, Postpartum, and Breast-Feeding

There is a "susceptibility gap" in infants from the time they are born until the time they can develop their own vaccine-induced immunity; this gap can be closed by the "gift" of maternal immunization.[12] Whereas vaccination during pregnancy poses theoretical risks to the developing fetus, there is no evidence directly linking any routine vaccines, even live ones, to birth defects (see *Chapter 7: Addressing Concerns about Vaccines—Miscarriage and Birth Defects*). Transplacentally acquired maternal antibodies may blunt the humoral immune response to infant vaccinations,[13] although there is little evidence that cellular responses are blunted[14]; for certain vaccine-preventable diseases the benefits of maternal immunization outweigh this risk. Pregnant women should be vaccinated when the risk for exposure to disease is high and the infection would pose a significant risk to the mother or fetus.[15] The *maternal immunization platform* is analogous to the childhood and adolescent platforms (see **Table 8.1**),[16] and the American College of Obstetricians and Gynecologists (ACOG) recommends that obstetrician-gynecologists make vaccinating women a routine part of practice and it offers strategies for integrating immunizations into routine care.[17,18] In 2020, ACOG, the American Academy of Family Physicians, American College of Nurse-Midwives, and Association of Women's Health, Obstetric and Neonatal Nurses issued a call to action on maternal immunization, summarized in **Table 6.4**.

Pregnancy is an *indication* for influenza immunization[19]—it is safe, cost-effective, and over 90% effective in preventing hospitalization of infants due to influenza in the first 6 months of life[20] (protection against influenza illness is greatest in the first 8 weeks[21]). Vaccination also prevents women from being hospitalized during pregnancy,[22] and there is no evidence of adverse health effects in the children of women who are vaccinated during pregnancy.[23] IIV should be given regardless of trimester in order to prevent severe disease in the mother and still provide benefit to the baby. Women who do not receive influenza vaccine during pregnancy should be vaccinated before hospital discharge.[24]

Pregnancy is also an indication for RSV vaccine.[25] Efficacy in preventing medically-attended severe lower respiratory tract disease in infants is 82% through 90 days of age and 69% through 180 days of age, and no safety signals were seen in the pivotal Phase 3 trial.[26] Options for protecting infants against RSV are maternal vaccination or passive immunization with nirsevimab; while there are no known harms if both approaches are used, coordination between obstetric and pediatric providers is important to avoid using both approaches in most infants.

TABLE 6.1 — Vaccination of Persons With Altered Immunity

General Notes

- Live vaccines are usually contraindicated (exceptions are noted below)
- Non-live vaccines are safe, but responses may be suboptimal
- Vaccine doses given ≤14 d before, or at any time during, periods of severe immunosuppression are considered invalid and should be repeated ≥3 mo after immunosuppressive therapy is discontinued, unless a protective immune response is documented
- Immunosuppressive therapy should be initiated ≥4 wk after receipt of live vaccines and ≥2 wk after non-live vaccines; however, required therapy should not be delayed because of recent vaccination
- All eligible patients and household members should be immunized against influenza (see *Chapter 20: Influenza*) and COVID-19 (see *Chapter 12: COVID-19*). The ACR conditionally recommends use of higher dose and adjuvanted IIVs in adults with rheumatic and musculoskeletal disease who are on immunosuppressive medications (off-label recommendation for 18-64 y). In addition, the ACR recommends holding methotrexate (but not other medications) for 2 wk after receipt of IIV (but not other non-live vaccines).
- Immunity to *S pneumoniae* should be optimized in all patients (**Figure 6.1**)
- RZV should be given to certain adults[a]

Immune Deficiency Category/Examples	Safety Issues	Special Considerations
Persons with HIV infection Perinatally or postnatally acquired	MMR and VAR are contraindicated in severe immunosuppression[b] MMRV, LAIV, Ty21a, and pre-event live, attenuated smallpox vaccine (ACAM2000)[c] are contraindicated YFV and dengue vaccine may be contraindicated (see *Chapter 13—Dengue and Chapter 33—Yellow Fever*)	Most patients who are well-controlled on antiretroviral therapy[d] or are natural long-term non-progressors may be immunized according to routine schedules Routine vaccines (including RV[e], unless immune deficiency is suspected) may be given to perinatally-exposed infants who are being evaluated for HIV infection[f]
		Infants should be tested for HBsAb and HBsAg 1-2 mo after completing the 3-dose HepB series[g] MMR and VAR may be given to children with HIV infection who do not have severe immunosuppression[b,h] Immunity to *H influenzae* type b should be optimized[i] Immunity to *N meningitidis* should be optimized (**Figure 6.2**)[j] HepA series should be given if ≥1 y and not immune; anti-HAV IgG antibody should be measured ≥1 mo after series completion[k] HepB series should be given if ≥60 y and not immune[l] Patients receiving IGIV may receive MMR and VAR 14 d before the next infusion, if not otherwise contraindicated (vaccination should be repeated, if not otherwise contraindicated, after the infusions have been discontinued) Patients receiving weekly IGSC should not receive MMR or VAR

Continued

TABLE 6.1 — *Continued*

Immune Deficiency Category/Examples	Safety Issues	Special Considerations
B-cell (humoral) deficiencies X-linked agammaglobulinemia, common variable immunodeficiency, IgG subclass deficiency, antibody deficiency with normal immunoglobulins (vaccine non-responder state or antibody dysfunction syndrome), transient hypogammaglobulinemia of infancy	MMRV, YFV, dengue vaccine and pre-event live, attenuated smallpox vaccine (ACAM2000)[c] are contraindicated LAIV and Ty21a are contraindicated in severe deficiencies but may be considered in less severe conditions	Non-live vaccines are not effective in patients with severe humoral deficiencies but may be effective in those with less severe conditions Some degree of cell-mediated immunity may be generated in patients with B-cell deficiencies No data are available for RV MMR and VAR may be considered in patients who are not receiving IGIV or IGSC[m] Immunity to *H influenzae* type b should be optimized[i] Patients with selective IgA deficiency may receive all vaccines
T-cell (combined humoral and cell-mediated) deficiencies Severe combined immunodeficiency, DiGeorge syndrome, hyper-IgM syndrome (CD40 or CD40 ligand deficiency), bare lymphocyte syndrome, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (chronic mucocutaneous candidiasis), Wiskott-Aldrich syndrome, ataxia-telangiectasia	Live vaccines are contraindicated in complete deficiencies but may be considered in partial deficiencies[n]	Immunity to *H influenzae* type b should be optimized[i] When giving routine MenACWY, a 2-dose primary series should be used (**Figure 6.2**)[o]
Phagocyte disorders Chronic granulomatous disease, leukocyte adhesion deficiency, Chédiak-Higashi syndrome, myeloperoxidase deficiency, hyper-IgE/recurrent infection syndrome (Job's syndrome), secondary granule deficiency, congenital and cyclic neutropenia	Ty21a is contraindicated Cholera vaccine may be contraindicated Live viral vaccines are contraindicated if there is accompanying T-cell or NK-cell dysfunction	Live viral vaccines may be given to patients with chronic granulomatous disease or cyclic neutropenia[p] Patients with chronic granulomatous disease are not at increased risk for invasive pneumococcal disease and should be immunized according to the routine schedule
Complement deficiencies and inhibitor use Deficiency of individual early (C1-C4) or late (C5-C9) components, deficiency of properdin, mannose-binding lectin, Factor D, Factor H, or Factor I, secondary deficiency due to complement consumption, iatrogenic deficiency induced by complement inhibitors[q]	—	All vaccines may be given Immunity to *H influenzae* type b should be optimized[i] in persons with early component deficiencies Immunity to *N meningitidis* should be optimized (**Figure 6.2**)
Anatomic and functional asplenia Congenital, traumatic, or surgical asplenia, sickle cell disease,[r] polysplenia syndrome, celiac disease, alcoholic liver disease	LAIV is contraindicated	All vaccines except LAIV may be given Immunity to *H influenzae* type b should be optimized[i] Immunity to *N meningitidis* should be optimized (**Figure 6.2**) Immunity to encapsulated bacteria should be optimized ≥2 wk before elective splenectomy

Continued

TABLE 6.1 — *Continued*

Immune Deficiency Category/Examples	Safety Issues	Special Considerations
Steroids Asthma, inflammatory bowel disease, rheumatoid arthritis, spondyloarthropathies, systemic lupus erythematosus, other autoimmune disorders	Live vaccines are contraindicated in some patients	Vaccination should not be withheld because of concerns about exacerbating an underlying inflammatory condition Patients receiving steroids in any form who have evidence of immunosuppression should not receive live vaccines Patients whose underlying disease is immunosuppressive should not receive live vaccines, except under special circumstances See note[s] for dose-based guidelines
Disease-modifying antirheumatic drugs and biologic response modifiers[t] Inflammatory bowel disease, rheumatoid arthritis, spondyloarthropathies, systemic lupus erythematosus, psoriasis, atopic dermatitis, other autoimmune/autoinflammatory disorders	Live vaccines are generally contraindicated during active therapy Some products could cause immunosuppression in newborns of women treated during pregnancy	Vaccination should not be withheld because of concerns about exacerbating an underlying inflammatory condition If possible, vaccination should occur ≥2 wk before initiation of therapy Non-live vaccines may be given (see note below regarding anti–B-cell therapies) Live vaccines may be considered ≥3 mo after immunosuppressive therapy is discontinued (see note below regarding anti–B-cell therapies)
		For anti–B-cell therapies, both live and non-live vaccines should be held for ≥6 mo after therapy is discontinued The ACR conditionally recommends HPV in previously unvaccinated persons 27 to 45 y with rheumatic and musculoskeletal disease who are on immunosuppressive medications (the routine ACIP recommendation for this age group is shared clinical decision-making) Infants of mothers treated with certolizumab pegol or infliximab may receive RV, but RV should be deferred in infants born to mothers treated with other BRMs during pregnancy[u] Breast-fed infants of mothers who are receiving anti-TNF drugs may receive RV[u]

Continued

TABLE 6.1 — *Continued*

Immune Deficiency Category/Examples	Safety Issues	Special Considerations
Chemotherapy and immunosuppressive radiation therapy Hematologic malignancies, solid tumors	Live vaccines are generally contraindicated during active therapy	Live vaccines may be considered ≥3 mo after immunosuppressive therapy is discontinued Routine non-live vaccines (except for IIV) should be avoided ≤14 d before starting therapy and until ≥3 mo after therapy is discontinued[v] Immunity to *H influenzae* type b should be optimized[i] Anti-HAV IgG antibody should be tested ≥1 mo after HepA series if given while receiving therapy[k] See note[w] regarding acute leukemia Consider revaccination of patients who received ≥1 dose of COV during anti–B-cell therapy that was administered over a limited period (eg, as treatment for a malignancy); follow the schedule for unvaccinated persons and start 6 mo after completion of the therapy (**Figure 12.7**)
CD19-targeted CAR-T therapy[x] Hematologic malignancies	Live vaccines are contraindicated during active therapy	IIV should be given ≥2 wk before lymphodepletion or ≥3 mo after therapy COV should be given before therapy, but COV may also be given ≥3 mo after therapy (CDC recommends that patients who received ≥1 dose of COV before or during therapy should be revaccinated starting ≥3 mo after therapy and should follow the schedule for unvaccinated persons [**Figure 12.7**]) Non-live vaccines may be given ≥6 mo after therapy and ≥2 mo after receipt of IGIV Live and non-live adjuvanted vaccines may be given ≥1 y after therapy if fully immune reconstituted (CD4 count >200/mcL, and CD19 or CD20 positive B-cells >200/mcL, and no concomitant immunosuppressive or cytotoxic therapy)

Continued

TABLE 6.1 — *Continued*

Immune Deficiency Category/Examples	Safety Issues	Special Considerations
Solid organ transplantation[y] Renal, heart, liver, lung, small bowel, or multi-organ transplant	Live vaccines are contraindicated during intensive immunosuppressive therapy but may be considered under certain circumstances (see **Table 6.2**) MMRV is contraindicated	Vaccination should not be withheld because of concerns about stimulating rejection of a transplanted organ Immunizations should be optimized before patients receive immunosuppressive medications to prevent rejection (**Figure 6.3**) Patients should be caught-up on all age-appropriate immunizations in advance of transplantation[z] Routine yearly IIV may resume ≥6 mo after transplantation, but IIV may be given as soon as 1 mo post-transplantation if there is a community outbreak of influenza; vaccination with other non-live vaccines may resume 2-6 mo after transplantation Live vaccines should be withheld for 2 mo following discontinuation of anti-rejection therapies When giving routine MenACWY, a 2-dose primary series should be used (**Figure 6.2**)[o]
Hematopoietic cell transplantation[y,A] Various malignancies, aplastic anemia and other hematologic disorders, lysosomal storage diseases, metabolic diseases, primary immunodeficiencies, autoimmune diseases	Live vaccines are contraindicated during active therapy	Patients should be as up to date as possible before conditioning begins Routine revaccination is recommended (**Table 6.3**) Vaccination with non-live vaccines may resume 3-6 mo after transplantation Live vaccines may be given up to 4 wk before conditioning (giving them within 4 wk runs the risk of disease caused by the vaccine virus once the patient becomes immunosuppressed) Non-live vaccines may be given up to 2 wk before conditioning (giving them within 2 wk runs the risk of poor "take") RZV may be re-administered 6-12 mo after allogeneic HCT and 3-12 mo after autologous HCT[B]

AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices; ACR, American College of Rheumatology; BRM, biologic response modifier; CAR-T, chimeric antigen receptor T-cell; DMARD, disease-modifying antirheumatologic drug; HAV, hepatitis A virus; HBsAb, hepatitis B surface antibody; HbsAg, hepatitis B surface antigen; HCT, hematopoietic cell transplant; IGIM, immune globulin intramuscular; IGIV, immune globulin intravenous; IGSC, immune globulin subcutaneous; TNF, tumor necrosis factor

[a] Immunocompromised persons ≥19 y should receive the 2-dose RZV series (Anderson TC, et al. *MMWR*. 2022;71:80-84). Immunodeficiency states listed in the recommendation include HCT, solid organ transplantation, hematologic malignancies, breast cancer, other solid tumors, autoimmune and inflammatory conditions, and HIV infection. The interval between doses is 2-6 mo but may be as short as 1 mo in certain situations.

[b] *Severe immunosuppression* in patients with HIV infection is defined as follows: age ≤5 y, CD4 percentage <15% sustained for ≥6 mo; age ≥6 y, CD4 percentage <15% sustained for ≥6 mo or CD4 count <200 cells/mcL sustained for ≥6 mo. These criteria are applicable whether or not symptoms are present.

Continued

TABLE 6.1 — *Continued*

[c] The non-live, viral, nonreplicating smallpox vaccine (Jynneos) is safe to administer to immunocompromised persons (Rao AK, et al. *MMWR*. 2022;71:734-742).

[d] Persistence of immunity and memory responses may be suboptimal if vaccination occurred before effective therapy was started.

[e] Cortese MM, et al. *MMWR*. 2009;58(RR-2):1-25.

[f] Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-exposed and HIV-infected Children. Clinical Info HIV.gov Web site. https://clinicalinfo.hiv.gov/en/guidelines/pediatric-opportunistic-infection/whats-new (accessed July 18, 2023). Note that HIV infection is excluded in non–breast-fed infants with negative virologic tests (eg, PCR) at ≥1 mo and ≥4 mo, or 2 negative antibody tests at ≥6 mo (Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Clinical Info HIV.gov Web site. https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/whats-new-guidelines [accessed July 18, 2023]).

[g] If the HBsAb level is <10 mIU/mL and the HbsAg is negative, the patient should receive a second 3-dose HepB series followed by repeat HBsAb testing (Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-exposed and HIV-infected Children. Clinical Info HIV.gov Web site. https://clinicalinfo.hiv.gov/en/guidelines/pediatric-opportunistic-infection/whats-new [accessed July 18, 2023]).

[h] The usual schedule may be used (McLean HQ, et al. *MMWR*. 2013;62(RR-4):1-34); alternatively, Dose 2 of MMR may be given ≥28 d after Dose 1 and Dose 2 of VAR ≥3 mo after Dose 1 (a simple approach would be to give both vaccines at 12-15 mo and then both again 3 mo later—this would ensure optimal immunization before there is any deterioration in immune function). Children who received MMR and VAR before their HIV infection was effectively controlled should receive 2 appropriately spaced doses of each vaccine.

[i] The routine or catch-up Hib series in young children should be completed and one dose of Hib should be given to unimmunized children ≥60 mo (*unimmunized* means no infant series plus booster and no dose after 14 mo) (Briere EC, et al. *MMWR*. 2014;63[RR-1]:1-14). Any doses of Hib given <14 d of starting chemotherapy, or during chemotherapy, should be repeated ≥3 mo after chemotherapy is completed. Hib is not recommended for adults just because of HIV infection, regardless of their immunization history. Use of ActHIB and PedvaxHIB >5 y, and use of Hiberix >4 y, is off-label.

[j] HIV infection is a risk factor for invasive infection with certain meningococcal serogroups and a risk factor for suboptimal response to vaccination.

[k] Non-responders should be counseled about prevention of hepatitis A and the need for IGIM if exposed.

[l] HepB is recommended for all adults 19-59 y. Those ≥60 y with risk factors should be vaccinated and those ≥60 y without risk factors may be vaccinated.

[m] Antibodies in immune globulin can neutralize the vaccine virus and result in poor "take". Postvaccination antibody titers may be used to confirm responses. Use of MMR and VAR in immunodeficient persons is off-label.

[n] MMR and VAR may be given to DiGeorge syndrome patients with ≥500 CD3 T-cells/mcL, ≥200 CD8 T-cells/mcL, and normal mitogen responses. Use of MMR and VAR in immunodeficient persons is off-label.

[o] While not at particular risk for invasive meningococcal disease (unless there is an accompanying high-risk condition, like asplenia), these patients are at risk for poor response to vaccination and therefore need a 2-dose primary series.

[p] It is unclear whether patients with congenital neutropenia can receive live viral vaccines.

[q] Examples include eculizumab and ravulizumab. These are monoclonal antibodies to C5 that are used to treat paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. The risk of invasive meningococcal disease is increased 1,000-2,000-fold in patients taking these drugs (McNamara LA, et al. *MMWR*. 2017;66:734-737). Meningococcal vaccination may be ineffective in these patients, so prophylactic penicillin or amoxicillin should be considered while on therapy.

[r] May include patients with hemoglobin-S/beta thalassemia and hemoglobin-SC.

[s] Guidelines for live vaccines in patient receiving steroids:
- –*Topical, inhaled, and compartmental depot injections*: vaccination is acceptable
- –*Physiologic replacement*: vaccination is acceptable
- –*Less than 2 mg/kg/day (<20 mg/day if >10 kg; daily or alternating days) of prednisone or equivalent*: vaccination is acceptable
- –*Greater than or equal to 2 mg/kg/day (≥20 mg/day if >10 kg; daily or alternating days) of prednisone or equivalent for <14 d*: vaccinate right after stopping steroid therapy (do not vaccinate if steroid therapy will extend to ≥14 d)
- –*Greater than or equal to 2 mg/kg/day (≥20 mg/day if >10 kg; daily or alternating days) of prednisone or equivalent for ≥14 d*: vaccinate 1 mo after stopping therapy

[t] *Traditional* DMARDs include methotrexate, hydroxychloroquine, sulfasalazine, azathioprine, 6-mercaptopurine, leflunomide, cyclophosphamide, cyclosporine. *Targeted* DMARDs include apremilast, tofacitinib. BRMs include tumor necrosis factor inhibitors (eg, etanercept, infliximab, adalimumab, golimumab, certolizumab), selective costimulation modulators (eg, abatacept), anti–B-cell therapies (eg, rituximab), Janus kinase inhibitors (tofacitinib, baricitinib, upadacitinib), interleukin blockers (dupilumab, ustekinumab, secukinumab, tocilizumab, risankizumab). The ACR maintains guidance on the use of COV in patients with rheumatic and musculoskeletal disease at https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf (accessed July 18, 2023).

[u] In general, the AAP recommends deferring RV until 12 mo after the last in utero exposure to a BRM (note that this might mean the baby ages out of eligibility to initiate the series). However, RV may be considered for infants whose mothers received the anti-TNF drugs certolizumab pegol (a pegylated humanized antibody Fab' fragment that does not cross the placenta) or infliximab (a humanized monoclonal antibody) (Biologic response-modifying drugs used to decrease inflammation. In Kimberlin DW, et al, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021). The ACR conditionally recommends giving RV to infants whose mothers received anti-TNF drugs during pregnancy but deferring RV until 6 mo in infants whose mothers received rituximab in the second and third trimesters. Anti-TNF drugs are not transferred through human milk.

Continued

TABLE 6.1 — *Continued*

[v] Any doses of Hib given within 14 d of starting chemotherapy, or during chemotherapy, should be repeated ≥3 mo after chemotherapy is completed.

[w] Studies demonstrate loss of immunity to some vaccine antigens after successful treatment for acute leukemia (Nilsson A, et al. *Pediatrics*. 2002;109:e91; Patel SR, et al. *Clin Infect Dis*. 2007;44:635-642; Esposito S, et al. *Vaccine*. 2010;28:3278-3284). Some centers favor testing for antibodies once chemotherapy is completed, with selective revaccination using antigens for which antibody levels have fallen below protective levels. The 2017 European Conference on Infections in Leukaemia recommended a booster dose of all vaccines in those children who were fully vaccinated before the diagnosis of acute lymphoblastic leukemia and completed chemotherapy 3-6 mo earlier (Mikulska M, et al. *Lancet Infect Dis*. 2019;19:e188-e199).

[x] Hayden PJ, et al. *Ann Oncol*. 2022;33:259-275.

[y] There are no national standards on whether to offer transplantation to patients who refuse vaccination (Feldman AG, et al. *Pediatr Res*. 2020;87:277-281).

[z] Susceptible patients ≥12 mo should receive a total of 2 doses (if time allows) of MMR (the minimum interval is 4 wk) and 2 doses of VAR (the minimum interval is 12 wk under 13 y and 4 wk thereafter). The last dose of either should be given ≥1 mo before transplantation. MMR may be given to infants 6-11 mo who are not immunosuppressed and have ≥4 wk before transplantation; if transplantation is delayed, MMR should be repeated at 12 mo (as long as transplantation is still ≥4 wk away). Some guidelines suggest the same approach for VAR. The last dose of any non-live vaccine should be given ≥2 wk before transplantation to ensure "take".

[A] HCT presents a complicated vaccination paradigm: the underlying disease itself may be immunosuppressive; the therapy used to prepare for transplantation ablates existing immunity; allogeneic and autologous transplants differ in terms of degree of immunosuppression; immunosuppressive therapy may be given after the procedure (sometimes for life); patients may receive passive immunization, intentionally or unintentionally, through blood products; and graft versus host disease may further compromise immune function and lead to end-organ failure, including splenic dysfunction. Moreover, the adopted immune system of the donor provides unreliable immunity of uncertain duration; fortunately, immune memory can be stimulated by immunization after engraftment. Vaccination of donors for the benefit of the recipient is not recommended.

[B] The RZV series should be given 2 mo before prophylactic antiviral therapy is discontinued.

General references: General best practice guidelines for immunization: altered immunocompetence. CDC Web site. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html. Accessed July 18, 2023; Kimberlin DW, et al, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021; Rubin LG, et al. *Clin Infect Dis*. 2014;58:309-318; Bass AR, et al. *Arthritis Rheumatol*. 2023;75:333-348.

Pregnant women have a higher risk of severe outcomes from COVID-19[27] and should be vaccinated.[28] Vaccination during pregnancy is highly effective in preventing infection and hospitalization of mothers[29] and preventing hospitalization of their young infants; in fact, in a large US case-control study, maternal vaccination after 20 weeks of pregnancy was 69% effective at preventing infant hospitalization.[30] Receiving COV during pregnancy does not increase the risk of adverse pregnancy outcomes or fetal anomalies, and instead is associated with a reduced risk of stillbirth, preterm birth, and admission to the neonatal intensive care unit.[31]

Pregnancy is also an *indication* for administration of Tdap—it is safe and protects the infant against pertussis.[32] In fact, in a retrospective cohort study involving nearly 150,000 newborns, maternal Tdap was 91% effective in preventing pertussis in the first 2 months of life and 69% effective during the entire first year.[33] A dose of Tdap is recommended during *every* pregnancy, early in the third trimester so as to maximize transfer of antibody to the infant (in 2023, both Adacel and Boostrix were labeled for use during pregnancy, although administration of >2 doses of either remains off-label).[34] Neonatal concentrations of anti-pertussis antibody are the highest when mothers are vaccinated between 27 and 30 weeks' gestation.[35]

While blunting of infant responses to pertussis and even CRM-conjugated vaccines is possible,[36,37] it is thought that immunization of pregnant women could prevent virtually all infant pertussis deaths.[38] Data from the Vaccine Safety Datalink (VSD) suggested a slightly increased risk of chorioamnionitis in women receiving Tdap during pregnancy.[39] However, a comprehensive study of 8178 vaccinated and 60,372 unvaccinated pregnant women in New Zealand showed no association between vaccination and chorioamnionitis, as well as a host of other adverse outcomes, including preterm labor, pre-eclampsia, gestational hypertension or diabetes, fetal growth restriction, antenatal bleeding, placental abruption, premature rupture of membranes, preterm delivery, and fetal distress.[40] Further analyses from the VSD show no increases in infant hospitalizations or deaths following vaccination during pregnancy.[41] Fathers and other infant caregivers should also have received a dose of Tdap (either Td or Tdap may be used for the routine decennial tetanus and diphtheria boosters). Uptake of Tdap during pregnancy increased markedly between 2006 and 2015.[42]

Women who might become pregnant should be immune to rubella. Documented history of at least 1 properly administered dose of a rubella-containing vaccine is sufficient proof of immunity (**Table 22.2**), although many women are tested for rubella antibody before conception or early in pregnancy, regardless of their vaccination history. Pregnant women who are not immune to hepatitis A and are at increased risk for infection or severe outcome should receive HepA.

FIGURE 6.1 — Optimizing Immunity to *S pneumoniae*

<table>
<tr><th colspan="2" rowspan="2"></th><th colspan="6">Age</th></tr>
<tr><th>≤23 mo</th><th>2-4 y</th><th>5 y</th><th>6-18 y</th><th>19-64 y</th><th>≥65 y</th></tr>
<tr><td colspan="2">Routine immunization for healthy persons</td><td rowspan="4">Doses of PCV15 or PCV20 at 2, 4, 6, and 12-15 mo (PCV13 may be used if it is the only available vaccine)
A series started with PCV13 may be completed with PCV15 or PCV20 without giving additional doses (the PCV series does not need to be restarted)
Fewer doses needed if immunization initiated >6 mo (see catch-up schedule, Figure 8.2)
No "special" immunization, regardless of condition</td><td>Follow catch-up schedule (Figure 8.2)</td><td colspan="3">Not recommended</td><td rowspan="4">Footnote c</td></tr>
<tr><td rowspan="3">Special immunization for high-risk persons</td><td>Chronic medical condition[a]</td><td>3 doses of PCV <12 mo, no doses 12-23 mo, and current age 24-71 mo: 1 dose of PCV15 or PCV20</td><td colspan="2">All recommended doses of PCV received ≤5 y, including ≥1 dose of PCV20: no additional doses</td><td>Footnote d</td></tr>
<tr><td>CSF leak or cochlear implant</td><td>No previous doses or any incomplete schedule and <3 doses by 24 mo: 1 dose of PCV15 or PCV20 ≥8 wk after the most recent dose and another dose of PCV15 or PCV20 ≥8 wk after that
All recommended doses of PCV received ≤5 y, including ≥1 dose of PCV20: no additional doses</td><td colspan="2">All recommended doses of PCV received ≤5 y, using PCV13 or PCV15 only (no doses of PCV20 or PPSV23 received): 1 dose of PCV20 or 1 dose of PPSV23 ≥8 wk after last dose
No doses of any PCV:
Option 1—1 dose of PCV20
Option 2—1 dose of PCV15 followed by 1 dose of PPSV23 ≥8 wk after PCV15</td><td>Footnote e</td></tr>
<tr><td>Immunocompromised[b]</td><td>All recommended doses of PCV received ≤5 y, using PCV13 or PCV15 only (no doses of PCV20 received): 1 dose of PCV20 or 1 dose of PPSV23 ≥8 wk after last dose</td><td colspan="2">All recommended doses of PCV received ≤5 y, including ≥1 dose of PCV20: no additional doses
All recommended doses of PCV received ≤5 y, using PCV13 or PCV15 only (no doses of PCV20 or PPSV23 received):
Option 1—1 dose of PCV20 ≥8 wk after last dose
Option 2—1 dose of PPSV23 ≥8 wk after last dose, then PCV20 ≥5 y after the dose of PPSV23
Option 3—1 dose of PPSV23 ≥8 wk after last dose, then PPSV23 ≥5 y after the dose of PPSV23
No doses of any PCV:
Option 1—1 dose of PCV20
Option 2—1 dose of PCV15 followed by 1 dose of PPSV23 ≥8 wk after PCV15</td><td>Footnote f</td></tr>
</table>

AAP, American Academy of Pediatrics; CGD, chronic granulomatous disease; IDSA, Infectious Diseases Society of America

Age-appropriate pneumococcal immunization should first be assessed and completed when appropriate, then consideration should be given to "special" pneumococcal immunization.

[a] Chronic heart disease (cyanotic congenital heart disease, cardiac failure, congestive heart failure, cardiomyopathy; excludes hypertension); chronic lung disease (chronic obstructive pulmonary disease, emphysema, asthma [for persons ≤18 y, this only includes moderate or severe persistent asthma]; diabetes mellitus (type 1 and 2 but not gestational); chronic kidney disease; alcoholism (persons ≥19 y only); chronic liver disease; current cigarette smoking (persons ≥19 y only; does not include vaping).

[b] Sickle cell disease (may include hemoglobin-S/beta thalassemia and hemoglobin-SC); other hemoglobinopathies; congenital or acquired asplenia; primary immune deficiency (B-cell or T-cell deficiencies, complement deficiency [especially C1 through C4; IDSA guidelines include deficiency of mannan-binding lectin], phagocyte defects [excludes CGD]); immunosuppression (long-term systemic corticosteroids, other immunosuppressive drugs [includes biologics], radiation therapy); HIV infection; chronic renal failure on maintenance dialysis; nephrotic syndrome; hematologic malignancy (leukemia, lymphoma [includes Hodgkin disease], multiple myeloma); generalized malignancy; solid organ transplant.

[c] See the following table:

Continued

FIGURE 6.1 — *Continued*

Prior vaccines	Option A	Option B
None (or only PCV7)	PCV20	PCV15 and PPSV23 ≥1 y† after PCV15
PPSV23 only (any age)	PCV20 ≥1 y after last dose	PCV15 ≥1 y after last dose
PCV13 only (any age)	PCV20 ≥1 y after last dose	PPSV23 ≥1 y† after last dose
PCV13 (any age) and PPSV23 <65 y	PCV20 ≥5 y after last dose	PPSV23 ≥5 y‡ after last dose
PCV13 (any age) and PPSV23 ≥65 y	PCV20 ≥5 y after last dose (shared clinical decision-making)	

† ≥8 wk if high-risk

‡ If immunocompromised or with CSF leak or cochlear implant, the minimum interval for PPSV23 is ≥8 wk since last PCV13 and ≥5 y since last PPSV23; for others, the minimum interval for PPSV23 is ≥1 y since last PCV13 and ≥5 y since last PPSV23

Pneumococcal Vaccine Timing for Adults. CDC Web site. https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.

[d] See the following table:

Prior vaccines	Option A	Option B
None (or only PCV7)	PCV20	PCV15 and PPSV23 ≥1 y after PCV15
PPSV23 only (any age)	PCV20 ≥1 y after last dose	PCV15 ≥1 y after last dose
PCV13 only (any age)†	PCV20 ≥1 y after last dose	PPSV23 ≥1 y after last dose (review at 65 y)
PCV13 (any age) and PPSV23 (any age)	No vaccine recommended (review at 65 y)	

† These adults were never recommended to receive PCV13.

Pneumococcal Vaccine Timing for Adults. CDC Web site. https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.

[e] See the following table:

Prior vaccines	Option A	Option B
None (or only PCV7)	PCV20	PCV15 and PPSV23 ≥1 y after PCV15
PPSV23 only (any age)	PCV20 ≥1 y after last dose	PCV15 ≥1 y after last dose
PCV13 only (any age)	PCV20 ≥1 y after last dose	PPSV23 ≥1 y after last dose (review at 65 y)
PCV13 (any age) and PPSV23 (1 dose, any age)	PCV20 ≥5 y after last dose	No vaccine recommended (review at 65 y)

Pneumococcal Vaccine Timing for Adults. CDC Web site. https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.

[f] See the following table:

Prior vaccines	Option A	Option B
None (or only PCV7)	PCV20	PCV15 and PPSV23 ≥8 wk after PCV15
PPSV23 only (any age)	PCV20 ≥1 y after last dose	PCV15 ≥1 y after last dose
PCV13 only (any age)	PCV20 ≥1 y after last dose	PPSV23 ≥8 wk after last dose then PPSV23 ≥5 y after Dose 1 of PPSV23 (review at 65 y)
PCV13 (any age) and PPSV23 (1 dose, any age)	PCV20 ≥5 y after last dose	PPSV23 ≥5 y† after last dose (review at 65 y)
PCV13 (any age) and PPSV23 (2 doses, any age)	PCV20 ≥5 y after last dose	No vaccine recommended (review at 65 y)

† The minimum interval for PPSV23 is ≥8 wk since last dose of PCV13 and ≥5 y since last dose of PPSV23

Pneumococcal Vaccine Timing for Adults. CDC Web site. https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf.

Adapted from Kobayashi M, et al. *MMWR*. 2022;71:109-117; Kobayashi M, et al. *MMWR*. 2022;71:1174-1181; Pneumococcal vaccination: who and when to vaccinate. CDC Web site. https://www.cdc.gov/vaccines/vpd/pneumo/hcp/who-when-to-vaccinate.html; Advisory Committee on Immunization Practices. CDC Web site. https://www.cdc.gov/vaccines/acip/index.html; Pneumococcal Vaccine Timing for Adults. https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf. All web sites accessed July 18, 2023.

FIGURE 6.2 — Optimizing Immunity to *N meningitidis*

		Vaccine	Age					
			2-23 mo	2-9 y	10 y	11-18 y	19-55 y	≥56 y
Routine immunization for healthy persons		MenACWY	Not recommended			MenACWY-CRM MenACWY-D, or MenACWY-T at 11-12 and at 16 y	Not recommended[e]	
		MenB	Not recommended			2-dose series of MenB-4C or MenB-FHbp at 16-18 y (SCDM)[f]	Not recommended[g]	
Special immunization for high-risk persons	**Complement deficiency**[a]	MenACWY	MenACWY-CRM series followed by regular boosters[h]	MenACWY-CRM, MenACWY-D, or MenACWY-T (2-dose primary series followed by regular boosters)[i,j]				
		MenB	Not recommended		2-dose series of MenB-4C or 3-dose series of MenB-FHbp followed by regular boosters[k]			
	Asplenia[b]	MenACWY	MenACWY-CRM series followed by regular boosters[l]	MenACWY-CRM, MenACWY-D, or MenACWY-T (2-dose primary series followed by regular boosters)[i,j]				
		MenB	Not recommended		2-dose series of MenB-4C or 3-dose series of MenB-FHbp followed by regular boosters[k]			
	HIV infection[c]	MenACWY	MenACWY-CRM series followed by regular boosters[l]	MenACWY-CRM, MenACWY-D, or MenACWY-T (2-dose primary series followed by regular boosters)[i,j]				
		MenB	Not recommended			2-dose series of MenB-4C or 3-dose series of MenB-FHbp[m] at 16-18 y (SCDM)	Not recommended[g]	
	Travel and other exposures[d]	MenACWY	MenACWY-CRM or MenACWY-D series[n]	Travel and outbreak exposure: 1 dose of MenACWY-CRM, MenACWY-D, or MenACWY-T[o] Microbiologists and residents of endemic areas with ongoing exposure: 1 dose of MenACWY-CRM, MenACWY-D, or MenACWY-T followed by regular boosters[j,p]				
		MenB	Not recommended		2-dose series of MenB-4C or 3-dose series of MenB-FHbp for microbiologists and persons exposed during outbreaks[k] Regular boosters for microbiologists and boosters for certain persons exposed during outbreaks[k]			

SCDM, shared clinical decision-making

Age-appropriate meningococcal immunization should first be assessed and completed when appropriate, then consideration should be given to "special" meningococcal immunization. See *Chapter 2: Vaccine Infrastructure in the United States—Policy and Recommendations* for explanation of SCDM. MPSV4, a pure polysaccharide vaccine, was historically preferred in certain situations when one-time vaccination was anticipated, but manufacture of the vaccine was discontinued in 2017.

[a] Persistent deficiency of C3, C5 through C9, properdin, Factor H, and Factor D (C2 and Factor I are not included), as well as patients receiving complement inhibitors (patients should begin immunization at least 2 wk before starting therapy, if possible; antibiotic prophylaxis should also be considered).

[b] Anatomic or functional asplenia, including sickle cell disease (may include hemoglobin-S/beta thalassemia and hemoglobin-SC).

[c] Considered a risk factor for invasive disease caused by serogroups A, C, W and Y, but not B.

[d] Persons traveling to, or residents of, countries where meningococcal disease is hyperendemic or epidemic (Saudi Arabia requires vaccination in the 3 y before travel to Mecca for the Hajj and Umrah); microbiologists with ongoing exposure to *N meningitidis*; and members of a defined risk group during community or institutional outbreaks of a vaccine serogroup.

[e] First-year college students 19-21 years of age living in residence halls should receive at least one dose of MenACWY-CRM, MenACWY-D, or MenACWY-T on or after their 16th birthday; in general, first-year students ≤21 y should have received one dose of either vaccine within 5 y of matriculation. Other persons 19-21 y who have not received a dose after the 16th birthday may be vaccinated.

Continued

FIGURE 6.2 — *Continued*

[f] The minimum interval between doses of MenB-4C is 1 mo and between doses of MenB-FHbp for healthy persons is 6 mo. If Dose 2 of MenB-FHbp is given ≤6 mo after Dose 1, another dose should be given ≥4 mo after Dose 2.

[g] A MenB series may be given at 19-23 y, but the preferred age is 16-18 y.

[h] DTaP can interfere with the immune response to meningococcus if given in the 4 wk before MenACWY-D; therefore, if MenACWY-D cannot be given before or on the same day as DTaP, the general recommendation is to wait 6 mo after giving DTaP before giving MenACWY-D (however, if MenACWY-D is inadvertently administered in the 6 mo after DTaP administration, the dose does not need to be repeated). Because DTaP does not interfere with the immunogenicity of MenACWY-CRM, and given the interference of MenACWY-D with PCV13 (see *Footnote l*) and the frequency of DTaP and PCV13 doses in infancy, MenACWY-CRM seems like the logical choice for infants and toddlers who are at risk for invasive meningococcal disease (however, the ACIP does not express a preference in this situation). The usual schedule is doses at 2, 4, 6, and 12 mo. If initiated at 3-6 mo, a 3- or 4-dose series is given, with Dose 2 (and Dose 3 if applicable) ≥8 wk after the previous dose until a dose is received at 7 mo or older, followed by an additional dose ≥12 wk later and after 12 mo. If initiated between 7-23 mo, the schedule is 2 doses separated by ≥3 mo, with Dose 2 being given after 12 mo. If MenACWY-D is the only meningococcal vaccine available, it may be used; the usual schedule at this age is doses at 9 and 12 mo, with the first dose being given ≥4 wk after completion of all PCV13 doses and all doses being given before or concomitantly with DTaP. For older children, any MenACWY vaccine may be used, but the "spacing rules" with DTaP still apply for MenACWY-D. Regardless of which vaccine is used under 24 mo, the first booster is given 3 y after the last dose; thereafter, doses are given every 5 y (any MenACWY vaccine may be used for the booster doses).

[i] For children who are eligible to receive DTaP, the "spacing rules" between DTaP and MenACWY-D apply (see *Footnote h*). A 2-dose primary series is given to immunocompromised persons because their response to one dose may be suboptimal. The minimum interval between the 2 doses is 8 wk. If Dose 1 has already been received, Dose 2 should be given at the earliest opportunity, and then boosters as appropriate. If the last dose is received before 7 y, the first booster is given in 3 y; otherwise, the first booster is given in 5 y. Either way, boosters are given every 5 y thereafter (any MenACWY may be used for the booster doses). For adolescents, the 5-yr boosters "reset the clock" for the routine dose at 16 y. Thus, for example, a high-risk child who receives 2 doses of MenACWY at 9 y would receive boosters at 14 y and every 5 y thereafter (the routine dose at 16 y would not be given).

[j] MenACWY-CRM is labeled for use at 2 mo-55 y; MenACWY-D at 9 mo-55 y; and MenACWY-T at ≥2 y. Use of multiple doses of MenACWY is off-label except for the infant series of MenACWY-CRM or a single booster dose at 15-55 y; 2 doses of MenACWY-D at 9-23 mo or a single booster dose at 15-55 y; and a single booster dose of MenACWY-T at ≥15 y.

[k] MenB boosters are recommended every 2-3 y for microbiologists and persons ≥10 y with complement deficiency, complement inhibitor use, or asplenia (the first booster should be given 1 y after completion of the primary series). A one-time booster dose is recommended for persons exposed during an outbreak if it has been >1 y since completion of a primary series (an interval as short as 6 mo may be considered by public health officials). The same product should be used for all doses, including boosters (if the previously received product is not known, the series should be restarted with the new product). If Dose 3 of MenB-FHbp is given ≤4 mo after Dose 2, another dose should be given ≥4 mo after Dose 3. If Dose 2 of MenB-FHbp is inadvertently given ≥6 mo after Dose 1, Dose 3 is not necessary. Use of MenB-4C and MenB-FHbp at >25 y is off-label. MenB is not recommended for travel.

[l] MenACWY-D can interfere with the immunogenicity of PCV13. Therefore, MenACWY-CRM is preferred for young children who are at high risk for both invasive meningococcal and pneumococcal disease, which includes those with asplenia and HIV infection. The usual schedule is doses at 2, 4, 6, and 12 mo. If initiated at 3-6 mo, a 3- or 4-dose series is given, with Dose 2 (and Dose 3 if applicable) ≥8 wk after the previous dose until a dose is received at ≥7 mo, followed by an additional dose ≥12 wk later and after 12 mo. If initiated between 7-23 mo, the schedule is 2 doses separated by ≥3 mo, with Dose 2 being given after 12 mo (if MenACWY-D is the only meningococcal vaccine available, it may be used; the usual schedule at this age is doses at 9 and 12 mo, with the first dose being given ≥4 wk after completion of all PCV13 doses and all doses being given before or concomitantly with DTaP). Regardless of which vaccine is used under 24 mo, the first booster is given 3 y after the last dose; thereafter, doses are given every 5 y (any MenACWY vaccine may be used for the booster doses, but the "spacing rules" with DTaP still apply for MenACWY-D [see *Footnote h*]).

[m] While not considered high-risk for invasive serogroup B disease, persons with HIV infection should receive the 3-dose series if MenB-FHbp is used because they may not respond optimally to the vaccine.

[n] Despite the potential for interference between DTaP and MenACWY-D, the "spacing rules" (see *Footnote h*) between the two vaccines do not need to be followed if MenACWY-D is the vaccine that is available, and the child is traveling or involved in a community outbreak. The usual schedule of MenACWY-CRM at this age is doses at 2, 4, 6, and 12-15 mo. The usual schedule of MenACWY-D is 2 doses 12 wk apart at 9-23 mo. Children who received HibMenCY-T (MenHibrix) in the past are not protected for travel and should receive either MenACWY-CRM or MenACWY-D.

[o] Until 2017, MPSV4 was recommended for adults ≥56 y for whom only one-time vaccination was anticipated. Since the vaccine is no longer available, use of MenACWY is considered acceptable (off-label recommendation for MenACWY-CRM and MenACWY-D).

[p] If the first dose is received before 7 y, the first booster is given in 3 y; otherwise, the first booster is given in 5 y. Either way, boosters are given every 5 y thereafter (any MenACWY vaccine may be used for the booster doses).

Adapted from Mbaeyi SA, et al. *MMWR*. 2020;69(RR-9):1-41.

FIGURE 6.3 — Vaccination of Solid Organ Transplant Patients

On the left is the time period before transplantation, when routine vaccines may be given and special vaccines may be called for, depending on the underlying disease and degree of immune competency. Live vaccines may be given up to 4 wk before the anticipated transplantation; after that point, the concern is that peri-transplant immunosuppression could result in disease caused by the vaccine. Non-live vaccines may be given up to 2 wk before the anticipated transplantation; after that point, there is concern that peri-transplant immunosuppression could result in suboptimal responses. On the right is the time period after transplantation. In general, resumption of vaccination is delayed during the immediate post-transplant period, when immunosuppression is greatest; however, IIV may be given as soon as 1 mo post-transplant if there is a community outbreak. Other non-live vaccines may be given in the period 2-6 mo after transplantation but should be withheld during any period of intense immunosuppression out of concern for suboptimal responses. The routine schedule is usually not resumed until 6 mo post-transplantation. Live vaccines are generally contraindicated after transplantation.

In considering vaccination and pregnancy, clinicians should be aware of the following:

- Approximately 2% of all newborns have a major congenital malformation; it follows that some women who are vaccinated during pregnancy will have infants with birth defects. While a causal relationship with the vaccine may be lacking, there may be a tendency to attribute the birth defect to the vaccine.
- Very few vaccines have been tested for safety and efficacy in large numbers of pregnant women. Historically, pharmaceuticals, including vaccines, were assigned specific categories (A, B, C, D, and X) in an attempt to indicate the risk of use during pregnancy. This system was abandoned in 2014; labels now contain a summary of the risks of use during pregnancy and lactation, a discussion of the supportive data, and information to help providers counsel women about administration while pregnant.[43]
- Live vaccines are generally contraindicated during pregnancy, with the exceptions noted in **Table 6.5**. However, inadvertent receipt of live vaccines is not a reason to terminate a pregnancy. If a pregnant woman is known to be susceptible to varicella and someone in the environment develops a rash after vaccination with VAR, close contact should be avoided until the vaccinee's lesions are crusted (the Varivax package insert [March 2023] mentions the possibility of transmission from vaccinees without rash). Some manufacturers maintain registries of women inadvertently vaccinated during pregnancy; the phone numbers for reporting are usually given in the package insert. Merck, for example, maintained a registry of women inadvertently given VAR during pregnancy from 1995 to 2012[44]; there were no outcomes suggestive of congenital varicella syndrome in any of the 928 pregnancies reported, and the prevalence of major birth defects was similar to the general population.
- Pregnancy should be avoided during the 4 weeks after receipt of MMR, MMRV, YFV, and VAR.
- The only live vaccine that is contraindicated in household contacts of pregnant women is live, attenuated smallpox vaccine (pre-event).
- Immune responses in pregnant women may be suboptimal, and there is the theoretical concern that in-utero antigen exposure could lead to immune tolerance in the baby.
- There are no known risks of passive immunization during pregnancy. In fact, IGIV is *recommended* for susceptible pregnant women exposed to measles, and VariZIG is recommended for susceptible pregnant women who are exposed to varicella, because the risk of complicated disease in the mother is high (see *Chapter 22: Measles, Mumps and Rubella* and *Chapter 32: Varicella*).

TABLE 6.2 — Use of MMR and VAR in Susceptible Pediatric Solid Organ Transplant Patients

Vaccination	Criteria
Decisions about use of MMR and VAR in transplant patients should be made in collaboration with the appropriate transplant medicine providers and will depend on the risk of exposure to illness in the community. Families should be informed about possible adverse events like fever and rash and should be instructed to seek medical attention if these occur.	
Defer	Any one of the following: ■ Cardiac, lung, or multi-visceral transplant ■ Clinically unwell ■ High-level immune suppression ■ Current rejection ■ Use of novel biologic agents (other than those listed here) ■ Use of any of the following – Anti-thymocyte globulin in the past 1 y – Alemtuzumab in the past 2 y – Rituximab in the past 1 y
May be considered	Meets *Probably safe* criteria but has ≥1 of the following: ■ Received mycophenolate mofetil (MMF)/ mycophenolate sodium ■ Received anti-thymocyte globulin ≥1 y earlier ■ Received alemtuzumab ≥2 y earlier ■ Received rituximab ≥1 y earlier ■ Has persistently elevated Epstein-Barr virus load ■ Liver transplant recipient who is undergoing immune suppression withdrawal with the goal of cessation, or who is deemed to have "functional tolerance"
Probably safe	All of the following: ■ Does not meet *Defer* or *May be considered* criteria ■ Clinically well ■ All 3 of the following: – 1 y post-transplant AND 2 mo after any rejection episode

Continued

TABLE 6.2 — *Continued*

Vaccination	Criteria
Probably safe (*continued*)	– Steroids (prednisone equivalent) <2 mg/kg/day or total cumulative <20 mg/ day AND tacrolimus <8 ng/mL for two consecutive readings and cyclosporine <100 ng/mL for two consecutive readings (if receiving these drugs) – ALC >1500 for children ≤6 y and >1000 cells/μL for children >6 y AND CD4 >700 cells/μL for children ≤6 y and >500 cells/μL for children >6 y AND normal total serum IgG for age

Adapted from Suresh S, et al. *Pediatr Transplant*. 2019;23:e13571. The criteria are derived from data on kidney and liver transplantation (few data exist for heart, lung, intestine, and multi-visceral transplantation). In this guideline, MMR is suggested only for susceptible patients living in, or traveling to, high-incidence areas for measles or mumps, as well as in outbreak situations; routine vaccination in low-incidence situations is discouraged because the risks may outweigh the benefits. In contrast, VAR is routinely recommended for susceptible patients. See **Tables 22.2** (measles, mumps, and rubella) and **32.2** (varicella) for definitions of *susceptible*.

- Breast-feeding is not a contraindication to the use of any vaccines, including live ones, except for pre-event use of live, attenuated smallpox vaccine. YFV should be avoided in breast-feeding women, but it can be given when the mother's risk of acquiring yellow fever is high (breastfeeding women who receive YFV should consider temporarily suspending breastfeeding, pumping, and discarding pumped milk for at least 2 weeks).

The rationale for immunization during pregnancy is solid,[45] and most pregnant women will accept vaccination if it is recommended by their health care provider.[46] In 2008, an ACIP working group offered guidance on the drafting of recommendations for vaccination during pregnancy and breast-feeding,[47] and since then regulatory and legal barriers to vaccination during pregnancy and breast-feeding have been lifted. Of particular note, pregnant women are no longer classified as a "vulnerable population" with respect to participation in clinical research, and the National Vaccine Injury Compensation Program (see *Chapter 3: Standards, Principles, and Regulations—National Vaccine Injury Compensation Program [VICP]*) now covers both mothers and children who were in utero at the time the mother received a covered vaccine.[48]

TABLE 6.3 — Revaccination of HCT Recipients[a]

Vaccine	Age	When to Initiate After Transplantation	Regimen[b]	Comments
COV	≥6 mo	≥3 mo	Follow the schedule for unvaccinated immunocompromised persons (**Figure 12.7**)	Patients who received ≥1 dose of COV before or during treatment should be revaccinated
DTaP	<7 y	≥6 mo	3-5 doses	Number of doses depends on age
DTaP/Tdap	≥7 y	3 DTaP then 1 Tdap		Alternative regimen: give a dose of Tdap followed by either 2 doses of DT or Td. Use of DT and DTaP >6 y, Adacel and Boostrix <10 y, and Adacel >64 y is off-label.
HepA	≥1 y	2 doses		Especially important for patients with GVHD because of potential for serious consequences of infection. IGIM and vaccine are recommended for immunocompromised persons who are traveling (**Table 6.6**). Test for antibody to HAV ≥1 mo after vaccination.
HepB	All ages	3 doses		Test for HBsAb 1-3 mo after Dose 3; if negative, repeat the 3-dose series one time. Patients with GVHD are at risk for serious consequences of infection.
Hib	≥6 wk	3 doses		3 doses are given 4 wk apart starting 6-12 mo after transplant, regardless of Hib vaccination history. Use of ActHIB and PedvaxHIB >5 y and Hiberix >4 y is off-label.
HPV9	9-45 y	3 doses		The schedule is 0, 2, 6 mo. From 27-45 y, HPV is recommended based on SCDM.
IIV	≥6 mo	1 yearly		May be given as early as 4 mo after transplantation if there is a community outbreak, but a second dose 4 wk later should then be considered. Children 6 mo-8 y being vaccinated for the first-time post-transplant need 2 doses ≥4 wk apart in the same season. Chemoprophylaxis should be considered for all patients during community outbreaks or after exposure, regardless of vaccination status. LAIV is contraindicated.
IPV	≥6 wk	3 doses		May be given as early as 3 mo after transplantation.
MenACWY	11-18 y	2 doses Revaccination at 16-18 y		HCT patients are not at risk for invasive meningococcal disease per se unless they have other risk factors (**Figure 6.2**) such as anatomic or functional asplenia (commonly seen with chronic GVHD). However, all children should receive MenACWY at 11-12 y (HCT patients receive a 2-dose primary series) followed by one-time revaccination at 16-18 y. HCT patients who are 16-18 y should receive a 2-dose primary series only. Revaccination is recommended every 5 y for all who remain at high risk. MenACWY-D should not be used concomitantly with PCV13 in children who are functionally or anatomically asplenic. MenACWY-CRM is labeled for use at 2 mo-55 y; MenACWY-D at 9 mo-55 y; and MenACWY-T at ≥2 y. Use of multiple doses of MenACWY is off-label except

Continued

TABLE 6.3 — *Continued*

Vaccine	Age	When to Initiate After Transplantation	Regimen[b]	Comments
MenACWY (*continued*)				for the infant series of MenACWY-CRM or a single booster dose at 15-55 y; 2 doses of MenACWY-D at 9-23 mo or a single booster dose at 15-55 y; and a single booster dose of MenACWY-T at ≥15 y.
MenB	≥10 y	2 doses of MenB-4C or 3 doses of MenB-FHbp		See above regarding meningococcal disease risk. Patients with anatomic or functional asplenia should receive a MenB series, with periodic booster doses per **Figure 6.2**; they should also be placed on penicillin prophylaxis. Others may be vaccinated at 16-18 y (SCDM).
MMR	≥1 y	Contraindicated if <24 mo since transplantation 2 doses if ≥24 mo since transplantation, seronegative and immunocompetent		Defer MMR after last dose of antibody-containing product (see **Table 5.2**). Patients who have chronic GVHD should not be vaccinated. Defer MMR for 8-11 mo after cessation of immunosuppressive therapy for GVHD. Use of MMR in immunocompromised persons is off-label. IGIV should be given to all measles-exposed patients regardless of personal history of disease or vaccination. MMRV should not be used.
PCV PPSV23	≥6 wk	4 doses of PCV20	—	Vaccination may begin 3 mo after transplantation. The first 3 doses of PCV20 should be given at 4-wk intervals; Dose 4 should be given 6 mo after Dose 3 or 12 mo after transplantation, whichever is later. PCV15 may be used as an alternative to PCV20; in this case, 3 doses of PCV15 should be given at 4-wk intervals, followed by a dose of PPSV23 ≥1 y after the last dose of PCV15 (substitute PCV15 for PPSV23 if the patient has GVHD). Patients who have already received PCV13 or PCV15 after transplantation can transition to PCV20 at any time (the previous doses of PCV13 and PCV15 "count"). Patients with chronic GVHD who are functionally asplenic should be placed on penicillin prophylaxis.
RV	—		—	Cannot be initiated beyond infancy.
RZV	≥19	2 doses	—	Series should start 6-12 mo after allogeneic and 3-12 mo after autologous HCT and should be completed before antiviral prophylaxis is discontinued
VAR	≥1 y	Contraindicated if <24 mo since transplantation 2 doses if ≥24 mo since transplantation, seronegative and immunocompetent		Defer VAR after last dose of antibody-containing product (see **Table 5.2**). Patients who have chronic GVHD should not be vaccinated. Use of VAR in immunocompromised persons is off-label. VariZIG should be given to exposed patients who are not immune to varicella. MMRV should not be used.

Continued

TABLE 6.3 — *Continued*

GVHD, graft versus host disease; HBsAb, hepatitis B surface antibody; HCT, hematopoietic cell transplantation; IGIM, immune globulin intramuscular; IGIV, immune globulin intravenous; SCDM, shared clinical decision-making

[a] This table gives recommendations for repeat vaccination in patients who were already immunized before transplant (HCT patients should be revaccinated regardless of the source of stem cells). First time, age-appropriate non-live vaccines can be given beginning 6 mo after transplant; live vaccines can be considered beginning 24 mo after transplant. Here are some examples: 1) a 6-y-old who was transplanted at 2 y and is now considered immunocompetent may receive 2 doses of MMR ≥1 mo apart and 2 doses of VAR ≥3 mo apart (for convenience, they could receive MMR and VAR now and MMR and VAR in 3 mo); 2) a 12-y-old who was transplanted 6 mo ago and had never received HPV can begin the 3-dose series now.

[b] **Table 5.1** gives minimum ages and intervals between doses and **Figure 8.2** (4 mo-6 y) and **Figure 8.3** (7-18 y) give catch-up schedules. In the case of revaccination of HCT patients, a 4-wk interval between doses of the same vaccine is reasonable.

Adapted from CDC. *MMWR*. 2000;49(RR-10);1-125; Tomblyn M, et al. *Biol Blood Marrow Transplant*. 2009;15:1143-1238; Rubin LG, et al. *Clin Infect Dis*. 2014;58:309-318; Pergam SA, et al. *Biol Blood Marrow Transplant*. 2019;25:e321-e330; Cordonnier C, et al. *Lancet Infect Dis*. 2019;19:e200-e212. General Best Practice Guidelines for Immunization. CDC Web site. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html. Accessed July 18, 2023.

TABLE 6.4 — Immunization for Pregnant Women: A Call to Action

- Assess vaccine status and discuss which vaccines should be received and when, ideally during the first prenatal visit.
- Strongly recommend that all pregnant women and anyone who resides in their households receive an influenza vaccine annually.
- Strongly recommend that all pregnant women receive a Tdap vaccine between 27 and 36 wk of gestation in each pregnancy, preferably during the earlier part of this time period.
- If a pregnant woman declines vaccination, inquire about her reasons; reintroduce the discussion and offer the immunization at the next office visit.
- Become educated on the safety and efficacy of vaccines during pregnancy and be comfortable communicating this information thoroughly to patients.

Adapted from Maternal Immunization Task Force. https://www.acog.org/programs/immunization-for-women/activities-initiatives/immunization-for-pregnant-women-a-call-to-action. Accessed July 18, 2023.

Newborns

Newborn immunity is complex. De-novo humoral responses are impaired, and protection during the first few months of life largely derives from transplacental maternal IgG. However, this is potentially a double-edged sword, since higher concentrations of antibody at birth correlate with decreased responses to primary infant immunization.[49] Newborns also have increased regulatory T-cells and decreased Th1-cells, presumably to prevent in-utero cellular responses to maternal tissues.

Nevertheless, newborns can respond well to some vaccines. In the US, the only vaccine routinely given at birth is HepB. HepB is immunogenic in infants and protection persists at least into young adulthood. Other advantages of the birth dose include potentially reducing the number of concurrent injections that must be given at the 2-month visit, increasing the likelihood that the entire 3-dose series (and other vaccine series) will be completed. The birth dose also emphasizes the importance of immunization for new parents, laying the groundwork for the routine infant schedule.

Preterm and Low Birth Weight Infants

Preterm (<37 weeks' gestation) and low birth weight (<2500 g) infants are at particular risk for vaccine-preventable diseases because of immune system immaturity and the possibility of decreased maternal antibody levels (robust transport of maternal IgG does not

TABLE 6.5 — Vaccine Use During Pregnancy

Administer Because of Pregnancy[a]	Administer in Certain Situations[b]	Contraindicated or Not Recommended[c]	Inadequate Data For Recommendation[d]
COV	AVA	Adenovirus	Cholera
IIV	Dengue	HepB-CpG	Ebola
RSV[e]	HepA	HepB3	Hib
Tdap	HepB	HPV9[f]	JEV
	IPV	LAIV	PCV13, PCV15, PCV20
	MenACWY	MMR[f]	PPSV23
	MenB	Live, attenuated, smallpox (ACAM-2000; pre-event)[g]	RZV[f]
	RAB	VAR[f]	Ty21a
	Smallpox (postexposure)		
	Td (Tdap preferred)		
	Typhoid (TViPSV)		
	YFV		

ACIP, Advisory Committee on Immunization Practices

[a] Pregnancy is an indication to give these vaccines.

[b] Pregnancy may be listed as a precaution for these vaccines, but they are not contraindicated during pregnancy; vaccines in this category may be given if there is a specific indication or special circumstance. Examples include AVA for a pregnant woman under emergency use provisions as directed by public health authorities; HepB for an unvaccinated pregnant injecting drug user; HepA for a pregnant woman who is not immune and is at increased risk for infection or severe outcome; RAB for a pregnant woman who is bitten by a bat; MenACWY for an unvaccinated pregnant woman who has been diagnosed with a terminal complement component deficiency; and YFV for a pregnant woman who is traveling to an endemic area and will not be able to avoid exposure. For the vaccines in this column, providers should use their best judgment in balancing the risks and benefits and should engage the patient in decision-making.

[c] Adenovirus vaccine, LAIV, MMR, and VAR, are contraindicated because they are live and there is the theoretical risk of harm to the fetus. Live, attenuated smallpox vaccine is known to cause fetal harm; one would use it in a pregnant woman only if there had been a definite exposure to smallpox. Inadvertent administration of these vaccines during pregnancy is not a reason to terminate the pregnancy. Pregnancy should be avoided for 1 mo following MMR, VAR and YFV and 6 wk following adenovirus vaccine. ACIP recommends against routine use of HPV in pregnant women, although this is a non-live vaccine that theoretically carries little risk of fetal harm.

[d] For vaccines in this category, ACIP either is silent on the matter or specifies that there is no recommendation. As of July 2023, recommendations for use of TBE vaccine had not been published.

[e] RSV vaccine during pregnancy protects infants from RSV-associated disease. An alternative to maternal vaccination is the use of nirsevimab, an anti-RSV monoclonal antibody, in infants.

[f] Vaccinate after pregnancy when appropriate.

[g] Data are insufficient to determine the risks of using the non-live, viral, nonreplicating smallpox vaccine (Jynneos) during pregnancy, although animal models show no evidence of harm to the developing fetus.

Adapted from Guidelines for vaccinating pregnant women. CDC Web site. https://www.cdc.gov/vaccines/pregnancy/hcp-toolkit/guidelines.html. Accessed July 18, 2023.

occur until the third trimester). Comorbidities contribute to risk and cause delays in immunization.[50] Initiating the immunization series in the nursery not only protects the child but also improves coverage rates later on.[51] Preterm and low birth weight infants should be vaccinated according to the routine schedule, using the routine doses, at the appropriate chronologic age; whereas responses to some antigens may be lower than those seen in term infants after the primary series, the majority of infants will be protected after the booster doses.[52] The only vaccine for which birth weight is relevant is HepB (**Table 18.2**).

RV should be given to preterm infants who are clinically stable and are being discharged from the nursery or who are already home, keeping in mind that the first dose should be given between 6 weeks and 14 weeks 6 days of age. Those who are remaining in the hospital should not receive RV—the vaccine virus strains are shed in the stool and there is the theoretical risk of transmission to other infants who may be acutely ill or ineligible for vaccination. Of note, some neonatal units have cautiously implemented rotavirus vaccination.[53]

Data are conflicting as to whether or not vaccination of preterm infants leads to significant cardiorespiratory events; nevertheless, such infants should be closely observed for at least 48 hours following vaccination.[54,55] Note that preterm birth is a precaution for MenACWY-CRM in infants <9 months of age because of the possibility of apnea with the intramuscular injection.

Inborn Errors of Metabolism

As many as 1 in 2500 children have genetic defects in enzymes that are required for breaking down organic compounds, so called *inborn errors of metabolism* (IEM). In as much as infections can precipitate crises in these children, prevention of disease through vaccination is important. However, some IEMs cause enough neurodevelopmental deterioration to raise issues for certain vaccines—for example, progressive neurological symptoms associated with an IEM would be a precaution for administration of DTaP but would also place a patient on the priority list for IIV. Other IEMs—notably, adenosine deaminase deficiency, purine nucleoside deficiency, high 5-nucleotidase levels, glycogen storage disease (GSD) Ib/Ic, Barth syndrome, methylmalonic aciduria, propionic acidemia, and lysinuric protein intolerance[56]—are associated with immune deficiency and represent a potential barrier to use of live vaccines. In these cases, immune function studies should be used as a guide to safe vaccination.

In general, the risk of metabolic decompensation depends on the defect and can be categorized as high (amino acid disorders, organic acidemias, urea cycle disorders, fatty acid oxidation disorders, mitochondrial disorders, and GSDs types 0, I, III, VI, and IX), moderate (lysosomal storage disorders, peroxisomal disorders, purine and pyrimidine disorders) or low (phenylketonuria, carbohydrate disorders, and GSDs types II, IV, V, VII, and VIII).[57] Fortunately, there is little evidence that even the highest risk children have increased adverse events following vaccination, and the possibility of metabolic decompensation may be substantial if a high-risk child contracts the natural disease. The AAP suggests that most children with IEM can be immunized on time and according to the routine childhood schedule.[58]

Adults ≥65 Years of Age

Older persons are at increased risk for vaccine-preventable diseases because of immune senescence, which also impairs their ability to respond well to vaccines.[59] As the world's population ages—the number of people ≥60 years of age is expected to reach 2 billion by 2050—attention has been drawn to the concept of *life-course immunization*, underscoring that vaccines are not just for kids.[60]

Approximately 90% of all influenza-associated deaths occur in persons ≥65 years of age.[61] Unfortunately, historical influenza vaccine efficacy is only slightly above 50% for those over 60 years of age and is even lower for those over 75. Higher dose and adjuvanted influenza vaccines demonstrate enhanced immunogenicity in older persons and are now preferred over standard inactivated vaccines—see *Chapter 20: Influenza*. Influenza vaccination has benefits beyond just preventing respiratory disease—it prevents cardiovascular morbidity and mortality as well.[62]

In 2004, it was estimated that pneumococcal pneumonia caused 1.4 million hospital days, nearly 200,000 emergency department visits and 16,000 deaths among persons ≥65 years of age in the US.[63] There is strong evidence of PPSV23 efficacy against invasive pneumococcal disease, with evidence of lower efficacy against pneumonia.[64] Results from the CAPITA (Community Acquired Pneumonia Immunization Trial in Adults) study—a randomized placebo-controlled trial of PCV13 conducted in the Netherlands in 84,496 subjects ≥65 years of age—showed that efficacy was 46% against vaccine-type pneumococcal pneumonia and 75% against vaccine-type invasive disease.[65] This prompted a new approach to immunizing adults ≥65 years of age in the US. namely giving PCV13 first, taking advantage of the demonstrated efficacy and the priming expected from a conjugate vaccine, and following up with PPSV23 to boost and broaden the immune response.[66] However, by 2019 it was clear that herd immunity induced by the childhood PCV13 program was protecting older adults; accordingly, the ACIP changed the recommendation for PCV13 in healthy persons ≥65 years of age from routine to one based on shared clinical decision-making.[67] The approval of higher valency PCVs in 2021, and the recognition that non-PCV13 serotypes continued to cause disease in older adults, prompted another change in the recommendations—healthy persons ≥65 years of age who have not previously received

PCV or whose vaccination history is unknown should receive one dose of either PCV20 (without subsequent PPSV23) or one dose of PCV15 followed by one dose of PPSV23 ≥1 year later.[68]

The severity of COVID-19 is directly related to age (**Figure 12.2**). For this reason, older adults are considered high priority for COVID-19 vaccination. Likewise, older adults are at risk for serious lower respiratory tract disease caused by RSV (see *Chapter 26: Respiratory Syncytial Virus*). See also *Chapter 34: Zoster* for prevention of shingles in older adults.

Health Care Personnel

Health care personnel (HCP) refers to all paid and unpaid persons who work in health care settings (including residential institutions) and have the potential to be exposed to patients or infectious materials. This includes physicians, nurses, nursing assistants, therapists, technicians, pharmacists, students, trainees, contractual staff, volunteers, and those who work in clerical, dietary, housekeeping, laundry, security, maintenance, administrative, billing, emergency medical, dental, laboratory, and autopsy capacities. HCP are at risk for acquiring vaccine-preventable diseases and transmitting them to their patients and their own families. The risk of infection might be particularly high for people working in emergency departments or ambulatory care settings, especially if the facility serves underimmunized populations. The consequences of transmission to patients might be particularly high wherever there are vulnerable patients, such as intensive care units, newborn nurseries, obstetric wards, chronic care facilities, and oncology or transplant units.

The rationale for immunization of HCP rests on three principles: 1) the role played by HCP in disease transmission to others; 2) the personal risks of disease acquisition; and 3) the role played by HCP as patient advocates.[69] Health care facilities should develop vaccination policies for all HCP, and these should be part of comprehensive occupational health and patient safety programs. Immunizations should be provided at no cost to the worker. Whereas vaccination cannot be forced upon HCP, some institutions have developed strategies wherein individuals must sign a release form to opt out, acknowledging that exposure to a vaccine-preventable disease may result in leave without pay and that worker's compensation benefits would not apply unless the disease actually developed. Other institutions have dismissed workers who refuse to be vaccinated (see *Chapter 3: Standards, Principles, and Regulations—Mandates and Exemptions*).

Comprehensive immunization recommendations for HCP were published in 1997[70] and were updated in 2011.[71] HCP should receive all routinely recommended vaccines. Those that deserve particular attention are discussed below.

- *HepB*: Cases of hepatitis B in HCP decreased dramatically in the 1980s and 1990s, due largely to routine vaccination and improved infection control practices. Immunization against hepatitis B is recommended for all HCP who are likely to be exposed to blood or blood-containing body fluids. In fact, the Bloodborne Pathogens Standard (see *Chapter 3: Standards, Principles, and Regulations—Occupational Safety and Health Administration [OSHA]*) mandates that vaccination be made available at no cost to employees with potential blood contact. Here are some general guidelines[72]:
  - Only HCP who come from high-prevalence geographic regions or who belong to specific risk groups, such as men who have sex with men, should be tested for hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb) before vaccination. Those who are chronically infected (HBsAg-positive) should not be excluded from work but should be counseled about which exposure-prone procedures they may perform safely. Those who are previously infected (positive for both HBsAb and hepatitis B core antibody [HBcAb]) but not chronically infected (negative for HBsAg) are considered immune and do not need vaccination.
  - All HCP who are not naturally immune and whose activities involve the potential for exposure to blood or body fluids should have received a complete HepB series.
  - For those who were never vaccinated in the past, testing for HBsAb should be done 1 to 2 months after the series is completed. An HBsAb level ≥10 mIU/mL is considered protective and nothing further needs to be done (for immunocompetent HCP who demonstrate an adequate response to vaccination, periodic testing for HBsAb is not recommended). If the level is <10 mIU/mL, a second 3-dose series should be given, with repeat HBsAb testing 1 to 2 months after completion. If the level is ≥10 mIU/mL, the person is considered protected.
  - HCP who received a complete HepB series any time in the past should be tested for HBsAb. If the level is ≥10 mIU/mL, they are considered protected and nothing further needs to be done. If it is <10 mIU/mL (antibody commonly wanes after many years), they should receive 1 dose of HepB and HBsAb should be measured 1 to 2 months later. A robust response (≥10 mIU/mL) indicates prior immune memory and nothing further needs to be done; a poor response (<10 mIU/mL) indicates the need for completing another HepB series, with repeat testing after the series is completed. An alternative strategy for recently-vaccinated HCP who are seronegative is to administer another complete HepB series and test for HBsAb 1 to 2 months later.

  - HCP who remain seronegative after two complete HepB series should be tested for HBsAg (chronic carriage can explain failure to respond to the vaccine) and HBcAb (antibody to the core antigen indicates prior natural infection). Those who are not previously infected (HBcAb-negative) and not immune (HBsAb-negative) are considered vaccine non-responders and should be counseled about precautions to prevent hepatitis B infection and the need for hepatitis B immune globulin if there is an exposure.
  - Guidelines for the management of potential occupational exposure to hepatitis B are given in **Table 18.3**.
- *IIV and LAIV*: HCP are at high risk of acquiring influenza at work and transmitting it to their patients, many of whom are at high risk for complicated disease. Moreover, hospital outbreaks have been associated with low HCP vaccination rates.[73] All HCP should be immunized against influenza in the fall of each year. HCP who are in close contact with severely immunosuppressed patients (the equivalent of HCT patients who are in protective environments) should only receive IIV; HCP who receive LAIV should avoid contact with such patients for 7 days after vaccination. HCP who work in the neonatal intensive care unit may receive LAIV. HCP who themselves are too old to receive LAIV or have medical contraindications may nevertheless administer LAIV to others.
- *MMR*: HCP are at high risk for acquiring measles and medical settings play a prominent role in perpetuating outbreaks.[74] Mumps transmission also occurs in medical settings.[75] Moreover, responding to hospital-associated measles and mumps outbreaks is expensive. Before it was eliminated from the US, rubella transmission in medical settings was well documented. For these reasons, all HCP should be immune to measles, mumps, and rubella (see **Table 22.2** for evidence of immunity). HCP with documentation of having received 2 properly timed doses of MMR are presumed to be immune to measles, mumps, and rubella (technically speaking, immunity to rubella is defined as at least 1 appropriately administered dose of vaccine; practically speaking, most people get 2 doses because they receive the rubella vaccine as MMR). Serological tests are not recommended in this circumstance (in fact, the history of being vaccinated trumps negative serological test results). HCP without evidence of immunity should receive 2 doses of MMR separated by ≥28 days. There is no risk of horizontal transmission of the viruses in MMR.
- *Tdap*: Pertussis is transmitted in hospitals and serological studies show that exposure of HCP is common. To boost pertussis immunity, all HCP should receive a dose of Tdap, regardless of age and regardless of when the last dose of Td was received. Persons ≥65 years of age may be vaccinated (use of Adacel for persons >64 years of age is off-label).[76] The dose of Tdap "resets the clock" for subsequent decennial tetanus and diphtheria boosters, and either Td or Tdap may be used for those.
- *VAR*: Nosocomial transmission of varicella can occur from cases of chickenpox as well as shingles, and the consequences can be devastating to certain patients. Providers with unrecognized varicella could expose many patients and other HCP, resulting in time-consuming and costly responses. All HCP should be immune to varicella (see **Table 32.2** for evidence of immunity). HCP who are not immune should receive 2 doses of VAR separated by 4 to 8 weeks. Even though VAR is a live vaccine, vaccinated HCP can return to work immediately. However, if a vaccine-related rash develops, they should avoid contact with persons who are not immune and are at risk for severe or complicated disease, at least until the lesions are crusted over (if there are only macules and papules, they should wait until there are no new lesions within a 24-hour period). Vaccinated HCP who are exposed to chickenpox or shingles should be observed carefully during the 8 to 21 days after exposure; symptoms suggestive of varicella should prompt a medical leave, and if varicella develops, the worker should remain on leave until all the lesions are crusted or faded and there are no new lesions within a 24-hour period. HCP who have had only one dose of VAR and are exposed to chickenpox or shingles should receive a second dose within 5 days of exposure (as long as it has been at least 4 weeks since the first dose) and should be observed carefully as above. Those who do not receive a second dose, or who receive a second dose >5 days after exposure, should be furloughed during days 8 to 21 postexposure. Exposed HCP with no evidence of immunity should be vaccinated and furloughed as above; those who cannot be vaccinated (eg, pregnant or immunocompromised) and are at risk for complicated disease should receive VariZIG.

International Adoptees, Refugees, Immigrants and Others Vaccinated Outside the United States

The Immigration and Nationality Act requires all immigrants entering the US to show proof of having received all ACIP-recommended vaccines before a visa is granted. The CDC uses the following criteria to determine which ACIP-recommended vaccines are required: the vaccine must be age-appropriate and must either protect against a disease that has the potential to cause an outbreak or protect against a disease that has been eliminated or is in the process of being eliminated in the US.[77] Based on these criteria, HPV and RZV are not required. International adoptees ≤10 years of age can be exempted from this requirement, but the adoptive parents must sign an affidavit indicating their intention to comply with

immunization requirements within 30 days after the child arrives (children coming from Hague Convention countries such as China and the Philippines cannot be exempted). Refugees are exempted from immunization requirements at the time of entry but must show proof of immunization at the time they apply for permanent residency (since 2012 the CDC has had a program to vaccinate refugees overseas before they come to the United States[78]).

The following issues are germane to the immunization management of persons from other countries, particularly international adoptees[79]:

- Vaccination records are considered valid only if they are in written form and contain the vaccines, dates of administration, proper intervals between doses, and age at the time of immunization (one exception is influenza vaccine, for which self-report is considered valid).
- Written records must be translated and interpreted correctly, and even then, may be inaccurate or fraudulent.
- In general, vaccine doses are considered valid if the schedule, including minimum ages and intervals, is similar to the US schedule (exceptions include doses of Aimmugen, a form of HepA, and Twinrix Jr., a combination of HepA and HepB, which is considered valid only for the HepB component).
- Even written records indicating adequate vaccination do not necessarily predict immunity.[80]
- Many immigrant adults are susceptible to vaccine-preventable diseases.[81]
- Some children will need additional vaccines to comply with the US schedule.
- Vaccines in some countries may have inadequate potency, especially because of improper handling. Country of origin predicts seroprotection, with the highest rates in children adopted from Eastern Europe, then, in descending order, India, Latin America, China, and Africa.[82]
- Serologic correlates of protection exist for some diseases but not for others. Testing may be expensive, and the results require interpretation.
- International adoptees may have subclinical vaccine-preventable diseases that constitute a risk to close contacts in the US. For example, children from endemic countries may have hepatitis A without jaundice when they arrive. This is the basis for HepA vaccination of persons who will be in close contact with them during the first 60 days after arrival (the first dose should be given at least 2 weeks before arrival).[83]

Here are a few things to know about specific vaccines (see also *Chapter 8: Routine Schedules* as well as individual vaccine chapters):

- *Diphtheria, tetanus, and pertussis*—If the record shows ≥3 doses of DTP or DTaP, testing for IgG antibody to diphtheria and tetanus can be done. If the levels are protective, the recorded doses are considered valid, and age-appropriate immunization can be completed. If the levels are indeterminant, a single dose of DTaP may be given and antibodies rechecked 1 month later; protective levels indicate an anamnestic response, the previous doses are considered valid, and age-appropriate immunization may continue. Revaccination without testing is safe and avoids the problem of interpreting results. Providers should be aware that local adverse reactions can occur with Doses 4 and 5 of DTaP. If a severe local reaction occurs with DTaP revaccination, IgG antibody to diphtheria and tetanus should be measured; if the levels are protective, no further doses of DTaP should be given.
- *COV*—The requirement for nonimmigrant and noncitizen air passengers to show proof of vaccination against COVID-19 before boarding a flight to the US, enacted on October 30, 2021, was lifted on May 12, 2023.[84]
- *Hepatitis A*—Children 12 to 23 months of age without documentation of complete vaccination or serologic evidence of immunity should be vaccinated on arrival.
- *Hepatitis B*—A person who received a complete HepB series is considered protected, and additional doses are not needed if ≥1 dose was given at ≥24 weeks of age (if the last dose was given at <24 weeks of age, another dose should be given at ≥24 weeks of age). People who are incompletely vaccinated or unvaccinated should be caught up. All people born in Asia, the Pacific Islands, Africa, and other regions where hepatitis B is endemic should be tested for HbsAg. Household members of HBsAg-positive children or adults should be vaccinated if they are not already immune.
- *Haemophilus influenzae* type b—Since interpretation of serologic tests is difficult, age-appropriate vaccination is suggested (Hib is not routinely recommended at ≥5 years of age).
- *Neisseria meningitidis*—Adolescents in other countries are not routinely vaccinated (the United Kingdom is an exception).
- *Measles, mumps, and rubella*—Revaccinating with 1 or 2 doses of MMR is the simplest approach (there is no harm in doing so even if the patient has natural or vaccine-induced immunity). Whereas serologic testing for IgG antibody to measles and rubella is widely available, mumps immunity can only be assumed if the record shows receipt of MMR or MMRV and the patient has IgG antibodies to measles. Patients who only received measles or measles-rubella vaccine need revaccination.

- *Streptococcus pneumoniae*—PCV may not be routine in non-industrialized countries, so age-appropriate revaccination may be warranted.
- *Polio*—Revaccinating persons <18 years of age with IPV is the simplest approach. Children who received OPV in developing countries may be sub-optimally protected. Immunity to all 3 serotypes is required in the US, and children receiving OPV after April 2016 probably received 2-valent (serotypes 1 and 3) vaccine (see *Chapter 24: Polio*).
- *Rotavirus*—Infants ≤8 months, 0 days of age with an incomplete RV series initiated outside the US should complete the series by age 8 months, 0 days. The RV series should not be initiated for infants ≥15 weeks, 0 days of age.
- *Tetanus, diphtheria, pertussis*—Children ≥7 years of age who are incompletely vaccinated against pertussis should receive Tdap. If additional doses of tetanus or diphtheria vaccine are needed, Td should be used after the dose of Tdap.
- *Varicella*—VAR is not part of the routine schedule in most countries.
- *Zoster*—For persons who have not received zoster vaccine, the RZV series should be offered at the first clinical encounter. It is not necessary to ask about a personal history of varicella or to have serologic testing done prior to vaccination.

Travel Outside the United States

Travelers going to Canada, Western Europe, Australia, and New Zealand are probably at no higher risk for illness than those traveling within the US, although the situation with COVID-19 variants is dynamic and unpredictable. Measles is a common vaccine-preventable disease associated with travel, with exposures occurring both in destination countries as well as on airplanes and in airports (of note, the United Kingdom is now considered a measles-endemic region).[85] For some destinations, consideration may need to be given to specialized vaccines or to accelerated schedules for routine vaccines, depending to some extent on what circumstances the traveler will encounter. Travel to certain areas may require other measures, including malaria chemoprophylaxis, insect avoidance, food hygiene, and ensuring the availability of emergency medical services. Moreover, certain persons may be at higher risk than others for particular diseases. In an international study of nearly 40,000 returned travelers from 1997 to 2007, the most common vaccine-preventable diseases were enteric fever (typhoid and paratyphoid), acute viral hepatitis, and influenza.[86] Risk factors for infection with *S typhi* were traveling to visit friends and relatives and travel to South Central Asia; business travel was a risk factor for influenza and prolonged travel for hepatitis A.

Travel medicine clinics, which may be available at local health departments, academic medical centers, or in private practice settings, maintain up-to-date information and provide vaccination services for travelers. Consultation should take place at least 4 to 6 weeks before departure in order to allow for the development of protective immunity after vaccination (more time may be required if certain vaccines will need to be ordered). Also, it is not enough to know where a person will be traveling, as the duration of stay and the particular activities in which the person will be engaged can help determine risk—a 2-day stay, for example, in an urban hotel carries different risks than extended field work in rural areas.

All travelers should be up to date on routinely recommended vaccines, including COV. Some special considerations are listed below.

- *Childhood vaccination schedule*: The routine childhood schedule (**Figure 8.1**) provides some flexibility in the timing of doses. For example, Dose 3 of HepB and IPV can be given as early as 6 months of age and Dose 4 of Hib and PCV as early as 12 months of age. Dose 4 of DTaP can be given as early as 12 months of age provided that at least 6 months have elapsed since Dose 3. VAR can be given as early as 12 months of age. Infants 6 to 11 months of age who will be traveling anywhere outside the US (even places like Canada, but not including US territories like Puerto Rico, the Virgin Islands, American Samoa, etc) should receive MMR, but that dose does not count towards the routine childhood series (there's the risk that it will not "take" because of maternal antibody), and the child should be revaccinated beginning at 12 months of age. Vaccination of infants <6 months of age is not necessary because most will already be protected by maternal antibodies. International travel for infants exposed to biologic response modifiers (other than certolizumab) in utero should be discouraged for the 12 months following the last maternal dose during pregnancy. All persons ≥1 year of age should have a history of 2 doses of MMR documented before traveling (the minimum interval is 28 days). A documented history of 2 doses of VAR at ≥1 year of age is also recommended (unlike MMR, VAR is not recommended for traveling infants <1 year of age); the minimum interval from 1 to 12 years of age is 3 months and at ≥13 years of age is 4 weeks. See below for discussion of other routine vaccines such as HepA, HepB, influenza and polio.
- *Adult vaccination schedule*: Adults should be up to date on all recommended vaccines (**Figure 8.5** and **Figure 8.6**). Tetanus and diphtheria boosters are recommended every 10 years and may be given as either Td (in persons who have already received a dose of Tdap) or Tdap (whether or not a previous dose of Tdap has been given). However, if >5 years have elapsed since

TABLE 6.6 — Pre-exposure Hepatitis A Prophylaxis

Age	Health Status	HepA[a]	IGIM[b]
<6 mo	Healthy	No	Yes
	Immunocompromised[c] or chronic liver disease[d]	No	Yes
6-11 mo[e]	Healthy	Yes[f]	No
	Immunocompromised[c] or chronic liver disease[d]	Yes[f]	Risk assessment[g]
12 mo-40 y	Healthy	Yes	No
	Immunocompromised[c] or chronic liver disease[d]	Yes	Risk assessment[g]
≥41 y	Healthy	Yes	Risk assessment[g]
	Immunocompromised[c] or chronic liver disease[d]	Yes	Risk assessment[g]

IGIM, immune globulin intramuscular

These recommendations apply to unimmunized persons.

[a] One dose of HepA at any time before departure is likely to provide protection for most healthy persons. Those who received Dose 1 in the past 6 mo do not need another dose before departure, but they should receive Dose 2 at an interval of 6-18 mo. Those who received Dose 1 >6 mo earlier should receive Dose 2 before departure. IGIM should be given if HepA is contraindicated or refused.

[b] The dose of IGIM is 0.1 mL/kg for stays up to 1 mo and 0.2 mL/kg for stays up to 2 mo. Repeat doses of 0.2 mL/kg should be given every 2 mo during extended stays. There is no maximum dose. If both HepA and IGIM are indicated they should be given simultaneously at different sites (eg, separate limbs). MMR and VAR, if indicated, should be deferred for 3 mo after receipt of IGIM (see *Footnote e* for infants 6-11 mo).

[c] Congenital or acquired immunodeficiency; HIV infection; chronic renal failure or on dialysis; solid organ or stem cell transplant recipient; immunosuppressive therapy.

[d] Chronic hepatitis B or C; cirrhosis; fatty liver disease; alcoholic liver disease; autoimmune hepatitis; transaminases more than twice the upper limit of normal.

[e] MMR is indicated for healthy infants in this age group traveling outside the US and may be given at the same time as HepA. Because MMR cannot be given at the same time as IGIM, and because measles is more severe in infants than hepatitis A, MMR should be given preference over IGIM (keep in mind that MMR is contraindicated in certain immunocompromised persons).

[f] Doses of HepA in this age group are off-label and do not count as part of the routine 2-dose series given at 12-23 mo.

[g] IGIM may be considered for persons at increased risk of infection (eg, traveling to a highly endemic area, visiting rural settings, trekking in back country areas, or frequently eating or drinking in areas with poor sanitation), at risk for suboptimal response to vaccination (eg, persons with HIV infection), or at increased risk for complications of infection (see *Footnotes c* and *d*). For persons traveling in <2 wk, IGIM may be administered at the same time as HepA but at a different anatomic site.

Adapted from Nelson NP, et al. *MMWR*. 2020;69(RR-5):1-38.

the last dose and the person will be working in situations where dirty wounds might be incurred, or traveling to regions where diphtheria outbreaks have occurred, a booster dose should be considered.

- *HepA*: Recommendations for preventing hepatitis A in travelers to endemic regions are given in **Table 6.6**. Risk is considered high pretty much everywhere in the world except for North America, Japan, Australia, New Zealand, and Western Europe.
- *HepB*: HepB is recommended for all unvaccinated persons traveling to or working in countries with intermediate to high levels of endemic transmission, which, again, includes much of the world. Since exposure to blood or body fluids (through, for example, sexual contact or emergency medical treatment) may not be predictable, all travelers should be immunized.
- *Influenza*: Yearly influenza vaccine is recommended for everyone ≥6 months of age. Priority should be given to persons traveling to areas with influenza activity. This includes the southern hemisphere during April through September and the tropics at any time of year. Travel with organized tourist groups that include persons from the tropics or southern hemisphere is also a risk factor. People who were vaccinated during the preceding fall or winter *do not* need to be revaccinated before summer travel; however, those who are vaccinated only before summer travel *do* need to be revaccinated the next fall. Vaccine should be given at least 2 weeks before travel but can be given up to the day of travel if this is not possible. Priority should also be given to persons at risk for complicated influenza. Patients should understand that the vaccine strains used in the northern hemisphere during the fall may not optimally match the strains circulating in the southern hemisphere during April through September.[87]
- *Polio*: There are only 2 countries—Afghanistan and Pakistan—where polio continues to be endemic, but there are many others where some transmission of polio still occurs and where travelers may be at risk. If an infant is traveling to an area where polio has circulated in the last 12 months, the first dose of IPV can be given as early as 6 weeks of age, followed by an accelerated schedule with Doses 2 and 3 being given at 4-week intervals; the minimum interval between Dose 3 and Dose 4 is 6 months.[88] All persons ≥18 years of age who are unimmunized or incompletely immunized should complete a primary series with 3-valent IPV. Those who are traveling to an area where transmission is occurring should receive an accelerated schedule. If there is enough time, they should receive 2 doses separated by 4 to 8 weeks and a third dose 6 to 12 months after the second; if there are fewer than 8 weeks before departure, 3 doses should be given at 4-week intervals. If necessary, the series for both

children and adults can be completed in the destination country, using either trivalent IPV or OPV. Adults who were completely immunized in childhood with 3-valent OPV or IPV may receive an additional dose of IPV before travel to an area with continued circulation of polio.

In 2014, because of continued virus circulation in some countries, the World Health Organization declared the international spread of polio to be a "public health emergency of international concern." In response to this declaration, several countries (check the Web sites below for updates) now require proof of polio vaccination between 4 weeks and 12 months prior to *departing* the country (so that people *leaving* those countries do not spread polio elsewhere). This means that some travelers *going to* those countries who might not otherwise have needed an "extra" dose before travel should now receive one. So, for example, children and adolescents who are up to date on polio immunization—as well as adults who were up-to-date as children *and* had a previous adult booster for travel—who plan to stay >4 weeks and whose last dose of polio vaccine was >12 months before they anticipate *departing the destination country* (to return home, for instance), should receive an additional dose of IPV before they leave the US. Children who receive this "extra" shot between 18 months and 4 years of age will still need a booster at ≥4 years of age. Persons who will be in one of the designated countries for >12 months will need to get the "extra" immunization (IPV or OPV) while there. The situation has become somewhat complicated by the switch from 3-valent to 2-valent OPV in some countries (see *Chapter 24: Polio*).

Here are some considerations regarding diseases related to travel:

- *Rabies*: Travelers to most parts of the world should be vaccinated if exposure to animals is expected. At particular risk are persons spending a lot of time outdoors, especially in rural areas, or who are involved in activities such as bicycling, camping, hiking, and outdoor work. Children are considered at higher risk because they tend to play with animals and may not report bites. Spelunkers are also at risk because of potential exposure to bats.
- *Japanese encephalitis*: Immunization should be considered for travelers to East Asia, South Asia, Southeast Asia, and parts of the Southern and Western Pacific. The risk for short-term travelers and those staying in urban centers is very low. Risk increases with prolonged visits to rural settings and with extensive outdoor, evening, and nighttime exposures, including bicycling, camping, working outdoors, or sleeping in unscreened structures without bed nets.
- *Invasive meningococcal disease*: Travelers to Central, East and West Africa as well as Saudi Arabia should receive MenACWY. Risk is increased for travelers to sub-Saharan Africa (the "meningitis belt") during the dry season, especially if there is prolonged contact with local populations.
- *Typhoid fever*: Exposure is likely pretty much everywhere except North America and Western Europe. Risk is higher for those visiting relatives or friends and those who will not have access to cooked foods and safe beverages. Manufacture and distribution of Ty21a was discontinued from January 2021 to June 2022 due to decreased demand during the COVID-19 pandemic.
- *Yellow fever*: Risk is highest in Central, East and West Africa and parts of tropical South America. If there is no yellow fever in the country, vaccination may still be required of travelers coming from endemic areas, even if they are just in transit. For example, there is no risk of acquiring yellow fever in Haiti, but the country requires some travelers from endemic areas to have been vaccinated so that yellow fever is not introduced into the country. Vaccination must occur at a certified center and vaccinees must receive an *International Certificate of Vaccination or Prophylaxis* that carries a Uniform Stamp. Some countries with endemic yellow fever may waive the requirements for travelers coming from noninfected areas and staying <2 weeks. Vaccination is also recommended for travel to countries that lie in yellow fever-endemic zones but do not officially report the disease.
- *Cholera*: A live attenuated oral cholera vaccine (Vaxchora) is available for use in persons 2 to 64 years of age who are traveling to an area with active cholera transmission. A single dose should be taken at least 10 days before potential exposure. Manufacture and distribution of oral cholera vaccine was discontinued from May 2021 to May 2023 due to decreased demand during the COVID-19 pandemic.
- *Ebola*: Vaccination is recommended for persons ≥18 years of age who are responding to an Ebola virus disease outbreak.
- *Dengue*: Vaccination is recommended for children 9 to 16 years of age who have laboratory evidence of previous infection and live in endemic areas.
- *Tick-borne encephalitis*: In February 2022, the ACIP voted to recommend TBE vaccine for persons moving or traveling to endemic areas who will have extensive exposure to ticks.

Finally, a word about *mandatory vaccines*. The only vaccine covered by international health regulations at the present time is YFV. However, some countries have their own regulations. For example, Saudi Arabia requires meningococcal vaccine for pilgrims visiting Mecca for the Hajj, and some countries may require the vaccine for persons returning from the Hajj. No country requires cholera vaccination as a condition of entry.

The following Web sites are very helpful in planning vaccination for travel (accessed July 18, 2023):

- *Centers for Disease Control and Prevention: Travelers' Health:* http://wwwnc.cdc.gov/travel
- *World Health Organization: Travel Advice*: https://www.who.int/travel-advice
- *International Society of Travel Medicine:* http://www.istm.org

Miscellaneous Special Situations

Other conditions and situations that warrant special consideration are outlined in **Table 6.7**.

Coverage Rates in Special Populations

Vaccine uptake in persons who are at special risk for vaccine preventable diseases is suboptimal (**Table 6.8**). Reasons for this may include provider and patient knowledge gaps; lack of clear-cut guidelines; concerns about efficacy and safety; diversion to more "pressing" issues in persons with chronic or debilitating diseases; and lack of coordination between specialty and primary care providers.

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TABLE 6.7— Vaccination in Other Special Circumstances[a]

Condition or Circumstance	Possible Increased Risks
Animal workers and veterinarians	Anthrax and rabies
Bleeding diathesis	Bleeding (for IM injection, use a 23-gauge or smaller needle, apply firm pressure without rubbing for ≥2 min, and schedule injections shortly after regular clotting factor infusions)
Children and adolescents taking aspirin	Reye syndrome with influenza or varicella[b]
College students living in dormitories	Influenza and invasive *N meningitidis*
Foreign field personnel	Travel-related vaccine-preventable diseases
Food handlers	Transmission of hepatitis A[c]
Foresters	Rabies
Group homes and nonresidential day care facilities for developmentally disabled persons	Hepatitis A[d]
Homeless persons	Hepatitis A[d]
Illegal drug users	Hepatitis A[d,e] and hepatitis B
Laboratory workers	Infection with laboratory pathogens for which vaccines are available
Men who have sex with men	Hepatitis A, hepatitis B, and human papillomavirus
Military personnel	Adenovirus, anthrax, influenza, invasive *N meningitidis*, smallpox, and travel-related vaccine-preventable diseases
Morticians	Hepatitis B
Native Americans and Alaska Natives	Invasive *H influenzae* type b and invasive *S pneumoniae*[f]
Providers of essential community services	Influenza
Public safety workers	Hepatitis B
Residents of long-term care facilities	Influenza
Sewage workers	*Not* at increased risk for typhoid or hepatitis A in the US
Spelunkers	Rabies
Staff of correctional facilities	Hepatitis B and influenza
Staff of day care centers	Influenza
Staff of institutions for developmentally disabled	Hepatitis A, hepatitis B, and influenza

Continued

TABLE 6.7 — *Continued*

IM, intramuscular

[a] Risks that are particular to the conditions or circumstances are shown.

[b] Patients should receive IIV. Aspirin therapy is a contraindication for LAIV and a precaution for VAR.

[c] HepA is not routinely recommended but could be considered on a local basis.

[d] In settings where a high proportion of persons have risk factors for hepatitis A, providers may assume that unvaccinated adults are at risk for infection and may offer vaccination. Standing orders should be considered.

[e] The risk of hepatitis A may be increased in health care facilities that focus on persons with injecting or noninjecting drug use. Standing orders should be considered.

[f] Hib-OMP (PedvaxHIB) is preferred for the primary series in American Indians and Alaska Natives because it provides earlier protection. Routine immunization of otherwise healthy Native Americans and Alaska Natives with PPSV23 is not recommended, unless called for by public health authorities in specific communities where risk is increased.

TABLE 6.8 — Vaccine Coverage Rates in Special Circumstances

High-risk Condition or Circumstance	Population/Setting	Findings
Sickle cell disease	Children born in Michigan, 1995-2014	>25% not optimally immunized against pneumococcus at milestone ages[a]
Splenectomy	Adults in Nova Scotia, 1990-2002	83% not optimally immunized against pneumococcus[b]
	Adults in US with incident asplenia, 2010-2018	72% not immunized against meningococcal serogroups A, C, W, and Y and 90% not immunized against serogroup B[c]
Solid organ transplantation	Adults enrolled in US health maintenance organizations, 1995-2005	48% not immunized against influenza[d]
Immunosuppressive medication	Rheumatology clinic patients in Boston, 2008-2010	46% not optimally immunized against pneumococcus[e]
Cancer chemotherapy	Childhood cancer survivors in Park Ridge, Illinois	33% of patients and/or caregivers unaware of the importance of vaccination after completion of chemotherapy[f]
Complement deficiency	Children and adults with incident diagnosis of complement deficiency, 2005-2018	95% not immunized against meningococcal serogroups A, C, W, and Y and 98% not immunized against serogroup B[g]
HIV infection	Children and adults with incident diagnosis of HIV infection, 2016-2018	84% not immunized against meningococcal serogroups A, C, W, and Y[h]
Chronic lung, heart, or kidney disease	US adults, 2012-2013	37%-54% not immunized against influenza[i]
Pregnancy	US, 2019-2020	39% not immunized against influenza and 43% not optimally immunized against pertussis[j]
≥65 y	US, 2020	31% not immunized against influenza and 29% not immunized against pneumococcus[k]
Health care personnel	US, 2017-2018	22% not immunized against influenza[l]
	US, 2009	31% not immunized against hepatitis B[m]
Backpacking in Southeast Asia	Thailand, 2008	82% not immunized against rabies (4% had potential exposures while traveling)[n]

[a] Wagner AL, et al. *J Pediatr*. 2018;196:223-229.
[b] Langley JM, et al. *BMC Infect Dis*. 2010; doi: 10.1186/1471-2334-10-219.
[c] Ghaswalla PK, et al. *Vaccine*. 2021;39:272-281.
[d] Harris K, et al. *Vaccine*. 2009;27:2335-2341.
[e] Desai SP, et al. *Rheumatol*. 2011;50:366-372.
[f] Choi DK, et al. *Pediatr Blood Cancer*. 2020;67:e28565.
[g] Marshall GS, et al. *Clin Infect Dis*. 2021; doi: 10.1093/cid/ciab917.
[h] Ghaswalla PK, et al. *JAMA Net Open*. 2022;5:e228573.
[i] Lu P-J, et al. *Am J Med*. 2016; doi: 10.1016/j.amjmed.2015.10.031.
[j] Razzaghi H, et al. *MMWR*. 2020;69:1391-1397.
[k] BRFSS Prevalence & Trends Data. CDC Web site. https://www.cdc.gov/brfss/brfssprevalence/index.html. Accessed July 18, 2023.
[l] Black CL, et al. *MMWR*. 2018;67:1050-1054.
[m] Lu P-J, et al. *Vaccine*. 2011;29:7049-7057.
[n] Piyaphanee W, et al. *Am J Trop Med Hyg*. 2010;82:1168-1171.

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75. Bonebrake AL, et al. *Emerg Infect Dis*. 2010;16:426-432.
76. CDC. *MMWR*. 2011;60:13-15.
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78. Vaccination program for U.S.-bound refugees. CDC Web site. https://www.cdc.gov/immigrantrefugeehealth/guidelines/overseas/interventions/immunizations-schedules.html. Accessed July 18, 2023.
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Addressing Concerns About Vaccines

In September, 2020 the chief executive officers of 9 biopharmaceutical companies—AstraZeneca, BioNTech, GSK, Johnson & Johnson, Merck, Moderna, Novavax, Pfizer, and Sanofi—signed a pledge regarding their efforts to develop COVID-19 vaccines: to make the safety and well-being of vaccinated individuals top priority, adhere to high scientific and ethical standards, and only submit for approval candidates that demonstrate safety and efficacy in Phase 3 clinical trials.[1] The fact that these things had to be said (as if they weren't already guiding principles) is emblematic of the unprecedented attention that the pandemic thrust upon the vaccine enterprise. At the time of the pledge, half of Americans said they would not take a COVID-19 vaccine.[2] Concerns about COVID-19 vaccines arose on the backdrop of a modern anti-vaccination "movement" that had been gaining steam since the 1980s. Even before COVID-19 was a thing, the World Health Organization declared vaccine hesitancy to be one of 10 major threats to global health.[3]

Good things have come from public concern about vaccines—the replacement, for example, of DTwP with the less reactogenic DTaP. However, while the sensational claims made by antivaccination activists, celebrities, wealthy financiers, and rogue "researchers" have not held up to scientific scrutiny, they have nevertheless received airtime and established an Internet presence. As a result, well-meaning parents are concerned about vaccinating their children[4] and many adults who should be vaccinated are opting out. This has translated directly into personal and public harm.[5]

Communicating Risks and Benefits

Understanding Vaccine Hesitancy

The perceived value of vaccines paradoxically decreases as their effectiveness increases—when disease is no longer prevalent, people perceive no benefit from vaccines. When vaccines work, *nothing* (as opposed to *disease*) happens. This fact, combined with widespread attention given to rare adverse events, leads to the perception that vaccines do more harm than good.

Vaccine hesitancy is a state of mind regarding immunization characterized by uncertainty, indecision, conflict, or even opposition.[6] It is a complex phenomenon that is context specific, varying by time, place, and product.[7] Conceptualizing vaccine hesitancy as a psychological state rather than a behavior is important[8]; in this context, *vaccine refusal* is a behavior that derives from extreme hesitancy. Vaccine hesitancy itself is contagious, or at least generalizable. This phenomenon was noted in Denmark from 2013 to 2015, when negative media coverage regarding HPV appeared to drive a decrease in MMR uptake.[9] During the COVID-19 pandemic, concerns about COVID-19 vaccines seemed to "spill over" into concerns about routine childhood immunization[10] and influenza vaccine[11], for which the risk-benefit calculus had not changed.

Attitudes along the spectrum from vaccine acceptance to refusal are deeply rooted in human nature.[12] For example, we place a lot of weight on anecdotal experience, and that leads us to assume causal relationships where none actually exist. We exhibit *confirmation bias*—the tendency to seek out evidence supporting what we already believe and to ignore contradictory evidence (many people begin with the *belief* that vaccines are harmful, then seek *validation* for this belief—even seeking out providers who share those beliefs[13]). We have an intuitive sense of numbers that upholds small experiences and makes it difficult to see the big picture, something called *folk numeracy* (people worry about the 3 vaccinated kids in the same school who develop diabetes, but they have difficulty conceptualizing a prospective cohort study with 4.7 million person-years of follow-up).[14]

We all have trouble thinking *probabilistically*, that is, coming to conclusions after calculating odds (ie, risks versus benefits); because of this, we are prone to think *heuristically*—that is, to (subconsciously) employ shortcut ways of thinking that simplify complex decision-making.[15] Here's an example—a person is more tolerant of a bad outcome when it results from their own *inaction* rather than *action* (this is referred to as the *do no harm* heuristic, or *omission bias*—the intuition that it is morally worse to cause harm by *doing something* as opposed to *not doing* something). So, hospitalization with influenza (something that just *happens* to a child who does not get the vaccine) is (psychologically speaking) more tolerable than side effects of the influenza vaccine (a bad thing that a parent *causes* by choosing vaccination for their child). When faced with heuristic thinking like this, providers should try to reframe *inaction* into *action*—in other words, parents should understand that *not vaccinating* their children is an *action* that leaves their children susceptible to disease. "Good" heuristics like *altruism* appear to have little influence on parents' decision to vaccinate their children.[16]

Other cognitive and emotional biases conspire to propagate vaccine hesitancy.[17] For example, people tend to make immediate, automatic judgments on an emotional or intuitive basis (*moral intuition*), then subconsciously circle back to analyze the situation (*moral reasoning*).[18] They come at the latter from a moral framework that determines in large part how they will view things. Thus, for example, vaccine hesitant parents whose moral foundation favors *purity*[19] might respond to arguments that vaccines do not contain poisons, or that the real "poison" is the disease. Parents whose moral framework minimizes *authority* might need reassurance that the Advisory Committee on Immunization Practices (ACIP) is not the reason you want their children to be vaccinated; in other words, it's not about the *authority* of the ACIP, it's about the concern you have for their children and the harm that can be prevented.

People tend to perceive meaningful patterns in meaningless noise, something referred to as *patternicity*; this can lead to false conclusions about associations between vaccines and adverse events. And they intrinsically believe that if one event closely follows another, it must have been *caused* by it (articulated in the Latin phrase, *post hoc ergo propter hoc*, or *after this, therefore because of this*). Moreover, people have a sense of *agenticity*—the belief that something or someone must be behind things ("There *must* be a conspiracy to cover up the dangers of vaccines, otherwise we would know about them").[20] Understanding these aspects of human nature is a good place to start in shepherding people from *belief to science*—a task that has become all the more difficult in an age of consumerism, pop culture, and celebrity.[21]

Table 7.1 suggests pathways by which societal and individual characteristics may lead to vaccine hesitancy.

Risk Versus Benefit

Safe does not mean *harmless*. All vaccines have side effects—pain, redness, swelling, and tenderness, for example—but this does not mean they are unsafe. Few things in life are truly harmless, so with vaccines, as with all things, we must make decisions about risks versus benefits. In this context, it must be understood that a huge body of evidence demonstrates that serious adverse events associated with vaccination are extremely rare.[22]

Each year in the United States, 350 people are killed in bath- or shower-related accidents, 200 people choke to death on food, and 40 people are killed by lightning. Yet we take baths, eat, and engage in outdoor activities because the benefits outweigh the risks. Vaccines are considered *safe* because the harm they prevent (*diseases*) far outweighs the harm (*side effects*) they cause. In general, the rigor under which vaccines are developed and tested, outlined in *Chapter 2: Vaccine Infrastructure in the United States—Vaccine Development and Licensure*, is under-appreciated by the lay public. The Centers for Disease Control and Prevention (CDC) provides a useful infographic on this in an attempt to improve understanding (https://www.cdc.gov/vaccines/parents/infographics/journey-of-child-vaccine-h.pdf; accessed July 21, 2023).

Balancing the risks and benefits of vaccines is complex, involving as it does the frequency and magnitude of side effects,

TABLE 7.1 — Pathways to Vaccine Hesitancy

Characteristic	Translation into Negative Attitudes Towards Vaccination
Societal level	
Culture of anti-science[a]	Science isn't always right, and there are other ways to look at things
Poor science literacy[b]	Scientists fail because they can't prove that vaccines are 100% safe
Distrust of government[c]	The agencies that make recommendations are instruments of a government that cannot always be trusted
Celebrity-ism[d]	There must be a good reason why this famous person is against vaccination
Historical injustices[e]	They've experimented on people in the past, and it could happen again
Individual level	
Fear-based cognitive style[f]	I'm afraid to put these substances into my baby
Bandwagoning heuristic[g]	It seems like everyone else is concerned about vaccines, so maybe I should be too
Anecdotal thinking[h]	One bad outcome in a vaccinated child is enough to deter me from vaccination
Probability neglect[i]	The thought of a bad reaction is so overwhelming that I tend to ignore what the statistics show
Identity[j]	We (my people) don't take that vaccine

[a] Otto SL. *Fool Me Twice: Fighting the Assault on Science in America*. New York, NY: Penguin Random House; 2011.
[b] Augustine NR, et al. *Rising Above the Gathering Storm, Revisited*. Washington, DC: National Academies Press; 2010.
[c] Public trust in government: 1958-2021. Pew Research Center Web site. https://www.pewresearch.org/politics/2021/05/17/public-trust-in-government-1958-2021/. Accessed July 21, 2023.
[d] Hoffman SJ, et al. *Arch Pub Health*. 2015; doi: 10.1186/2049-3258-73-3.
[e] Momplaisir F, et al. *Clin Infect Dis*. 2021;73:1784-1789.
[f] Poland CM, et al. *Vaccine*. 2011;29:6145-6148.
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[h] Offit PA. *Expert Rev Vac*. 2003;2:89-91.
[i] Sunstein CR. *Yale Law J*. 2002;112:61-107.
[j] Ruiz JB, et al. *Vaccine*. 2021;39:1080-1086.

the incidence and severity of disease, and whether or not alternatives are available. **Table 7.2** illustrates how this balancing act plays out for a variety of vaccines. For example, the 1 in 10,000 risk of intussusception (IS) caused by rhesus-human reassortant rotavirus vaccine-tetravalent (RRV-TV; RotaShield) was enough to suspend use of the vaccine in 1999—because IS can be serious, the risk was substantial, and rotavirus, while causing many infant hospitalizations, does not cause many deaths in the US. On the other hand, immune thrombocytopenia (ITP) is reversible and sufficiently rare after MMR vaccination as to permit universal use of the vaccine, with the caveat that one should be cautious in persons with a history of ITP. Striking a balance between risks and benefits is further illustrated by the current universal rotavirus immunization program, which continues despite evidence that RV1 and RV5 also—albeit very rarely—cause IS.[23]

Communication Strategies

Negative beliefs about vaccines center around themes like adverse effects, skepticism about effectiveness, perceived lack of necessity, mistrust, desire for autonomy, and morality concerns.[24] Simply providing factual information to patients does not appear to be enough to sway deeply held beliefs and attitudes, and it can, in fact, backfire.[25,26] Providers should remember that, by and large, people want to do the right thing; the challenge is to move them to an understanding that the right thing is to take vaccine protection over vulnerability to disease.

Structured approaches may help providers manage the vaccination conversation.[27,28] Motivational interviewing, a subtle form of counseling that activates the patient's own motivation for change, or, as it were, the parent's motivation to do the right thing for their children, may be helpful.[29,30] Be aware that codified communication strategies may come off as formulaic, and therefore disingenuous. Here's the bottom line: nothing goes further than having a deep knowledge of the issues; a sincere, meaningful, and trustworthy connection with the family; and a strongly held personal conviction that vaccines save lives and prevent misery.

Here are some tips for navigating vaccine risk-benefit communication in practice:

- *Begin the discussion early*—Decisions about vaccinating infants may be made during pregnancy.[31] Administering Tdap, IIV, and COV to mom (and dad!) during pregnancy is a good way to emphasize the importance of immunization, especially as this relates to protecting children. The birth dose of HepB is an opportunity to discuss vaccines immediately after parenthood has begun. In preparing new parents for hospital discharge, vaccines should be portrayed as a routine part of childcare.
- *Have a plan*—Outline which vaccines are scheduled for today's

TABLE 7.2 — Effect of Vaccine Adverse Events on Recommendations

Vaccine	Adverse Event	Estimated Attributable Risk	Effect on Recommendations
Any	Anaphylaxis	1 in 1,000,000[a]	Subsequent doses of vaccine contraindicated
RV5	Intussusception	1 in 67,000[b]	History of intussusception is a contraindication
MMR	Immune thrombocytopenia	1 in 40,000[c]	History of immune thrombocytopenia is a precaution
RV1	Intussusception	1 in 19,000[d]	History of intussusception is a contraindication
COV	Myocarditis	1 in 15,000[e]	Consider an 8-week interval between Dose 1 and Dose 2 for males 12-39 y
RRV-TV	Intussusception	1 in 10,000[f]	Product withdrawn in 1999
MMRV	Febrile seizures	1 in 2300[g]	Preference for combination vaccine retracted

[a] Bohlke K, et al. *Pediatrics*. 2003;112:815-820.
[b] Yih WK, et al. *N Engl J Med*. 2014;370:503-512.
[c] Mantadakis E, et al. *J Pediatr*. 2010;156:623-628.
[d] Weintraub ES, et al. *N Engl J Med*. 2014;370:513-519.
[e] Estimated risk for adolescent and young adult males receiving a second dose (Witberg G, et al. *N Engl J Med*. 2021;385:2132-2139; Oster ME, et al. *JAMA*. 2022;327:331-340; Ling RR, et al. *Lancet Resp Med*. 2022;10:679-688).
[f] Peter G, et al. *Pediatrics*. 2002;110:e67.
[g] Klein N, et al. *Pediatrics*. 2010;126:e1-e8.

visit. Give the pertinent Vaccine Information Statements (VISs) to the parent or patient (see *Chapter 3: Standards, Principles, and Regulations—Vaccine Information Statements [VISs]*). Explain why the vaccines are important and review contraindications. Make sure people understand the commonly expected side effects and how they should be managed. Briefly touch on any severe risks, and place today's vaccinations in the context of the overall schedule.

- *Start strong*—People are more likely to accept vaccination if the provider begins the conversation from a *presumptive* ("We have some shots due today") rather than a *participatory* ("What do you want to do about shots today?") position.[32]
- *Build trust*—Parents trust health care providers for accurate, honest information.[33] Building on this trust, the approach should be nonjudgmental, empathetic, mutually respectful—and *affirmative*. Providers can endorse a patient's right to question without lending validity to their concerns ("I know how much you love your daughter, and you are right to ask questions, but I can tell you straight-up that there is more formaldehyde in a pear than in all the vaccines combined").[34]
- *Personalize the narrative*—"I get a flu shot every year, without hesitation" carries a lot of weight. Stick with it: "If you had told me when I was a medical student that someday we'd be able to vaccinate against cancer, I might not have believed you. My kids got the human papillomavirus vaccine as soon as it was available, and I recommend that your kids get it now."
- *Normalize vaccination*—Parents should understand that the vast majority of children receive all recommended vaccines according to the recommended schedule. Whereas attitudes towards COVID-19 vaccination are strongly affected by perceived social norms,[35,36] messaging around social norms may not be that effective when it comes to parents' intent their children.[37] Instead, one of the strongest driving forces is the knowledge that other trusted parents are vaccinating their own children.[38]
- *Emphasize disease risks*—More mileage may be gained by replacing erroneous beliefs with new information on the consequences of disease, as opposed to trying to correct the erroneous beliefs.[39] Correction can backfire—in what has been called the *illusory truth effect*, people mistake repetition for truth, such that presenting a false claim (even in the context of debunking it) may increase belief in it[40]; however, a recent study demonstrated that repeating myths is not inferior to debunking strategies that do not repeat myths.[41] On the other hand, *danger-priming* can occur when disease is emphasized—dramatic illness narratives and images may paradoxically increase misperceptions about vaccines.[42] Much of this depends on who you are talking to, what you say, and how you say it.
- *Avoid "fact tennis"*—Endlessly countering the patient's "facts" with your own, tit-for-tat, is seldom productive. One or two volleys is enough before the direction of the conversation should be changed.
- *Use a team approach*—Communication should be a coordinated effort among doctors, nurses, and other office personnel. The receptionist can introduce the vaccination visit, give VISs, and

direct the parent or guardian to informational materials in the waiting room. Office nurses are accessible, highly invested in immunization, and can have a great impact on parents and patients. Each member of the team should be empowered and should know his or her role during the visit.

- *Organize visits effectively*—Face-to-face time with the provider can be increased by building efficiencies into the visit, beginning with a preparatory phone call to remind the parent or guardian to bring the child's shot record and perhaps introducing the vaccines that are scheduled for the visit. Use of a screening questionnaire for contraindications (**Table 4.9**) can be helpful. Simple, direct messages and easy-to-understand printed materials can eliminate some questions and help focus the discussion. Take-home or online materials may solidify concepts that were initiated during the visit. Consider scheduling vaccination visits at off-peak hours.
- *Be consistent*—Reach consensus on how specific issues will be handled. Communication is more difficult when providers in the same office endorse different vaccination practices.
- *Understand individual backgrounds*—Educational, emotional, religious, psychological, spiritual, philosophical, and intuitive foundations can affect risk perception, and messages should be nuanced with these things in mind. Some people are traditional and trusting of the medical establishment, while others are cautious, challenging, and alternative-oriented. Moreover, people tend to interpret evidence in ways that strengthen ties to their in-group, something referred to as *cultural cognition*.[43] Thus, for example, people whose cultural values emphasize *hierarchy* (as opposed to *egalitarianism*) and *individualism* (as opposed to *communitarianism)*, when faced with the prospect of mandatory vaccination (something their culture rejects), might perceive vaccines to be more risky than they actually are— and opposing the vaccine solidifies their relationship with their group.[44]
- *Consider sociodemographic factors*—Communities of color may have deeply-rooted distrust of government and medical institutions because of historical injustices they have suffered and healthcare inequities that persist. African Americans, for example, may be leery of vaccination (a medical/scientific proposition) because of the horror of the Tuskegee Syphilis Study—done in the name of medicine/science—and the suspicion that medical abuses may still be occurring.[45] This may be particularly true when it comes to new vaccines like those for COVID-19, which resonate with historical knowledge of unethical research practices[46] (the negative impact of COVID-19 vaccine hesitancy was amplified by the fact that communities of color were disproportionately affected by the disease[47]). Vaccination should be depoliticized—framed as a scientific paradigm (vaccine antigens generate antibodies that neutralize viruses), nudging people away from cultural or political positions ("We" don't vaccinate).
- *Layer information appropriately*—Information should be presented with sensitivity to individual intellectual needs. Providers should be aware of the patient's cognitive foundation and begin with information appropriate to that level. People who want to know more will ask. Many resources are available to assist providers in assessing needs and communicating accordingly.[48]
- *Put things into perspective*—Help parents and patients understand that there is often a difference between what we are afraid of and what the real risks are. For example, we are afraid of shark attacks, but we are 160,000 times more likely to be bitten by dogs.[49] We may fear side effects of vaccines, but we should be afraid of the diseases!
- *Manage expectations*—An analysis of 12 randomized, placebo-controlled trials of COVID-19 vaccines that included 45,380 participants showed that 76% of the systemic adverse events after Dose 1, and 52% after Dose 2, could be attributed to nocebo effects—that is, the adverse events were elicited by doses of placebo.[50] This suggests that widespread attention to possible COVID vaccine side effects raised the expectation for such and contributed to the misattribution of common symptoms to vaccination. The bottom line is that people—randomly—get headaches and fatigue, and that experiencing these symptoms after vaccination does not mean the vaccine caused them.
- *Be aware of pitfalls*—Know how words and phrases can be misconstrued (**Table 7.3**).
- *Check for understanding*—Make sure people understand what you have told them and ask if they have any questions.
- *Focus on the 99%*—The very small number of anti-vaccine adamant people are not likely to change their minds. Providers should focus their energies where they have a possibility of positive impact, realizing that for some, there simply is no trusted messenger.[51]

One of the deepest roots of vaccine hesitancy is the belief that health outcomes largely depend on individual choices and behaviors; seeing illness prevention as within their locus of control, people tend to see vaccination as a personal decision, one that is unfortunately influenced by misplaced public discourse regarding risks. With this in mind, the American Academy of Pediatrics (AAP) and the FrameWorks Institute developed evidence-based recommendations on reframing the vaccination paradigm, shifting the narrative from the individual to the collective and representing vaccination as "education for the immune system" (which prepares it to deal with illness) rather than representing vaccines as "injected substances that

TABLE 7.3 — Language and Meaning

Expression or Word	Technical Meaning	Common Interpretation
Biased	Having a systematic error that could lead to the wrong conclusion	Not having an open mind
Favor rejection of hypothesis	The data suggest that the hypothesis should be rejected	They do not know
Not statistically significant	The findings are likely to be due to chance alone	The findings are not important
Plausible	Theoretically possible	Factual or worthy of belief
Positive	Value greater than zero	Good
Relative risk	The ratio of two rates of risks	A relationship between risks
Statistically significant	The findings are not likely to be due to chance alone	The observed differences are important
Vaccine adverse event	Something temporally associated with vaccination	Side effect of vaccination

Adapted from Myers MG, Pineda D. Misinformation about vaccines. In: Barrett ADT, Stanberry LR. *Vaccines for Biodefense and Emerging and Neglected Diseases*. Maryland Heights, MO: Elsevier, Inc.; 2009.

affect the body" (which raises suspicion about potential harms).[52] **Table 7.4** provides a summary of their recommendations.

Teaching Vaccine Confidence

A survey conducted in 2005 showed that health care professionals graduating in the 1990s had less confidence in vaccine safety and efficacy compared to those graduating in the 1980s and earlier,[53] and a recent study showed that around 10% of primary care physicians do not believe that vaccines are safe, effective and important.[54] Potential explanations include decreased prevalence of vaccine-preventable diseases; increased awareness of adverse events; and (like the parents and younger patients they care for) less grounding in science and probabilistic thinking. In addition, providers today may feel less empowered to challenge antivaccine beliefs, resulting in a subtle assimilation of those beliefs.

A 2012 survey of pediatric residency directors revealed that 60% of programs did not have a formal curriculum in vaccine safety,[55] and a 2010 survey of (mostly pediatric) residents showed that only a third felt strongly that they had learned how to communicate about vaccines.[56] Recognizing that individual residency programs may not have the bandwidth to develop their own programs, the Pediatric Infectious Diseases Society offers a comprehensive curriculum called CoVER (Collaboration for Vaccine Education and Research), designed to enhance knowledge and competency in communicating about vaccination (available at https://pids.org/education-training/vaccine-education-program/; accessed July 21, 2023).

Vaccine Refusal

How should vaccine refusal be handled? First, listen to what the person is saying. Providers may mistake the need for information or reassurance for flat-out refusal. Some parents may be refusing a single vaccine for their child, whereas others may be refusing all the vaccines that are due at a given visit; few parents refuse all vaccines at all visits. Second, it must be recognized that while the decision not to vaccinate goes against the best medical advice, it rarely puts a person directly in harm's way, because most vaccine-preventable diseases are uncommon. In this context, refusing to vaccinate a child cannot be interpreted as actionable medical neglect. In situations where vaccine refusal could bring immediate harm to a child—after a tetanus-prone injury, for example—it may be appropriate to involve governmental agencies or the courts to force action in the child's best interest. While states may be reluctant to act unless there is immediate and substantial danger, the courts have repeatedly upheld compulsory immunization laws as a reasonable exercise of the state's power, even in the absence of epidemics (see *Chapter 3: Standards, Principles, and Regulations—Mandates and Exemptions*).

Third, people need to understand that the decision not to immunize places other people at risk. Outbreaks are spread by unvaccinated persons, and even vaccinated people can get the disease because of primary vaccine failure and waning immunity. In addition, some people cannot be immunized for medical reasons and can therefore only be protected by herd immunity. Thus, immunization can be construed as a *civic duty*, and failure to immunize can be seen as indirectly bringing the possibility of harm to others. Interestingly, some religious traditions see immunizations as an imperative—Judaism, for example, where immunizations are seen to fulfill the obligation to guard one's own health and prevent others from becoming sick.[57] The ontogeny of "religious" objections to vaccination may be more related to the aggregation of people with similar personal beliefs around a faith community than to any particular theology, and, globally, vaccine hesitancy may be more related to political, cultural, or historical factors than religious beliefs per se.[58]

Refusal to vaccinate forms—which explain why a vaccine is recommended, what the risks of vaccination are, and what the consequences of infection may be, including disease, death, permanent disability, transmission to others, and exclusion from school during

TABLE 7.4 — Reframing the Vaccination Discussion

Recommendation	Rationale	Step-by-Step
Talk about the benefits of vaccination for the common good, then connect those benefits to the individual	People tend to think if they make the right health choices, their immune systems will be strong, and vaccination will be optional	■ Lead with talking about how vaccination benefits the common good ■ Follow with talking about the individual benefits ■ Give examples of the community benefits of vaccination ■ Frame vaccination as a collective responsibility to keep everyone healthy
Establish the ethic that equitable access to vaccines improves the health of everyone	People often view disparities in vaccination rates in terms of personal decision-making, rather than lack of access; raising awareness of access issues strengthens the idea of collective responsibility	■ Talk about access as a way to prevent future disease and ensure the health of our communities ■ Be explicit about the ways that improving access is our collective responsibility ■ Explain the disparities in access before talking about the disparities in uptake ■ Provide examples of polices that increase access, building an understanding of systemic solutions
Emphasize long-term health and wellbeing instead of protection from harm	Focusing on threat leads to overthinking about the risks of acting; people tend to see the risks of opting out as lower than opting in, and the risks of inaction (not being vaccinated) are less tangible	■ Talk about how vaccines prepare people for long-term health and wellbeing ■ Frame vaccinations as a partnership among parents, children, patients, doctors, and the broader community to ensure wellness ■ Use historical examples of successful vaccination programs, drawing on people's lived experience in a world with less infectious disease morbidity
Explain how the immune system works more effectively after vaccination	Framing around the concept of training shifts the focus from what vaccines do (eg, they are injected into the body and cause physiologic change) to what the immune system does (eg, it learns from vaccines how to keep the body safe)	■ Draw on the analogy of software updates, which improve computing performance, efficiency, and safety
Talk about how through vaccination the body learns to read and comprehend the language of specific pathogens and gains proficiency in how to respond	People understand that literacy benefits both individuals and society and carries few risks, making the analogy particularly suited to an understanding of the immune system	■ Talk about vaccination as a process of gaining "immunological literacy" ■ Talk about vaccines as "texts" that the body can "read" in order to "remember" how to deal with the pathogen long after the vaccine has left the body

This table summarizes recommendations from the American Academy of Pediatrics and the FrameWorks Institute. While intended to guide the discussion with parents regarding vaccination of their children, the language is broadened here to allow for application in other situations.

Adapted from Communicating about vaccinations: evidence-based recommendations to shift the narrative. American Academy of Pediatrics Web site. https://www.aap.org/en/patient-care/immunizations/communicating-with-families-and-promoting-vaccine-confidence/communicating-about-vaccinations-evidence-based-recommendations-to-shift-the-narrative/. Accessed June 10, 2023.

outbreaks— are available for parents who do not want their children vaccinated.[59,60] It is not clear what legal protection these forms afford the provider; nevertheless, a signed form should be placed in the permanent medical record. Signing the form encourages parents to rethink the issue and to document the provider's efforts to communicate the risks and benefits of immunization. Some providers place an expiration date on the form in order to encourage readdressing the issue in the future.

The AAP takes the position that, in general, physicians should not discharge families from their practices because of vaccine refusal.[61] However, the AAP acknowledges that—while not something to be taken lightly—dismissal of vaccine-refusing families is an option, given certain caveats.[62] If unvaccinated children are retained in the practice, there are questions about how they should be handled—one poll found that 70% of parents wanted restrictions in place to prevent unvaccinated children from infecting others (about 30% thought dismissal would be appropriate).[63] Dismissing an established family for continuing to refuse vaccination after earnest attempts at education is one thing; not accepting a vaccine-refusing family from the get-go is different, and is perhaps less justifiable from an ethical point of view.[64]

There is no law that says a provider must acquiesce to a patient's wishes. Some providers are not willing to accept the liability of negotiating a modified schedule, and they worry about unimmunized kids in their waiting room. Some feel that negotiation is a slippery slope and that drawing a hard line behind the recommended schedule is the best way to send the message that vaccinations—at the proper time, in the proper doses, and according to the proper schedule—are a critical component of preventive medicine. Others believe that a hard line is not in the patient's best interest.[65] Failure to come to terms about immunization may predict a poor therapeutic relationship, which could negatively affect the care of the child; on the other hand, retention allows continued opportunities to break down barriers and protects the child from seeking care from less scientifically-based practitioners. The American Medical Association suggests that at the beginning of their relationship with patients, physicians should alert patients to issues that might threaten continuity of care.[66] It is worth noting that most adult medicine practices have dismissed patients for reasons that include repeatedly failing to follow health care recommendations,[67] and about half of pediatric offices surveyed in 2019 had a policy to dismiss families if they refuse vaccines in the primary series.[68]

Personal advocacy for vaccination, tempered by compassionate engagement and recognition of a shared, firm commitment to the child's or patient's well-being and underpinned by scientific data is the most important thing a provider can do to ensure that people are protected. Providers should also be mindful of the profoundly negative and stigmatizing views that the pro-vaccine public has towards vaccine refusers, and they should guard themselves against adopting similar sentiments.[69]

Antivaccinationism

An Internet search on the term "vaccines" yields many web sites containing non–peer-reviewed data, uninformed opinions, frightening anecdotes, and pseudoscientific arguments intermingled with legitimate concerns for adverse events; people, understandably, have trouble separating the *information* from the *misinformation.*[70] The organizations behind these web sites claim authority, credibility, and scientific rigor, which—along with some lay people, vocal celebrities, and fringe researchers—collectively constitute a modern antivaccination movement (in truth, antivaccinationism is nothing new).[71] Antivaccinationism is rooted in a host of underlying sentiments, from libertarianism to distrust of government and science; it is fueled by sensationalistic and irresponsible journalism, easy access to unfiltered analyses, conspiracy theories, and a cultural lack of critical thinking and understanding of science.[72-75]

Antivaccinationists offer strong emotive and political appeals, make explicit claims about vaccines that are unsupported or even contradicted by published data, and call people to action in opposing vaccine policy (**Table 7.5**). *Web 2.0*—defined by user participation, openness, and network effects[76]—has complicated matters (in fact, some of the "users" of social media sites are bots or trolls that promote antivaccinationism or sow the seeds of discord among human users[77]). Social media platforms tend to become "echo chambers"[78]—virtual communities of like-minded people who seek and share information with which they already agree, amplifying and reinforcing their beliefs. Analysis of the activity of 100 million Facebook users expressing views about vaccination in 2019 revealed clusters around pages with either undecided, pro- or anti-vaccination content.[79] Antivaccination clusters were centrally positioned and highly entangled with undecided clusters, characteristics that allowed for growth; this helps explain why antivaccination views have become so robust and resilient.

Table 7.6 lists common mottos, phrases, and rebuttals found on interactive antivaccination sites. Providers should be aware of these and should be prepared to address them. Moreover, they should recognize the extent to which social networks—essentially, other people—influence vaccination decisions,[80] and they should endeavor to become social media-savvy.[81] Individuals and organizations that oppose immunization or argue for alternative approaches share common sentiments; **Table 7.7** lists some of those ideas and the reasons why they represent flawed thinking.

The vast majority of Americans visit at least one vaccine-related webpage every year[82]; fortunately, most of those visits are to sites that are not skeptical about vaccinations, and it is important to note

TABLE 7.5 — Appeals Made by Antivaccination Organizations

Authoritative

- Present their organization as a legitimate, official body with scientific credibility
- Reference self-published works and alternative medicine literature
- Use indiscriminate citations (eg, letters to newspapers, television interviews)
- Draw alternative conclusions from peer-reviewed studies
- Endorse poorly conducted studies that promote antivaccine agendas
- Claim to present "both sides"
- Denigrate science that does not support antivaccination positions
- Continuously shift hypotheses when evidence fails to support vaccines causing harm

Emotive

- Paint an "us" (the organization, concerned parents) vs "them" (the medical establishment, government, pharmaceutical industry) picture
- Describe physicians as willing conspirators or manipulated pawns
- Pit parental love and compassion against cold, analytical science
- Feature anecdotal accounts of purported vaccine injury
- Suggest that responsible parenting means refusing vaccination
- Urge parents to resist coercion
- Warn the public about conspiracy
- Characterize vaccines as "unnatural" and suggest that a natural lifestyle will prevent disease
- Levy personal attacks on critics

Search for Truth

- Depict their struggle as a search for truth against a backdrop of cover-up
- Highlight excavated "facts" that were hitherto neglected
- Portray rank-breaking doctors as enlightened heroes
- Suppress dissenting opinions
- File legal actions

Adapted from Davies P, et al. *Arch Dis Child*. 2002;87:22-25; Kata A. *Vaccine*. 2012;30:3778-3789.

TABLE 7.6 — Tropes Used by Antivaccinationists

Phrase	Description
I'm not against vaccines—I'm in favor of safe vaccines	Denying opposition to vaccines and claiming to support legitimate research to improve safety
Vaccines are toxic	Highlighting potentially toxic ingredients and providing disingenuous explanations of their dangers
Vaccines should be 100% safe	Vaccination is dangerous because perfect safety cannot be guaranteed
They can't prove vaccines are safe	Demanding that advocates prove vaccines cause no harm rather than detractors prove that they do
You have to choose between diseases and vaccine injuries	Framing the debate as a false dichotomy between diseases and the harm caused by vaccines
Science was wrong before	Citing historical examples of scientific errors to imply that the science supporting vaccination is also in error
This many people can't be wrong	Implying that antivaccinationist claims are true because many people support them
I'm the expert for my child	Discounting the expertise of medical authorities in deference to parental authority

Adapted from Kata A. *Vaccine*. 2012;30:3778-3789.

that many social media platforms have started to take a stand against vaccine misinformation.[83] In responding to vocal antivaccinationists, providers should target the general public (not the antivaccinationists themselves) and call out the science denialism techniques they employ.[84]

The Costs of Public Concern

In 1928, Thomas and Thomas[85] famously asserted that things people perceive to be real (however unreal they may be) are real in their consequences. There is no better example of this than how ill-founded fear of vaccinations leads to public harm. A classic example is what happened in the United Kingdom in the late 1970s, where anecdotal reports claiming that the whole-cell pertussis vaccine caused encephalopathy led to a dramatic decline in immunization rates and a resurgence of disease (see *Pertussis Vaccine and Brain Damage*, below). Here's another example: claims in the late 1990s

TABLE 7.7 — Flawed Thinking About Vaccines

Claim	Why This Is Incorrect or Misleading
Doctors do not read the primary data and do not fully understand vaccines	Committees of experts review the primary data. Their record has been spot-on.
There is a conspiracy to misrepresent the data	There is no evidence of a conspiracy
Vaccine-preventable diseases are rarely seen in practice	This is evidence that vaccines work. Some diseases are not rare. Surveillance data trump anecdotal experiences.
Natural immunity is better than vaccine-induced immunity	The cost of natural immunity is the risk of serious disease
Vaccines are not adequately tested for safety	Vaccines are among the most thoroughly tested pharmaceuticals
Vaccines protect the public but not individuals	People benefit by becoming immune and, *as long as others are immunized*, by having less chance of exposure
Reports in VAERS and language in the package insert constitute accurate profiles of vaccine side effects	VAERS reports do not establish causality. Package inserts list events that may not be causally related to vaccination.
There is a middle ground between causality and coincidence	Either vaccines *do* or *do not* cause certain adverse events
Science fails because it cannot prove there is no connection between vaccines and certain adverse events	Science works by rejecting or failing to reject the null hypothesis

VAERS, Vaccine Adverse Event Reporting System

Adapted from Offit PA, Moser CA. *Pediatrics.* 2009;123:e164-e169.

that MMR causes autism (it doesn't) led to dramatic declines in vaccine uptake in the United Kingdom and subsequent outbreaks of measles (see *Autism*, below). Outbreaks of measles in the US have been driven by disease in unvaccinated persons.[86,87] A recent, poignant example of the costs of public concern comes from Japan, where routine administration of HPV to girls was suspended from 2013 to 2019 because of unsubstantiated (and later refuted) safety concerns.[88] This is estimated to have led directly to an additional 24,600 to 27,300 cases of cervical cancer and 5000 to 5700 deaths in the 1994 to 2007 birth cohort.

In 2005, an unvaccinated teenager returned to Indiana from a mission trip to Romania, unknowingly incubating measles.[89] Shortly thereafter there were 33 cases of measles among church members and 1 case in a hospital phlebotomist (who was not a church member); 3 people were hospitalized, and one spent 6 days on a ventilator. The vast majority of cases occurred in unvaccinated persons. Several things are worth noting in this outbreak. First, fear of adverse events was the main reason people refused vaccination. Some families even feared MMR because of the preservative thimerosal, which has *never* been part of the vaccine. Second, the church members were largely white, middle class, and well educated, reflecting the demographics of vaccine refusers (and international travelers) at that time. Third, the church itself had no official position on immunization—vaccine refusal was a subcultural phenomenon. Fourth, even though the attack rate was much higher in unvaccinated persons, some vaccinated people still got measles. This illustrates the real issue of primary vaccine failure and the fact that unvaccinated people place vaccinated people at risk. Fifth, the outbreak was almost entirely confined to church members—vaccination rates in the surrounding community were high enough to prevent spread. Finally, measles is just a plane flight away, and all it takes to ignite an outbreak is for the virus to land in a community with enough susceptible individuals.

Vaccine refusers tend to cluster geographically, creating well circumscribed pockets of susceptible people and laying the groundwork for outbreaks.[90] A telling example of this played out in New York City when, in September 2018, an unvaccinated boy returned from Israel incubating measles.[91] Over the next 10 months, 649 cases of measles were confirmed, the majority among unvaccinated members of the same Orthodox Jewish community. Forty-nine patients were hospitalized, and the public health response to the outbreak cost $8.4 million. Importantly, this community had been targeted by an anti-vaccination organization.[92]

In 2020, recognizing the potential impact of vaccine hesitancy on public health—and the imperative to strengthen public trust in COVID-19 vaccines—the CDC launched *Vaccinate with Confidence*, a strategic framework to strengthen vaccine confidence and prevent disease outbreaks (**Table 7.8**).[93] The last section in this chapter deals with the special case of public concerns about COVID-19 vaccines.

General Issues

Necessity of Vaccines

It is patently false that vaccine-preventable diseases were disappearing before we had vaccines. In the early 1980s, 1 in 200 children developed invasive *H influenzae* type b disease; shortly after the universal infant Hib immunization program began in the 1990s,

TABLE 7.8 — Vaccinate With Confidence

Protect Communities
■ Support awardees of the CDC's Immunization and VFC cooperative agreement (eg, state, city, and territorial health departments) to identify and respond to pockets of low vaccination coverage in their jurisdictions
■ Improve capacity of immunization programs to use IIS data and small-area analyses to pinpoint areas of low vaccination coverage and identify barriers to vaccination
■ Develop a community assessment tool kit to help local public health officials and other stakeholders identify factors related to undervaccination in communities
■ Help organizations with targeted and culturally sensitive approaches to increase coverage in undervaccinated communities
■ Build frontline immunization program capacity to respond to vaccine hesitancy through technical assistance, capacity-building activities, and dissemination of tools and materials
■ Characterize populations at risk for undervaccination to implement tailored approaches to increasing coverage
Empower Families
■ Disseminate materials and tools to health care providers to support earlier vaccine conversations with parents of young infants and with pregnant women
■ Reduce hesitancy and improve vaccine access at the nation's community health centers through development of culturally competent patient engagement strategies
■ Conduct formative research to develop effective communication messages and materials for parents and health care providers
Stop Myths
■ Work with social media companies to promote trustworthy vaccine information
■ Educate state policy-makers on vaccine safety and effectiveness
■ Engage state and local health officials to advance effective local responses and community-based initiatives to misinformation and hesitancy

CDC, Centers for Disease Control and Prevention; IIS, immunization information system; VFC, Vaccines for Children Program

Adapted from Mbaeyi S, et al. *Pediatrics*. 2020;145:e20200390.

the disease all but disappeared. This scenario has been replicated over and over again as new vaccines have been introduced.

Here are a few reasons why vaccines are still important even though many of the diseases are rare today:

- *Some diseases aren't rare*—Many vaccine-preventable diseases are still around. The choice not to vaccinate against pertussis, for example, is the choice to take a significant risk of getting the disease. Influenza kills tens of thousands of people and human papillomavirus infects millions every year in the US.
- *Diseases could easily re-emerge*—Some diseases continue to circulate at very low levels; if population immunity decreases, outbreaks can occur. This is exactly what happened between 1989 and 1991 in the US, when 55,622 cases of measles and 123 deaths from the disease were reported.[94] The most important contributing factor was low vaccine coverage, especially among preschoolers in inner cities. By 2000, after renewed efforts to achieve universal vaccination and implementation of the 2-dose schedule, measles was no longer endemic in the US. However, the large measles outbreak of 2019[95] illustrates how quickly a disease like measles can resurface.
- *Infections can be imported from other parts of the world*—Diseases such as polio and diphtheria still occur in other countries. Tourism, immigration, and international business travel contribute to the ease with which these diseases can be imported.
- *Some diseases cannot be eradicated or extinguished*—Tetanus, which is acquired from the environment (as opposed to other people), is an example.

Natural Versus Vaccine-Induced Immunity

Natural infection may induce stronger and longer-lasting immunity than vaccines. Whereas immunity from disease often follows a single natural infection, immunity from vaccines may require several doses and, in some cases, may wane with time. A notable example of waning immunity occurs with the acellular pertussis vaccine—by adolescence, many children have lost the protection imparted by the DTaP series. As a result, teenagers account for a large proportion of reported cases and serve as a reservoir for transmission in the community (Tdap is used to boost immunity in adolescents and adults).

However, there are some diseases for which vaccines are actually *better* at inducing immunity than natural infection. Infants who are infected with *H influenzae* type b do not develop effective antibody responses due to maturational defects in recognizing polysaccharide antigens (see *Chapter 1: Introduction to Vaccinology—Immunization*). Hib vaccines, on the other hand, are very effective in young infants.

The difference between vaccination and natural infection is the price paid for immunity. For chickenpox, the price paid for natural

immunity might be pneumonitis, respiratory failure, encephalitis, or necrotizing fasciitis. For *S pneumoniae*, it might be hearing loss from meningitis—and that would only buy you immunity to the one serotype that caused the infection. Likewise, for human papillomavirus, the price might be cervical dysplasia—and even if the dysplasia resolves without progression to cancer, the patient is still vulnerable to the other human papillomavirus types. The cost of vaccine-induced protection against these diseases is, well, the cost of the respective vaccines, plus a few minor side effects.

Immune Overload and Alternative Schedules

The routine childhood immunization schedule prevents 17 different diseases; that means over 50 separate vaccine doses by 18 years of age. Some people wonder if that is just too much.[96] The concern that vaccines might cause "immune overload" makes little sense when seen in the context of the countless antigens to which people are responding every day, including pathogens from the outside and organisms from within, like those in the mouth, nasopharynx, and gut. Most people are not sick most of the time, which indicates how robust the immune system is. Even vulnerable people, like neonates, seem to do just fine. Within hours of birth, the initially sterile gastrointestinal tract becomes heavily colonized with a wide variety of bacteria, some of which are potentially harmful. Yet the immune responses stimulated by colonization are, by and large, adequate to prevent invasion.

People fear that vaccines might weaken the immune system and thereby increase susceptibility to other (so-called *heterologous*) infections. Live attenuated vaccines may cause temporary suppression of delayed-type hypersensitivity, but this is not "immune overload" as much as it is the effect of viral replication on lymphocytes. There is no evidence that routine childhood vaccines increase the risk of infections; in fact, the opposite may be true. For example, a study from Germany found that children who received the diphtheria, pertussis, tetanus, Hib, and polio vaccines in the first 3 months of life actually had *fewer* heterologous infections.[97] Likewise, a study in Denmark that included 2,900,463 person-years of follow-up found no association between any of the childhood vaccines and hospitalization for any of seven different heterologous infectious diseases,[98] and a nested case-control study from the Vaccine Safety Datalink (VSD) showed no association between cumulative vaccine antigen exposure and emergency department visits or hospital admissions for heterologous infections.[99] Ironically, vaccine-preventable diseases themselves *do* increase the risk of heterologous infections. For example, influenza predisposes patients to pneumococcal and staphylococcal pneumonia; varicella increases susceptibility to invasive group A beta-hemolytic streptococcal infection; and severe measles can take out 40% of a person's pre-existing pathogen-specific antibody repertoire.[100]

Even though children receive more vaccines today than they did 60 years ago, the number of separate antigens contained in the routine schedule has drastically decreased (**Table 7.9**). In this sense, the vaccine schedule is "cleaner" than it used to be. Nevertheless, providers regularly encounter parents who want to "spread vaccines out" over time, and most of them honor such requests.[101,102] Parents are concerned about "too many vaccines too soon"; they worry that ill effects could occur from the accumulation of chemical additives and "toxins," and they object to a "one size fits all" formula. In one study, nearly a quarter of infants in New York State were found to be following an "alternative" immunization schedule.[103] Such alternative schedules are seductive—they reduce the cognitive dissonance between wanting to remain in favor of protection and fearing that vaccines are harmful. The problem is that alternative schedules do not provide optimal protection and are not evidence-based.[104]

Here are some take-home points:

- *Tailor-made schedules violate the social contract*. Any given individual has the luxury of delaying certain vaccines because the diseases are uncommon—*uncommon because most children are immunized on time*. The other children and their families have taken on a bit of personal risk (eg, sore arms) in part so that all children can be protected; in this context, delaying your child's vaccinations exploits the goodwill of others. If everyone chose delay, the diseases would resurge.
- *Alternative schedules necessitate prioritizing some vaccines over others*. None of the vaccines in the routine childhood schedule have priority over the others. This is because the occurrence, by importation or otherwise, of any of the diseases is unpredictable. The end of negotiation over alternative schedules—a fully immunized child—might justify the means, but it places the burden of prioritization on the provider. If the parent will only allow two shots on one day, which ones should be given and which ones deferred?
- *Spreading out vaccines requires more visits*. With the routine childhood schedule, series completion occurs in 4 or 5 visits by 15 or 18 months of age. Some alternative schedules require as many as 15 visits, delaying series completion until 42 months of age. The more scheduled visits there are, the more visits that will be missed, leading to further delays and costs.
- *Delaying vaccines creates real risk*. Consider this: infant DTaP doses in the US are given, on average, at days 76, 147, and 224. If, instead, they were given on days 60, 120, and 180 as recommended, there would be 278 fewer cases of pertussis, 103 fewer hospitalizations, and 1 life saved.[105] Consider this also: intentionally delaying vaccinations markedly increases the risk that children will not be fully covered by the second year

TABLE 7.9 — Maximum Number of Separate Antigens Represented by Vaccines Routinely Recommended for Children and Adolescents

Vaccine	1960	1980	2000	2020
Smallpox[a]	~200			
Diphtheria	1	1	1	1
Tetanus	1	1	1	1
Pertussis	~3000[b]	~3000[b]	5[c]	5[c]
IPV	15	15	15	15
MMR[a]		24	24	24
Hib			2	2
VAR[a]			69	69
PCV7/PCV13			8	14[d]
HepB			1	1
HepA				4
HPV9				9
RV[a]				20[e]
MenACWY				5
IIV4				16[f]
Total	~3217	~3041	126	186

[a] These are live vaccines. Estimates are given of the number of different proteins expressed during infection. Not all of these proteins necessarily represent an antigenic challenge to the host.
[b] Estimate of the number of proteins contained in DTwP.
[c] DTaP contains anywhere from 2 to 5 separate pertussis antigens.
[d] PCV13 replaced PCV7 in 2010.
[e] Rotavirus codes for 12 proteins, 6 structural and 6 nonstructural. RV1 therefore expresses 12 separate antigens and RV5, because it contains a mixture of reassortants, expresses a total of 20 separate antigens (some proteins expressed by each reassortant are the same).
[f] The vaccine contains 4 different strains of influenza virus. The influenza virion contains 8 structural proteins, 3 of which (hemagglutinin, neuraminidase, and M2) are embedded in the lipid envelope and one of which, M1, is closely associated with the envelope. Standard inactivated vaccines are made from the solubilized lipid envelope and therefore are estimated to contain as many as 4 antigens from each strain. However, only the hemagglutinin and neuraminidase are immunologically relevant.

Adapted and updated from Offit PA, et al. *Pediatrics*. 2002;109:124-129.

of life.[106] The only "accomplishment" of delayed vaccination is increased susceptibility to disease.

- *On-time vaccination is not harmful*. Even though the total number of vaccines given to infants (and consequently the number given per visit) has increased, the risk of adverse events, such as medically attended visits for fever, has not.[107] Moreover, on-time immunization has no adverse effect on neuropsychological outcomes 7 to 10 years later,[108] and the number of antigens received during the first 2 years of life is not associated with the risk of autism spectrum disorder (ASD).[109] The childhood immunization schedule, according to a 2013 report from the Institute of Medicine (IOM; now known as the National Academy of Medicine), is safe.[110]

Adjuvants

Adjuvants are substances that enhance the immune response to vaccine antigens (see *Chapter 1: Introduction to Vaccinology—Basic Vaccine Immunology*). Aluminum salts have been used as adjuvants for nearly a century, and hundreds of millions of people have received vaccines containing them. Whereas local reactions such as erythema, nodules, hypersensitivity, and granuloma formation have been reported, serious or persistent adverse events have not. In a meta-analysis published in 2004, vaccines containing aluminum-based adjuvant were seen to cause nearly twice as much erythema and induration in young children as those without adjuvant, but there was no increase in collapse, convulsions, or persistent screaming or crying.[111] In older children, aluminum-containing vaccines caused more localized, persistent pain, but not erythema, induration, or fever. In a sense, *the pain is part of the gain*—the inflammation (and hence pain) caused by the adjuvant also drives the immune response.

The burden of aluminum exposure from vaccines is far less than that necessary to cause neurotoxicity.[112] In fact, a study done in preterm infants showed no significant changes in urinary or serum aluminum levels after they received a total of 1200 mcg of aluminum in the form of Pediarix, PedvaxHIB, and Prevnar 13.[113] Infants are exposed to much more aluminum through their diets than through vaccines: whereas the total aluminum exposure from vaccines in the first 6 months of life is <5 mg, breast-fed infants ingest 7 mg, and formula-fed infants as much as 38 to 117 mg, over the same period of time.[114] See *Allergy and Autoimmune Disease—Asthma*, below, for the possible association between aluminum adjuvants and asthma.

Clinical studies of newer adjuvants (**Table 1.3**), including AS04,[115] MF59,[116] $AS01_B$,[117] CpG 1018,[118] and $AS01_E$[119] demonstrate overall safety, even though reactogenicity is, in some cases, increased.[120]

The term *autoimmune/autoinflammatory syndrome induced by adjuvants* (ASIA) was introduced in 2011[121] to describe enigmatic conditions seemingly caused by immune activation following expo-

sure to external stimuli, including vaccine adjuvants. The proposed diagnostic criteria for ASIA are very broad, potentially including all patients with an autoimmune disorder and large portions of the general population who have nonspecific symptoms.[122] A meta-analysis of studies conducted between 1990 and 2017 found no association between HepB—which contains an aluminum adjuvant—and any autoimmune disease,[123] and an international committee of experts has concluded that there is no compelling evidence of an association between adjuvants and autoimmunity.[124]

Additives

Vaccines contain ingredients in addition to antigens that have functions ranging from stabilizing the antigens to preventing them from adhering to the vial. The nature of these substances varies widely and includes proteins, sodium and potassium salts, buffers, sugars, antibiotics, preservatives, amino acids, inactivating agents, and detergents. Some of these are added purposefully in small quantities; others "leak through" from the manufacturing process and are present in only trace amounts. The "extra" substances contained in each vaccine are listed in the tables in *Section B: Diseases and Vaccines* under *"Excipients and contaminants"* (technically, an excipient is an inert substance used as a diluent or vehicle for a drug, but here it has a broader meaning, something along the lines of "everything except the antigen and adjuvant").

Some vaccine ingredients can trigger allergic reactions in sensitized individuals. A classic example is the residual egg protein in the yellow fever vaccine, which can trigger reactions in those who are egg-allergic. Another example is the neomycin in MMR. To some extent, these reactions can be avoided through proper screening (see *Chapter 4: Vaccine Practice—Screening*).

None of the other ingredients in vaccines have been demonstrated to be harmful in the quantities used. For example, influenza vaccines may contain up to 100 mcg of formaldehyde; for a 10-kg child, that would amount to 10 mcg/kg of exposure on one day. The (oral) reference dose for formaldehyde, which is an estimate of *daily* exposure that is likely to be without appreciable risk of deleterious effects *during a person's lifetime*, is 200 mcg/kg.[125] Moreover, a 10-kg child would be expected to have more than 2000 mcg of formaldehyde circulating in the blood at any given time, the result of normal biosynthetic processes.[126]

Adventitious Agents

Vaccines are often propagated in animal cell culture. Some, like RV5, are actually derived from animal viruses (the genetic backbone of RV5 is a bovine strain of rotavirus). Animal products, such as bovine fetal serum, may be used in the propagation of vaccine virus strains or may be added to the final product as stabilizers. For these reasons, contamination with animal agents is possible. Moreover, vaccines grown in human cell lines could potentially pick up unwanted infectious agents or genetic material. Despite rigorous screening procedures designed to detect contaminants before licensure, as time goes by and as our magnifying glass gets bigger, we are likely to find more of these contaminants, or *adventitious agents*. Then the question will be whether or not these agents represent a health threat.

HIV

In the late 1990s there was speculation that AIDS could be traced back to oral poliovirus vaccines that were administered in the Belgian Congo between 1957 and 1960. The assertion was that the vaccines were contaminated with simian immunodeficiency virus (SIV) from monkey kidney cells, and that people were inadvertently infected with SIV, which mutated into HIV. In truth, SIV is found in chimpanzees, not monkeys, and chimpanzee cells were never used to grow polio vaccine.[127,128] SIV and HIV are not very close genetically, and mutation from SIV to HIV would have required centuries, not years.[129,130] In addition, both SIV and HIV are enveloped viruses that are easily disrupted by extremes of pH; if given by mouth (as was OPV), both of these viruses would likely be destroyed in the acid environment of the stomach. Finally, original lots of the polio vaccine did not contain HIV, SIV, or chimpanzee genetic sequences when analyzed by molecular amplification techniques.[131,132]

SV40

The polio vaccine used in the late 1950s and early 1960s was contaminated with simian virus 40 (SV40), present in the monkey kidney cells used to grow the vaccine virus.[133] Concern was raised when SV40 DNA was apparently found in cancer biopsies from patients who had received the contaminated polio vaccine. However, it was also found in the cancers of patients who had not received the vaccine, including people born after 1963, a time when the vaccine no longer contained SV40. It turns out that some of the primers that were being used in the assays to detect SV40 DNA were directed at sequences that encode the T-antigen; these same sequences were also present in common laboratory plasmids.[134] When alternative T-antigen primers were used, only a few cancers were positive. Moreover, there was no evidence of T-antigen RNA transcript production and no T-antigen protein expression in the tumors. In the end, epidemiologic studies did not show an increased risk of cancers in those who received polio vaccine between 1955 and 1963.

Mad Cow Disease (MCD)

By the year 2000, more than 176,000 cows in the United Kingdom had developed bovine spongiform encephalopathy, or MCD—a progressive deterioration of the nervous system. At the same time, >70 people in the United Kingdom had developed a progressive neurologic condition termed variant Creutzfeldt-Jakob

disease (vCJD) that likely resulted from eating meat prepared from cows with MCD. Both MCD and vCJD are caused by prions, which are proteinaceous, self-replicating infectious particles. Because bovine-derived materials such as serum, albumin, and gelatin have been used in vaccine manufacture, there was theoretical concern that prions could be transmitted through vaccination. However, the MCD agent first entered cattle feed in the United Kingdom around 1980; since the vast majority of initial cases of vCJD were born well before then, childhood vaccines were not likely to be the cause.[135] There is no evidence that any case of vCJD was acquired from vaccination.[136] Prions are found in neuronal tissues of infected cows, which are not used in vaccine manufacture; moreover, fetal bovine serum (used to support cell cultures) and gelatin (derived from connective tissues of cows and pigs and used as a stabilizer) are not known to contain prions or transmit vCJD.

■ Endogenous Retroviruses

Measles vaccine, mumps vaccine, and YFV harbor endogenous avian retrovirus particles.[137,138] These viruses, which are intrinsic to the chick embryo fibroblasts in which the vaccines are propagated and are present even though the cells come from pathogen-free flocks, are not infectious for humans and represent no safety issue. In some cases, the DNA of adventitial agents can be detected in vaccines, without live particles.[139] This is the case, for example, with the detection of simian retrovirus proviral DNA in RV5 preparations—these sequences are present in the Vero (African green monkey kidney) cells in which the vaccine is grown. Vaccines grown in human cell lines, including rubella vaccine and VAR, may also harbor genetic sequences of human endogenous retroviruses; these sequences are present in our own genomes.

■ Porcine Circovirus

In 2010, it was discovered that RV was contaminated with porcine circovirus DNA and/or intact viral particles.[140-142] In the case of RV1, the porcine virus was probably replicating in the Vero cells used to make the vaccine; in the case of RV5, the DNA fragments were introduced by the trypsin used in the manufacturing process. Porcine circoviruses are not pathogenic for humans. In fact, these viruses are ubiquitous in pork products and can be found in human feces.[143] Tens of millions of doses of rotavirus vaccine have been given with no discernible related adverse events. Current formulations of RV1 and RV5 do not contain porcine circovirus or its DNA.

■ Nonspecific Negative Effects

Non-live vaccines can drive Th2 responses (see *Chapter 1: Introduction to Vaccinology—The Germinal Center Reaction*), which theoretically could leave infants more vulnerable to infectious diseases. The controversy over such nonspecific effects is centered on

the use of DTwP in developing countries, where some studies show an increase in nonspecific mortality related to use of the vaccine, particularly in females.[144,145] It is difficult, however, to sort out true effects from all of the confounders and biases inherent in ecological studies.[146] In fact, a 2016 systematic review noted that studies suggesting a higher mortality risk attributable to DTwP have been prone to biases and confounding.[147]

Potential associations between vaccination and premature mortality were explored in a VSD study from 2005 to 2011. A total of 1100 deaths were identified that had occurred within 12 months of any vaccination (almost 8.5 million doses) among >2 million patients 9 to 26 years of age.[148] No clustering of deaths around the time of vaccination was evident. In case-centered analyses, no unexpected deaths were found in the 30 days after vaccination, and, in fact, the risk of death from any cause was decreased during this time period. From 1997 to 2013, a time period when 2 billion doses of vaccine were distributed in the US, the Vaccine Adverse Event Reporting System (VAERS) received 2149 reports of death.[149] Among the 1244 evaluable childhood cases, causes of death included sudden infant death syndrome (SIDS) (44%), asphyxia (6%), septicemia (4.9%), and pneumonia (4.6%). Among the 526 adults, causes of death included circulatory diseases (46.9%), respiratory diseases (14.6%), infectious and parasitic diseases (11.8%), and cancers (3.8%). The reporting rate was about 1 death per million doses distributed, and the causes of death were consistent with those expected in the general population.

■ Fetal Tissue

Some vaccines—for example, rubella, adenovirus, HepA, RAB-HDC, VAR, and the IPV contained in pre-2020 formulations of Pentacel and Quadracel—are grown in cultured human embryo fibroblast cell lines (WI-38 or MRC-5) because these are the only cells that replicate the viruses well enough for mass production. Each of the human fibroblast cell lines was obtained from a single aborted fetus in the early 1960s (the rubella vaccine strain itself was originally isolated from an aborted fetus). These very same embryonic cells have been passaged in tissue culture in the laboratory since then, and no new fetal material has ever been involved. Receiving vaccines grown in these cells represents a moral dilemma for some people.[150]

In helping patients work through this, it may be worth emphasizing that the original abortions were done for therapeutic reasons, not for purposes of making vaccines, or even cell lines for that matter—cells were cultured from fetuses that were already dead in order to study immortalization and oncogenesis. Modern day vaccine producers never intended for fetuses to be aborted, and arguably the moral imperative to save lives through vaccination outweighs the objection to a singular, distant moral transgression. The Catholic

Church has made it clear that, despite its opposition to abortion, use of vaccines made in fetal cell lines is acceptable until alternatives are available.[151]

Allergy and Autoimmune Disease

Hygiene Hypothesis

The hygiene hypothesis holds that "clean living" brought on by economic development and the move from agrarian to urban lifestyle is responsible for the increase in allergic diseases that has been seen in developed countries.[152] The idea is that less exposure to microbiota early in life, while the immune system is maturing, results in more Th2-cells and fewer T-regulator cells (see *Chapter 1: Introduction to Vaccinology—The Germinal Center Reaction*), immunological biases that promote allergy and autoimmunity. However, several large epidemiologic studies suggest that preventing childhood infections through vaccination does not contribute to these immunological biases.[153] Furthermore, for live vaccines there is an inherent inconsistency in the idea, because in this case, vaccination *is* infection.

Asthma

A well-controlled study in the US identified 18,407 children with asthma who were born between 1991 and 1997 and compared them to a control group without asthma.[154] Exposure to DTwP, OPV, MMR, Hib, or HepB was no more common among cases than controls. In a population-based cohort study from the United Kingdom, a total of 6811 children enrolled between 1993 and 1997 were questioned about respiratory symptoms repeatedly until 2003.[155] No association between vaccination and asthma was seen, and, in a subsequent analysis, it was shown that delaying the first immunization beyond the first 2 months of life did not protect against wheezing at 5 to 10 years of age.[156] Other studies also refute an association between vaccinations and the development of asthma.[157]

However, a VSD study published in 2023 suggested that exposure to aluminum-containing adjuvants in the routine childhood immunization schedule is associated with the development of persistent asthma.[158] The study cohort included approximately 327,000 children seen between 2008 and 2014, of whom about 7500 developed asthma by 24 to 59 months of age. The cumulative amount of vaccine-associated aluminum exposure per child in the cohort was about 4 mg. Among children with eczema, aluminum exposure was positively associated with the development of persistent asthma, with an adjusted hazard ratio (aHR) of 1.26 per 1 mg increase in aluminum; for children without eczema, the aHR was 1.19. This study, which had many flaws,[159] does not establish a causal relationship; moreover, even if aluminum does predispose to asthma to some degree, the effect size is small enough not to warrant a change in immunization recommendations.[160]

Allergies

A study of over 600 children prospectively evaluated the risk of allergies following receipt of pertussis vaccine.[161,162] Infants were randomized beginning at 2 months of age to receive a 2-component DTaP, a 5-component DTaP, DTwP, or DT and were followed up at 7 years of age. No difference in the incidence of allergic diseases was observed between children who did or did not receive pertussis vaccine. In the PARSIFAL (Prevention of Allergy-Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle) study,[163] conducted in five European countries and involving over 12,000 children born between 1987 and 1996, no association was seen between measles vaccination and allergy. Similarly, a German study involving approximately 15,000 children showed no association between exposure to vaccines in the first year of life and the subsequent development of hay fever, asthma, and atopic dermatitis,[164] and a meta-analysis published in 2021 confirmed no association between any vaccine regimen and atopic dermatitis.[165]

Type 1 Diabetes (T1D)

T1D is caused by autoimmune destruction of pancreatic islet cells. One theory suggests that vaccines could nonspecifically enhance preexisting (subclinical) islet cell autoimmunity and lead to T1D. The data, however, do not support an association between vaccines and T1D. One study from the VSD compared 252 cases of type 1 diabetes with 768 matched controls without diabetes.[166] No association was found between diabetes and any routinely administered vaccine. In another study, 21,421 children who received Hib between 1988 and 1990 in the US were followed for 10 years; the risk of type 1 diabetes was 0.78 when compared with a group of 22,557 children who did not receive the vaccine.[167] A total of 739,694 children were included in the Danish cohort study of childhood vaccination and T1D, and there were 4,720,517 person-years of follow-up[168]; none of the childhood vaccines in any number of doses was associated with the development of diabetes. Finally, a large cohort study in Germany failed to show an association between vaccine exposure and the development of islet autoantibodies in children predisposed to develop diabetes.[169]

Molecular mimicry may also play a role in triggering T1D. Rotavirus infection (and, by implication, RV), has been suggested as a possible trigger of T1D because of peptide sequence similarities between VP7, the major immunogenic protein of the virus, and T-cell peptide epitopes present in islet cell autoantigens.[170] However, several large cohort studies in the US—one using a commercial claims database to follow over 2.8 million infants up to 12 years

of age[171] and another from the VSD that followed nearly 400,000 infants for about 5 years[172]—showed no association between receipt of RV and T1D. In fact, some studies actually show a protective effect of RV on T1D.[173,174]

Celiac Disease

Celiac disease is an autoimmune condition in which a genetically predisposed host develops sensitivity to wheat gluten proteins and related substances in rye and barley, causing intestinal villous atrophy and gastrointestinal symptoms. During the 1980s and 1990s there was an epidemic of symptomatic celiac disease among infants in Sweden, prompting concerns about contributing environmental factors, including vaccines. However, a large study based on a national disease registry and using ecological as well as case-referent approaches failed to show any relationship between infant vaccines and celiac disease.[175]

Other Autoimmune Diseases

The relationship between receipt of HPV and onset of autoimmune disease was studied in a cohort of 2.2 million young girls in France who were followed for a mean of 33 months.[176] No association was seen with 12 different autoimmune diseases. A weak association with inflammatory bowel disease (IBD) was detected, but this was likely due to prevalent cases being misclassified as incident cases. This study did show a robust association with Guillain-Barré syndrome (GBS), which is discussed below (see *Guillain-Barré Syndrome*).

Henoch–Schönlein purpura (HSP), a form of vasculitis mediated by IgA-containing immune complexes, often follows a minor infection, raising the possibility that it could also be triggered by vaccines. However, a case-crossover study conducted at 5 European pediatric centers from 2011 to 2016 showed no association between routine vaccination and the development of HSP.[177]

There was a slight increase in the incidence of IBD in young children beginning around 2007, right after reintroduction of routine rotavirus vaccination. However, a nested case-control study involving 2.4 million children over a 10-year period showed no association between receipt of RV and the development of IBD.[178]

Autism

In 1998, 12 children were described with chronic enterocolitis and regressive developmental disorder, 8 of whose parents linked the onset of symptoms to receipt of MMR[179]; the suggestion was that replication of the vaccine viruses in gut tissues caused inflammation, leading to the absorption of toxins that affected brain development. In 2010, the United Kingdom's General Medical Council found evidence of serious professional misconduct by some of the

authors,[180] and the original paper was retracted.[181] By 2011, it had become clear that the 1998 study was fraudulent.[182] Nevertheless, the paper had already sparked a new wave of antivaccinationism; MMR immunization rates fell, and measles—eliminated from the United Kingdom in 1994—was again endemic by 2008.[183]

It is estimated that 1 in 36 children today have autism.[184] While there is evidence that at least some of the increase in prevalence reflects expanded case definitions, recognition of milder cases, diagnostic substitution, and more public awareness,[185,186] the increase has nevertheless raised alarm. However, there is strong evidence that MMR is not the cause.

- There is no higher risk of exposure to MMR among IBD cases compared with controls without IBD,[187] and measles virus sequences are rarely detected in gastrointestinal tract tissues of children with autism and gastrointestinal disturbances.[188] These findings refute the MMR-gut hypothesis.
- The incidence of autism over time does not parallel the uptake of MMR.[189-191] In the United Kingdom there was no increase in autism after the introduction of MMR in 1988,[192] nor was there clustering of cases after receipt of MMR.[193] No new form of gastrointestinal disease or autism arises when MMR is introduced into populations.[194,195]
- Case-control studies around the world show that the odds of being diagnosed with autism among persons who have received MMR are essentially the same as those who have not received MMR.[196-199]
- Cohort studies—including one from Denmark that analyzed 1,647,504 person-years of exposure to MMR and 482,360 person-years of nonexposure[200]—show no association between MMR and autism or ASD. In fact, a meta-analysis of 5 cohort studies (involving 1,256,407 children) and 5 case-control studies (involving 9,920 children) found no relationship between autism and vaccination.[201]

High levels of mercury can damage the nervous system and kidneys. For decades thimerosal, an *ethylmercury* (as opposed to *methylmercury*, which is much more toxic) compound, had been added to some vaccines in order to prevent microbial contamination *of* multidose vials. In 1999, because the cumulative level of mercury represented by the routine infant vaccine schedule was slightly above the level considered to be safe, the Public Health Service (PHS) and the AAP called for manufacturers to eliminate thimerosal from vaccines (as of 2023, the only routine childhood vaccines in the US that still contained thimerosal as a preservative were some multidose vials of IIV).[202] This pre-emptive move by the PHS and AAP led to a drop in public confidence (*see below*).[203,204]

There is strong evidence that thimerosal does not cause autism.

- Ethylmercury from thimerosal-containing vaccines is rapidly eliminated and infant blood levels do not exceed safe thresholds.[205]
- Autism remained prevalent or continued to increase in areas where thimerosal was removed from vaccines.[206-208]
- Case-control studies show no relationship between ethylmercury exposure from vaccines or immunoglobulin preparations and ASD, subcategories of autistic disorder, or ASD with regression.[209]
- Cohort studies—including one from the United Kingdom involving 109,863 children[210] and another from Denmark involving 1,220,006 person-years of exposure to thimerosal and 1,660,159 person-years of nonexposure[211]—show no association with developmental disorders, autism, or ASD. In addition, a study in the US involving over 100,000 children found no consistent associations between exposure to thimerosal-containing vaccines and neurodevelopmental outcomes,[212] and no consistent associations were seen between earlier exposure to thimerosal-containing vaccines and the results of comprehensive neuropsychological test results among 1047 children.[213]

Authoritative bodies have unanimously rejected a link between vaccines and autism. That, however, has not stopped people from filing claims under the National Vaccine Injury Compensation Program (VICP; see *Chapter 3: Standards, Principles, and Regulations— National Vaccine Injury Compensation Program [VICP]*). In the early 2000s, because of the burden of petitions before the VICP, the vaccine court asked the petitioners to put forward test cases for their theories, in what became known as the Omnibus Autism Proceedings.[214] By 2010, the court had denied compensation in all of these cases, and appeals had been denied.[215,216]

Neurological Conditions

Encephalopathy

An uncontrolled case series published in 1974 described children who allegedly developed mental retardation and epilepsy following receipt of DTwP.[217] Over the next several years, fear of the vaccine caused a precipitous drop in pertussis immunization rates, resulting in >100,000 pertussis cases and hundreds of deaths.[218]

The National Childhood Encephalopathy Study (NCES), conducted in the United Kingdom from 1976 to 1979, suggested the possibility of a relationship between the vaccine and encephalopathy.[219,220] The IOM independently analyzed NCES data in 1991 and concluded that there was a rare but causal relationship with encephalopathy in the immediate postvaccination period, although there was no evidence of permanent brain damage.[221] A reanalysis by the IOM in 1994 concluded that DTwP did not cause encephalopathy.[222]

Other studies also refuted the initial NCES findings. For example, a UK study compared over 130,000 children who had received DTwP with a similar number who had received only DT and found no association with encephalopathy.[223] A study in Tennessee found 2 cases of encephalitis among 38,171 children who had received 107,154 DTwP doses; in both cases, the onset of symptoms was >2 weeks following immunization.[224] Finally, in a case-control study conducted in Washington and Oregon involving 218,000 children, 424 cases with neurological illness were each matched with 2 controls.[225] No association was seen with DTwP administration, even when the analysis was restricted to encephalopathy or complicated seizures and adjusted for factors that might have affected vaccine administration.

In a study published in 2006, the records of four large US health maintenance organizations were used to investigate this issue once again.[226] A total of 452 children with encephalopathy diagnosed between 1981 and 1995 were compared with matched controls without encephalopathy. Exposure to pertussis vaccine in any postvaccination time period was no more common among cases than controls. The maximum possible all-cause incidence of encephalopathy after pertussis immunization was 1 in 370,000, which is no different from the background rate of encephalopathy in young children.

In a landmark 2006 study, de novo mutations in the gene encoding a neuronal sodium channel protein were found in 11 of 14 patients who allegedly had suffered vaccine encephalopathy[227]; since then, additional cases have been reported.[228] These individuals are born with a molecular defect that would cause seizures and regression, *vaccines or no vaccines*. Despite this finding, and despite the fact that acellular pertussis vaccines have replaced whole-cell vaccines, encephalopathy remains a compensable injury under the VICP (see *Chapter 3: Standards, Principles, and Regulations—National Childhood Vaccine Injury Act*).

Guillain-Barré Syndrome

GBS is an acute, immune-mediated, demyelinating peripheral neuropathy characterized by progressive, ascending symmetric weakness. Cases usually occur after an infectious event, most notably *Campylobacter jejuni* enteritis.

1976 Swine Flu Vaccine

In 1976, there was an outbreak of a new A(H1N1) influenza strain among soldiers at Fort Dix, New Jersey.[229] The virus, desig-

nated A/New Jersey/76 (Hsw1N1) and colloquially called the *swine flu*, was closely related to the deadly 1918 pandemic strain; after circulating in pigs for years it had apparently jumped to humans. In retrospect, the outbreak may have been an anomaly—an animal virus introduced into a stressed, crowded, closed population, with little potential to spread to the public. However, fearing the start of a new pandemic, the US government instituted a mass campaign in which 45 million people were immunized over a 3-month period; more than 500 cases of GBS resulted, for an attributable risk of about 1 in 100,000.[230] The mechanism may have involved some form of molecular mimicry, supported by the observation that mice receiving that vaccine develop anti-ganglioside antibodies.[231]

■ Seasonal Influenza Vaccine

While some studies have suggested a causal relationship between seasonal influenza vaccine and GBS,[232] most have not. One, for example, looked at two influenza seasons in the US in the early 1990s and found a relative risk (RR) of 1.7, corresponding to approximately one additional case of GBS per million people vaccinated.[233] It is important to keep perspective here: in any given 6-week period of time, somewhere between 1 in 220,000 and 1 in 1.4 million people will develop GBS—*vaccine or no vaccine.*[234] Another study in the United Kingdom spanning the years 1992 to 2000 found 228 incident cases of GBS; seven cases occurred within 42 days of any immunization (three were after influenza immunization) and 221 were not associated with immunization, for a RR of 1.03.[235] A study from Canada published in 2006 demonstrated no seasonality of GBS and no increase in hospital admissions for GBS after the introduction of a universal influenza immunization program.[236] Finally, a large study from California found 415 incident cases of GBS in >30 million person-years; the odds of influenza vaccination in the 6 weeks prior to diagnosis were no different than the odds of vaccination in the preceding 9 months.[237]

The largest meta-analysis to date found an overall relative risk of GBS of 1.41 with any influenza vaccine.[238] However, a very large study from Canada underscores an important point.[239] Analyzing the health records of all Ontario residents eligible for health coverage between 1993 and 2011, 2831 incident hospital admissions for GBS were found. The risk of GBS within 6 weeks of influenza vaccination was 52% higher than during a control period, translating to an attributable risk of about 1 in a million. However, the risk of GBS after a health care encounter for *influenza disease* was about 17 per million. The bottom line is that if influenza vaccination *does* cause GBS, it does so infrequently enough that the risk can barely be detected. Moreover, with respect to GBS, *not being vaccinated* is riskier than *being vaccinated*, and the risk of GBS if you are vaccinated is extremely low.

■ 2009 A(H1N1) Pandemic Vaccine

Analysis of data from the adverse event monitoring systems that were put into place during the 2009 A(H1N1) pandemic influenza immunization program, covering 23 million vaccinated persons, showed about 1.6 excess cases of GBS per million vaccinees.[240] This is much smaller than the association seen with the 1976 vaccine. Importantly, antiganglioside antibodies were not detected in humans infected with or vaccinated against influenza 2009 A(H1N1), including a sample of those who actually developed GBS after vaccination.[241]

■ MenACWY-D

Shortly after licensure of MenACWY-D in 2005, cases of GBS associated with the vaccine were reported to VAERS.[242] Most of the cases occurred within 2 weeks of vaccination, a timeframe that would fit with a causal relationship. However, combined data from two studies showed no incident cases of GBS within 6 weeks of 2.3 million vaccinations, for an estimated upper 95% confidence limit of the attributable risk of 1 case per million doses, which is not above background rates.[243]

■ HPV

As mentioned above (see *Allergies and Autoimmune Diseases)*, a population-based French study published in 2017 showed an association between receipt of HPV and GBS. Strengths of this study were its large size, strict case definition, and background (unexposed) rates consistent with previous studies; furthermore, the results were robust to sensitivity analyses, and causality was suggested by clustering around the time of vaccination. However, in a VSD study conducted from 2006 to 2015, there was only one case of GBS occurring within 42 days of 2,773,185 doses of HPV4.[244] Likewise, an English self-controlled case series found no increased risk of GBS in any time period following receipt of HPV.[245] Both studies concluded that the attributable risk was around 1 in a million, or less.

■ Multiple Sclerosis, Transverse Myelitis, and Acute Disseminated Encephalomyelitis

The idea that vaccines might cause multiple sclerosis (MS), an autoimmune demyelinating disease characterized by exacerbations and remissions, was fueled by anecdotal reports of MS following HepB administration and case-control studies showing a slightly increased risk in vaccinated persons. Two large case-control studies subsequently evaluated whether HepB causes MS or whether HepB, tetanus, or influenza vaccines exacerbate symptoms of MS. The first, a cohort study in nurses, identified 192 women with MS and 645 matched controls.[246] There was no association between MS and any parameter of exposure to HepB. The second included 643 patients in Europe with MS relapse occurring between 1993 and 1997.[247] No

association was found between relapse and exposure to any vaccine in the 2-month period before relapse compared with the four previous 2-month periods. In a case-control study in France, 143 cases of MS in children <16 years of age were matched to 1122 controls; 32% of cases and 32% of controls had received HepB in the 3 years before the index date.[248] A subsequent study looked at first-ever episodes of acute inflammatory demyelination in children, irrespective of the subsequent course of the disease.[249] The rates of HepB vaccination in the 3 years before the index date were 24.4% for 349 cases and 27.3% for 2941 matched controls; the adjusted odds ratio did not support a causal relationship. A meta-analysis of 13 controlled studies published in 2018 found no association between HepB and MS or other central demyelinating conditions.[250]

Other well-controlled studies also found that influenza vaccine did not exacerbate symptoms of MS. In fact, influenza *infection* is more likely to cause an exacerbation of symptoms than influenza *immunization*; thus, influenza vaccine may actually prevent exacerbations of MS.[251] In a multicenter, prospective, randomized, double-blind trial of influenza vaccine among 104 patients with MS, immunization was not associated with exacerbation of symptoms or change in disease course.[252]

HPV4 also does not appear to trigger MS. A study from Denmark and Sweden that involved nearly 4 million females looked at vaccination history and the onset of MS and other demyelinating diseases (approximately 800,000 of the subjects had received about 2 million vaccine doses). No association was found, whether the data were analyzed by cohort or by self-controlled case series methodology.[253]

Vaccination has been postulated to trigger other demyelinating diseases, including acute disseminated encephalomyelitis (ADEM), transverse myelitis, and optic neuritis. Whereas *natural viral infections* are known to cause ADEM, there are no definitive data implicating any current vaccine. That's not to say that people do not get ADEM shortly after receiving, for example, influenza vaccine—they do,[254] but remember that the prevalence of influenza immunization is high and there will inevitably be people who receive a flu shot in the month before being diagnosed with ADEM. Flu shots are given in the respiratory viral season, and it may be those respiratory viruses triggering the ADEM rather than the vaccinations. In a VSD study encompassing the years 2007 to 2012, a time when nearly 64 million doses of any vaccine were administered to the study population, only 7 cases of transverse myelitis and 8 cases of ADEM had been vaccinated during the 5 to 28 days before onset of illness.[255] Similarly, in a study involving >20 million doses of vaccine administered in an integrated healthcare system, no association was found between the first-ever occurrence of optic neuritis (91 confirmed cases) and immunization; looking at all vaccines combined, any effect, if it existed, would be less than one case per million doses.[256] Finally, a nested case-control study in China conducted from 2011 to 2015, which included 272 cases of ADEM and 1096 controls, failed to show an association with any one of 14 different vaccines.[257]

Bell's Palsy

Bell's palsy is an acute, unilateral facial paralysis, manifesting as sagging of the eyebrow, inability to close the eye, drooping of the mouth, and loss of the nasolabial fold. Many cases in endemic areas are caused by Lyme disease, and most other cases are idiopathic. In 2000, an adjuvanted, intranasal, inactivated influenza vaccine that was licensed in Switzerland was found to cause Bell's palsy at an estimated rate of 130 cases per 100,000 vaccinees (the expected annual rate would be around 25 per 100,000).[258] Interestingly, while studies showed no evidence of an association between LAIV and Bell's palsy,[259] a signal of Bell's palsy following IIV was detected in the VAERS database.[260] However, a large population-based study failed to find any association between IIV—or any other vaccine, for that matter—and Bell's palsy in children.[261] Likewise, a study out of the General Practice Research Database in the United Kingdom that included >2000 cases of Bell's palsy found no association with IIV administration in the preceding 3 months.[262]

A self-controlled case-series analysis of approximately 50,000 people who were vaccinated with MenACWY-CRM from 2011 to 2013 detected a 5-fold increased incidence of Bell's palsy among those who were concomitantly given other vaccines.[263] Only 8 cases occurred in the predefined risk window, and all resolved completely. Given the small number of cases, it is possible that chance alone contributed to the observed effect. In addition, the contribution of underlying co-morbidities could not be assessed. A subsequent systematic review of concomitant administration of meningococcal vaccines with other vaccines in adolescents and adults failed to identify any significant safety concerns.[264]

See **Table 7.10** regarding COVID-19 vaccination and Bell's palsy.

Narcolepsy

Narcolepsy is a chronic disorder characterized by severe, irresistible daytime sleepiness and abnormal sleep-wake patterns. It is rare—occurring in about 1 per 100,000 person-years—and even rarer in children. That is why early reports out of Finland and Sweden of an increase in narcolepsy in children and adolescents who received Pandemrix, an AS03-adjuvanted inactivated vaccine for the 2009 pandemic A(H1N1) strain, were so alarming. About 30 million doses of Pandemrix were distributed, and the attributable risk was estimated to be around 1 in 18,000.[265] A weaker but significant association in adults was suggested.[266]

Narcolepsy type 1 is thought to be an autoimmune disease characterized by the loss of neurons in the posterior hypothalamus

TABLE 7.10 — Concerns Expressed About COVID-19 Vaccines Used in the United States

Concern	Comment
Vaccines made this quickly cannot be trusted	While the development of COVID-19 vaccines was rapid, it was nevertheless methodical.[a] ■ The genetic sequence of the virus was determined within weeks of the initial outbreak ■ The S-protein was quickly identified as a target of neutralizing antibodies ■ Existing vaccine technologies (eg, mRNA) were leveraged to create S-protein–based vaccines ■ Large, rigorous, placebo-controlled clinical trials demonstrated safety and efficacy ■ The data were reviewed by the FDA; EUAs were granted, and some products achieved full approval ■ The data were reviewed by the ACIP and recommendations for use were made using the EtR Framework (see *Chapter 2: Vaccine Infrastructure in the United States—Policy and Recommendations*) ■ Surveillance for adverse events continued to take place after implementation ■ Real-world evidence involving hundreds of millions of vaccinated individuals demonstrated that COVID-19 vaccines were safe and effective
Serious side effects may show up later	Serious adverse events with onset months to years following vaccination have rarely been seen with other vaccines.[b] As of July 2023, about 13.5 billion COVID-19 vaccine doses had been administered worldwide, with no related incident long-term side effects detected despite robust surveillance.
The vaccines can be shed and can cause COVID-19	The vaccines authorized for use in the US as of October 2023 are based on the SARS-CoV-2 S-protein. They are not live, replicating viruses. The vaccines may cause fever, chills, and other symptoms that overlap with COVID-19, but they cannot cause COVID-19. There is no part of these vaccines that is released or discharged from the vaccinated person.
Vaccination can make the disease worse	Vaccine-induced enhancement of disease was seen after the use of inactivated RSV and measles vaccines in the 1960s and more recently with dengue vaccines (see *Chapter 13: Dengue*).[c] Experimental animals vaccinated against COVID-19 do not develop enhanced disease when challenged.[d] For other coronaviruses, prior infection does not enhance disease. Severe COVID-19 is much less likely among vaccinated people than among unvaccinated people.[e]
Vaccination can trigger MIS-C	Vaccination protects against MIS-C,[f] although there is the rare occurrence of vaccine-induced myocarditis (see *Chapter 12: COVID-19*)
Fetal cell lines are used to make the vaccines	Fetal cell lines are not used to manufacture COVID–mRNA (Pfizer-BioNTech) or COV-mRNA (Moderna), although the HEK293 cell line, derived in the early 1970s from the kidney of an aborted fetus,[g,h] was used in testing the final products.[i] Fetal cell lines are not used in the manufacture or testing of COV-aPS (Novavax). The Vatican has stated that it is "morally acceptable to receive COVID-19 vaccines that have used cell lines from aborted fetuses in their research and production process."[j]
Vaccines that contain genetic material can alter a person's DNA	The genetic material in mRNA-based vaccines[k] degrades quickly after directing cytoplasmic ribosomes to make the S-protein; the cell's DNA, which resides in the nucleus, is not affected.[l]
Vaccination affects the menstrual cycle	Any stressor, including vaccination, could theoretically affect the hypothalamic-pituitary-ovarian axis, which regulates the timing of menstruation. Data from an international cohort of almost 20,000 users of the menstrual cycle tracking application, Natural Cycles, showed an increase in cycle length of <1 day among vaccinated versus unvaccinated women.[m]

Continued

TABLE 7.10 — *Continued*

Concern	Comment
Vaccination causes infertility	There are small areas of amino acid homology between the S-protein of SARS-CoV-2 and syncytin-1, a protein involved in placenta formation, raising speculation that COVID-19 vaccines (which employ the S-protein) could stimulate antibodies against the placenta.[n] However, these sequences are too short to generate autoimmunity, and anti–S-protein antibodies do not impair implantation or early pregnancy.[o] There is no change in ovarian reserve associated with vaccination,[p] and there is no evidence of decreases in fertility despite there being hundreds of millions of infected and/or vaccinated people worldwide.
Vaccines can cause Guillain-Barré syndrome	There is little homology between SARS-CoV-2 and human proteins, making molecular mimicry and induction of anti-myelin immune responses unlikely. The absence of an association between natural COVID-19 and GBS at the population level[q] suggests that vaccination with components derived from the virus would be safe. As of July 2023, after nearly 700 million vaccine doses were given in the US, there were only 999 GBS cases in the VAERS database[r]; even if each of those cases was caused by the vaccine (which is unlikely), the reporting rate would be less than the expected background rate.
Vaccines can cause Bell's palsy	A systematic review and meta-analysis showed that the odds of Bell's palsy among COV-mRNA recipients in randomized controlled trials was 3.57-fold higher than the odds among placebo recipients.[s] However, there was no association between vaccination and Bell's palsy in pooled data from observational studies, and, importantly, the odds of Bell's palsy after SARS-CoV-2 infection was 3.23-fold higher than after vaccination.
Vaccines can cause hearing loss	Whereas the reporting rate of hearing loss in VAERS does not exceed the reported incidence in the general population,[t] a large population-based cohort study in Israel suggested a potential association between COV-mRNA (Pfizer-BioNTech) and hearing loss, with an attributable risk of <1 per 100,000.[u]
Vaccines can trigger hyperthyroidism	By June 2023, after billions of doses of vaccine doses had been given worldwide, there were papers describing a total of about 60 new onset cases of Graves' disease following administration of a COVID-19 vaccine.[v] However, a single center study in the US showed no increase in the incidence of Graves' disease after the implementation of COVID-19 vaccination.[w] Moreover, a population-based, self-controlled case series study of 2.3 million vaccinees in Hong Kong showed no association between receipt of first or second doses of COV and any thyroid abnormality.[x]
Vaccines contain microchips that can track you	This myth originated from a study funded by The Gates Foundation wherein near-infrared fluorescent microparticles ("quantum dots") were co-deposited in the skin of rats along with IPV as a way of marking the animals' status as "immunized".[y] This technology—which, incidentally, does not involve microchips and cannot be used to track location—is not used in any COVID-19 vaccine.

ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; EtR, Evidence-to-Recommendations; EUA, Emergency Use Authorization; FDA, US Food and Drug Administration; GBS, Guillain-Barré syndrome; VAERS, Vaccine Adverse Event Reporting System

[a] Golob JL, et al. *JCI Insight*. 2021;6:e149187.

[b] The only examples that come to mind are the rare instances of reactivated vaccine strain VZV causing zoster and vaccine-associated poliomyelitis in immunocompromised persons who were inadvertently given OPV (the virus may persist and revert to virulence over time).

[c] Munoz FM, et al. *Vaccine*. 2021;39:3053-3066.

[d] DiPiazza AT. *Immunity*. 2021;54:1869-1882.

[e] Haas EJ, et al. *Lancet*. 2021;397:1819-1829.

[f] Zambrano LD, et al. *MMWR*. 2022;71:52-58.

[g] Vaccines and related biological Products advisory committee meeting, May 16, 2001. https://wayback.archive-it.org/7993/20170404095417/https://www.fda.gov/ohrms/dockets/ac/01/transcripts/3750t1_01.pdf. Accessed July 21, 2023.

[h] Graham FL, et al. *J Gen Virol*. 1977;36:59-72.

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TABLE 7.10 — *Continued*

[i] COV-Ad26 (Janssen) is produced in the PERC6 TetR cell line, which traces back to retinal tissue from a fetus aborted in the mid-1980s (Gallimore PH, et al. *Anticancer Res.* 1986;6:499-508). The FDA revoked emergency authorization for this vaccine in June 2023, as requested by the company, citing low demand for the product.

[j] Congregation for the Doctrine of the Faith: Note on the morality of using some anti-COVID–19 vaccines. Vatican Web site. https://www.vatican.va/roman_curia/congregations/cfaith/documents/rc_con_cfaith_doc_20201221_nota-vaccini-anticovid_en.html. Accessed July 21, 2023.

[k] Zhang C, et al. *Front Immunol*. 2019;10:594.

[l] DNA from COV-Ad26 (Janssen), which is no longer used in the US, enters the nucleus, and is transcribed into mRNA, which migrates into the cytoplasm for translation into protein. The vaccine DNA does not include coding regions for the enzymes necessary to replicate or integrate into host DNA (Custers J, et al. *Vaccine*. 2021;39:3081-3101).

[m] Edelman A, et al. *BMJ Med*. 2022;1:e000297.

[n] Girardi G, et al. *Obstet Gynecol*. 2022;139:3-8.

[o] Morris RS. *Fertil Steril Rep*. 2021;2:253-255.

[p] Yang L, et al. *JAMA Net Open*. 2023;6:e2318804.

[q] Keddie S, et al. *Brain*. 2021;144:682-693.

[r] About the Vaccine Adverse Event Reporting System. https://wonder.cdc.gov/vaers.html. Accessed July 21, 2023.

[s] Rafati A, et al. *JAMA Otolaryngol Head Neck Surg*. 2023;149:493-504.

[t] Formeister EJ, et al. *JAMA Otolaryngol Head Neck Surg*. 2022;148:307-315.

[u] Yanir Y, et al. *JAMA Otolaryngol Head Neck Surg*. 2022;148:299-306.

[v] Chen K, et al. *Eur J Med Res*. 2023;23:232.

[w] Endo M, et al. *Endocr Pract*. 2023; doi: 10.1016/j.eprac.2023.05.005.

[x] Wong CKH, et al. *BMC Medicine*. 2022;20:339.

[y] McHugh KJ, et al. *Sci Transl Med*. 2019; doi: 10.1126/scitranslmed.aay7162.

that produce hypocretin (also called orexin), which promotes wakefulness. There is a strong genetic predisposition marked by the major histocompatibility complex class II DQB1*06:02 allele, something that was seen in post-Pandemrix narcolepsy as well.[267] It is tempting to think that Pandemrix might have triggered autoimmunity in genetically predisposed persons, perhaps through molecular mimicry between viral antigens and orexin-bearing neurons. However, initial findings that a portion of the A(H1N1) hemagglutinin molecule might trigger T-cell responses against orexin-derived peptides could not be reproduced.[268,269] Also, the hemagglutinin hypothesis does not readily explain why narcolepsy was reported only after administration of Pandemrix and not after other pandemic A(H1N1) vaccines, including a similar one (Arepanrix) made by the same manufacturer (albeit at a different site) and containing the same adjuvant.

Interestingly, narcolepsy was associated with natural 2009 pandemic A(H1N1) infection in China,[270] and a study that included the entire population of Norway showed increased risk in Pandemrix-vaccinated people who were also infected, suggesting an interaction between natural infection and vaccination.[271] One hypothesis is that in some patients, wild-type 2009 A(H1N1) infection migrated through olfactory pathways to hypocretin-secreting cells in the hypothalamus; receipt of an adjuvanted vaccine around the same time might have amplified cytotoxic T-cell responses directed against those infected cells.[272]

In a study involving 540 million person-years of potential exposure in 7 countries on 4 continents, no association was seen between the introduction of any adjuvanted pandemic A(H1N1) vaccine and narcolepsy, except in Sweden, where there was a sharp peak in narcolepsy incidence, especially in children 5 to 19 years of age (of note, wild-type virus was circulating in Sweden at the time of the vaccination program).[273] Pandemrix was never licensed for use in the US, and it has not been used anywhere since the 2009-2010 influenza season. A study from the VSD looking at >1.5 million persons <30 years of age who received a US-licensed 2009 A(H1N1) vaccine in one form or another found 16 chart-confirmed incident cases of narcolepsy; none had the onset within the 180 days following vaccination, and the number of cases was less than that expected from the background incidence.[274]

Febrile Seizures

The first dose of MMRV causes fever more often than MMR and VAR given separately on the same day.[275] Since 2% to 5% of all children experience at least one febrile seizure in their lifetime,[276] it is not surprising that some children will have a seizure after they receive MMRV. In fact, a postlicensure study showed that the rate of febrile seizures after the first dose of MMRV was approximately twice as high (about 7 per 10,000) as after the separate vaccines

in the 5 to 12 days following vaccination.[277] Similarly, a VSD study showed an elevated risk of febrile seizures from days 7 to 10 postvaccination in children 12 to 23 months of age (receiving their first dose),[278] but not in children 4 to 6 years of age (presumably receiving their second dose).[279] These studies suggested that one febrile seizure attributable to the vaccine will occur for every 2300 to 2600 children receiving a first dose, prompting the ACIP to retract its historical general preference for MMRV for the first dose. A meta-analysis published in 2015 confirmed the 2-fold increase in seizure risk associated with MMRV.[280]

There is also an increased risk of febrile seizures when IIV and PCV13 are given on the same day to children <5 years of age.[281] The magnitude of the risk is <1 per 1,000 children vaccinated, and ACIP considers simultaneous administration acceptable. While considered benign by medical professionals, febrile seizures can be frightening for parents.[282] Ironically, MMRV, IIV, and PCV can *prevent* febrile seizures by preventing the respective diseases. Since febrile seizures occur early when the temperature is rapidly rising, management of fever with antipyretics is not likely to prevent them, and prophylaxis with antipyretics is not warranted.

Miscellaneous Concerns

Sudden Infant Death Syndrome

In the early 1990s, there were 5000 annual cases of SIDS in the US. In 1991, routine vaccination of infants with HepB was recommended—theoretically, every one of the 4 million babies born each year would receive 3 doses of HepB during the first 6 months of life. Predictably, there would be infants who die from SIDS the very day they received the vaccine—and there were, sparking concerns that HepB caused SIDS. By 2001, however, HepB uptake in infants had increased to about 90% and the number of SIDS deaths had *decreased* to about 1600 cases per year—a direct result of the "Back to Sleep" campaign initiated in 1994, in which parents were encouraged to place infants on their backs or sides when going to sleep. Several studies actually show lower SIDS rates among infants who receive vaccines when compared with those who do not.[283,284] While this may reflect biases wherein healthier or better-cared-for infants are the ones who are immunized, the data clearly do not implicate vaccines as a risk factor for SIDS. SIDS rates have continued to decline in the US, despite consistently high infant vaccine coverage rates.[285]

A study published in 2004 looked at a cohort of 361,696 infants born between 1993 and 1998.[286] A total of 1363 infants in the cohort died in the first 29 days of life; only 5% of them had been vaccinated with HepB, whereas 66% of those who survived the first month of life had been immunized. Moreover, there was no difference in the proportion of vaccinated and unvaccinated infants who died of unexpected causes, and the SIDS death rate was the same (3.3 per 100,000) for vaccinated and unvaccinated infants. Recent data suggest that infants who die from SIDS have abnormalities of the medullary serotonin system, which controls autonomic function and breathing.[287]

Kawasaki Disease

Kawasaki disease (KD) is an acute, inflammatory, small-to-medium sized vessel vasculitis manifest by prolonged high fever and some combination of rash, conjunctival suffusion, changes in the oral mucosa or peripheral extremities, and cervical lymphadenopathy; desquamation occurs in the convalescent phase, and ectasia or aneurysms can develop in the coronary arteries. In Phase 3 clinical trials of RV5, KD was reported in 5 of 36,150 vaccinees and 1 of 35,536 placebees within 42 days of vaccination, for an unadjusted RR of 4.9, which raised concern about an association. However, a study published in 2009 provided reassurance that RV5 does not cause KD.[288] VAERS reports from 1990 through mid-2007 were analyzed, yielding only 97 cases. No clustering of cases was seen after vaccination. The reporting rates for KD in the 30 days following vaccination were 0.65 per 100,000 person-years before the RV5 label was changed to include KD as a reported adverse event, and 2.78 per 100,000 person-years after the change; both rates were lower than the expected background incidence of 9 to 19 per 100,000 person-years.

A study from the VSD that looked at 207,621 doses of RV5 given from 2006 to 2008 failed to suggest an association between the vaccine and KD,[289] and a postmarketing study involving 85,000 infants who had received at least one dose of RV5 showed no association with KD during any follow-up period after any dose.[290] Finally, a VSD study that looked at all vaccines given to approximately 1.7 million children from 1996 to 2006 actually showed that the rate of KD was lower in the 42 days after vaccination compared to unexposed periods.[291]

Intussusception

RRV-TV was licensed in the US in 1998. Within a year, there were 15 reports of IS in the VAERS database; population-based studies suggested a causal relationship, and the product was eventually withdrawn.[292] The highest incidence of vaccine-associated IS was in the first 2 weeks after Dose 1, a time when viral replication peaks.

IS occurred once for every 10,000 children vaccinated with RRV-TV (the natural risk of IS in about 5 in 10,000). The risk was so small that it could not have been detected in the prelicensure trials, which involved only 11,000 infants. The next-generation of rotavirus vaccines, RV5 (RotaTeq) and RV1 (Rotarix), were each tested in approximately 70,000 children before licensure, and no

evidence of an association with IS was found.[293,294] Even these massive trials, however, could not detect extremely small associations. In fact, postmarketing surveillance in Mexico, Brazil, and Australia demonstrated an increased risk of IS.[295,296] Two landmark studies from the US were published in 2014. One involved over a half-million first doses of RV5 and showed an attributable risk of IS of 1 in 67,000[297]; the other was a VSD project that showed an attributable risk of 1 in 19,000 children receiving 2 doses of RV1 (the study found no increase in risk after RV5).[298] A meta-analysis published in 2015 suggested that the overall relative risk of IS after the first dose of either RV1 or RV5 is around 5.5, which is about 10-fold lower than that for RRV-TV.[299] Interestingly, the increased risk of vaccine-associated IS appears to be confined to high- and upper-middle income countries.[300]

As might have been expected from the above data, after the introduction of the rotavirus vaccine program in the US, rates of IS among infants 8 to 11 weeks of age increased, amounting to 7 to 26 attributable cases per year.[301] All RVs may increase the risk of IS.[302] While a study in India showing no increased risk of IS from a monovalent bovine-human reassortant RV casts some doubt on such a *class effect*, there are many confounding variables, including vaccination at an earlier age, coadministration of OPV, higher levels of maternal antibodies, malnutrition, and the prevalence of other enteric pathogens.[303] Even with an attributable risk of the order of 1 in 20,000 to 1 in 100,000, a universal vaccination program is still worthwhile.

Immune Thrombocytopenia

ITP is a (usually) self-limiting disorder wherein patients develop autoimmune-mediated sequestration and destruction of platelets. In as much as ITP typically follows a viral infection, which presumably triggers an aberrant antibody response, it is not too surprising that MMR vaccination—which is itself a viral infection—can cause ITP. A systematic literature review published in 2010 found the incidence of ITP associated with MMR to be a median of 2.6 cases per 100,000 doses, or about 1 in 40,000[304]; this is much lower than the incidence after natural measles. The same review found that the vast majority of cases of ITP associated with MMR vaccination were self-limited, and progression to chronic ITP appears to be less likely than ITP following natural viral infection; moreover, serious bleeding is rare.

A retrospective study involving 1.8 million children who received 15 million vaccine doses from 2000 to 2009 found 197 chart-confirmed cases of ITP.[305] The only early childhood vaccine linked to ITP was MMR, at an incidence of about 1 in 50,000. Most cases were acute and mild, and no vaccine-exposed cases developed serious permanent sequelae.

Miscarriage, Birth Defects, and Infertility

There is no evidence directly linking any routine vaccines to birth defects, and pregnancy remains an *indication* for certain vaccines (see *Chapter 6: Vaccination in Special Circumstances—Pregnancy, Postpartum, and Breast-Feeding*). A VSD study conducted from 2004 to 2013 looked at 52,856 infants born to mothers who had received IIV during the first trimester and compared them to 373,088 whose mothers had not received IIV in the first trimester. The respective prevalence of major structural birth defects was 1.6 and 1.5 per 100, suggesting no association.[306] In a retrospective cohort study involving nearly 150,000 infants, no association was seen between maternal influenza vaccination and prematurity, small for gestational age, low birth weight, respiratory distress syndrome, and admission to the neonatal intensive care unit, among other neonatal outcomes.[307] Similarly, a Danish study that involved all pregnancies in the country from 2006 to 2013 showed no association between maternal vaccination with HPV4 and multiple neonatal outcomes, including major birth defects, spontaneous abortion, and still birth.[308] These huge studies provide reassurance that non-live vaccines do not adversely affect pregnancy outcomes.

A VSD study conducted during the 2010-2011 and 2011-2012 influenza seasons reported a modest association between receipt of IIV in the first trimester and spontaneous abortion.[309] The risk was confined to women who had received a 2009 pandemic A(H1N1)-containing vaccine in the previous season. However, a systematic review of 40 studies conducted between 1976 and 2015 showed no association between influenza vaccination during pregnancy and spontaneous abortion and, in fact, suggested a protective effect on preterm birth and low birth weight.[310] The benefits of reduced influenza morbidity among pregnant women and their infants far outweigh the known risks of immunization.

There is no a priori reason to suspect a causal relationship between receipt of HPV and primary ovarian insufficiency (POI; also called premature ovarian failure and premature menopause). However, anecdotal reports surfacing around 2012 suggested just such a link in a handful of girls. In a cohort of nearly 200,000 female patients studied from 2006 to 2014, only one of 28 incident cases of idiopathic POI had received HPV before the onset of symptoms; there were nearly 60,000 young women in the cohort who had received the vaccine, and the case in question had received her last dose 23 months earlier.[311] These results make a relationship between HPV and POI very unlikely. In fact, data from the 2013 to 2016 National Health and Nutrition Examination Survey showed no association between HPV and self-reported infertility of any cause among women 1114 women aged 20 to 33.[312]

See **Table 7.10** regarding COVID-19 vaccination and ovarian function.

Chronic Fatigue

Chronic fatigue syndrome (CFS; now called systemic exertion intolerance disease[313]) is characterized by prolonged, debilitating fatigue, subjective complaints, and profound functional impairment. While data are inconsistent, studies suggest immune activation, leading some to suspect infection as a trigger. In as much as vaccines mimic infection, they have come under suspicion as well.[314] However, the data refute an association. For example, large, population-based studies in Norway and the Netherlands showed no increased risk of CFS with receipt of HPV.[315,316] Interestingly, one study showed an association between influenza *infection*, but not influenza *vaccination*, and CFS.[317]

Clustered Anxiety-Related Adverse Events

Clustered anxiety-related reactions—also known as mass psychogenic illness, mass hysteria and epidemic hysteria—are characterized by a constellation of similar, unexplained symptoms occurring among persons in a cohesive social setting (like a school) who share beliefs about the cause of the symptoms.[318] Several factors contribute uniquely to the genesis of clusters of anxiety-related reactions after vaccination, including needle phobia, episodes of vasovagal syncope, and vaccination in the group setting, where those waiting in line can see the reactions of those who have already received a shot. One of the most well-known events occurred in El Carmen de Bolívar, Columbia, in 2014.[319] Over a 4-day period, 15 adolescent girls from one school were hospitalized with tachycardia, shortness of breath, and limb numbness after receiving HPV. Within weeks, fueled by "viral" videos of vaccinated girls fainting, twitching, and arriving unconscious at emergency departments, over 600 similar cases were reported. By 2016, despite reassurances that these symptoms were not organically related to vaccination, HPV uptake among eligible girls had fallen from 98% to 88%. Incidents like this are probably under-reported in the literature.[320]

COVID-19 Vaccines

As discussed in *Chapter 2: Vaccine Infrastructure in the United States—Emergency Preparedness and Response,* COVID-19 vaccines were first deployed under Emergency Use Authorization (EUA). This led to the perception that the vaccines were less rigorously tested prior to release. The truth is that the studies that led to the issuance of the EUAs were among the largest placebo-controlled vaccine clinical trials ever done—much larger, in fact, than the trials that led to full approval of most routinely-used vaccines. Moreover, within 6 months of the first EUAs, >170 million Americans had been vaccinated, providing a much larger safety database than existed for any routine vaccine in the years immediately following full approval. Despite this, at a time (October 2021) when half of

TABLE 7.11 — Unique Factors Contributing to COVID-19 Vaccine Hesitancy

- Novelty of the pathogen
- Rapid evolution of the pandemic
- New vaccine technology
- Unprecedented speed of vaccine development
- Emergency use authorization (as opposed to full approval)
- Real-time awareness and amplification of rare side effects
- Need for booster doses (suggesting vaccine ineffectiveness)
- Loss of trust in authorities, medical establishment, media, and government
- Legal immunity afforded to manufacturers of pandemic vaccines[a]
- Inconsistent public messaging surrounding the pandemic[b]
- Changing policies, recommendations, and mitigation measures[a]
- Resonance with discrimination and historical medical injustices in minority communities[c,d]
- Weakened cognitive flexibility under severe stress related to the pandemic[e]
- Economic hardship brought on by the pandemic[f]
- Effects of sociocultural networks, reliance on social media, and politicization[g,h,i]
- Conspiracy theories[j]
- Purposeful dissemination of misinformation[k]

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the world's population had been vaccinated and only a few extremely rare serious adverse events had been linked to the vaccines, hundreds of millions of Americans refused to be vaccinated, leading to tens of thousands of unnecessary deaths.

Many of the root causes of COVID-19 vaccine hesitancy are the same as those underlying vaccine hesitancy in general; others relate to unique features of the pandemic and the pandemic response (**Table 7.11**). Common concerns about COVID-19 vaccines are listed in **Table 7.10**, along with information to assist in addressing those concerns.

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Routine Schedules

As discussed in *Chapter 2: Vaccine Infrastructure in the United States—Policy and Recommendations*, each year the Advisory Committee on Immunization Practices (ACIP) releases updated schedules for routine childhood and adult vaccination. Beginning in 2023, addenda to the schedules have been posted on the Centers for Disease Control and Prevention Web site to reflect incremental ACIP recommendations.

The 2023 child and adolescent recommendations were approved by the American Academy of Pediatrics (AAP), American Academy of Family Physicians (AAFP), American College of Obstetricians and Gynecologists (ACOG), American College of Nurse-Midwives (ACNM), American Academy of Physician Associates (AAPA), and National Association of Pediatric Nurse Practitioners. **Figure 8.1** gives the routine schedule and **Figures 8.2** and **8.3** give catch-up schedules. **Figure 8.4** is a guide to conditions in children and adolescents for which there may be special recommendations.

The 2023 adult recommendations were approved by the AAFP, ACOG, ACNM, AAPA, the American College of Physicians, the American Pharmacists Association, and the Society for Healthcare Epidemiology of America. **Figure 8.5** gives the schedule by age group and **Figure 8.6** by medical and other indications.

The schedules are shown in simplified format. Details, which include information from the footnotes of the published schedules as well as certain flexibilities within the schedules, are contained in the individual vaccine chapters in *Section B: Diseases and Vaccines.* Vaccination of high-risk persons and other special populations is discussed in *Chapter 6: Vaccination in Special Circumstances*.

An *immunization platform* is a milestone age (or age range) that warrants special attention as an opportunity to deliver age-appropriate vaccines, provide catch-up, assess for special risks, and underscore other preventive health measures. The three main childhood platforms beyond infancy—school-aged (4 to 6 years of age), early adolescent (11 to 12 years of age), and late adolescent (16 years of age)—are highlighted in gray in **Figure 8.1**. **Table 8.1** identifies immunization platforms that arguably exist throughout life, along with examples of their associated age-

specific developmental and health issues. While there may be benefit, and little harm, in highlighting immunization platforms, it is crucial that this not detract from the importance of *always* paying attention to immunization issues, at every visit and at every age.

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FIGURE 8.1 — Routine Immunization Schedule for Persons ≤18 y, 2024

Vaccine	Birth	Months of Age									Years of Age							
		1	2	4	6	9	12	15	18	19-23	2-3	4-6	7-8	9-10	11-12	13-15	16	17-18
RSV	*Footnote a*															*Footnote a*		
HepB	1	2			3													
RV			1	2	(3)													
DTaP			1	2	3			4				5						
Hib			1	2	(3)		3 or 4											
PCV15 or PCV20[b]			1	2	3		4											
IPV			1	2	3							4						
COV					**Figures 12.6** and **12.7**													
Influenza					Annual (2 doses if 6 mo-8 y and previously received 0 or 1 dose)													
MMR					Travel		1					2						
VAR							1					2						
HepA					Travel		1, 2											

Tdap																Pregnancy, wound management		
HPV9															1			
														Sexual abuse/ assault	1,2	3 doses if ≥15 y		
MenACWY			**Figure 6.2**												1		2	
MenB															**Figure 6.2**			
																1, 2		
PPSV23												**Figure 6.1**						
Dengue														Seropositive in endemic areas				
Mpox (Jynneos)																		

	"Platform" beyond early childhood (**Table 8.1**)
	Routine vaccination. Dose number in series is shown (parentheses indicate doses that may not be necessary, depending on which product is used).
	Age at which routine vaccination may begin.

Continued

FIGURE 8.1 — *Continued*

	Catch-up
	Vaccination based on shared clinical decision-making (see *Chapter 2: Vaccine Infrastructure in the United States—Policy and Recommendations*)
	Vaccination recommended for certain high-risk persons (see *Chapter 6: Vaccination in Special Circumstances*)
	Vaccination not recommended, not applicable, or no recommendation

ACIP, Advisory Committee on Immunization Practices

See individual vaccine chapters for specific recommendations. Many of the listed vaccines can be given as combinations (see *Chapter 35: Combination Vaccines*).

[a] Nirsevimab, a monoclonal antibody against RSV, is recommended for all infants <8 mo born during or entering their first RSV season. Children 8-19 mo who are at increased risk for severe RSV disease and are entering their second RSV season should also receive nirsevimab. If nirsevimab is not available or not feasible to administer, high-risk infants in the first or second year of life should receive palivizumab. Vaccination with RSV (Pfizer) is recommended for pregnant women at 32-36 wks' gestation in order to provide passive immunity to their infants (there is no lower age limit for maternal vaccination). Most infants do not need both active maternal vaccination with RSV (Pfizer) and passive immunization with nirsevimab. See *Chapter 26: Respiratory Syncytial Virus*.

[b] PCV13 may be used if it is the only available vaccine.

Adapted from Immunization schedules. CDC Web site. https://www.cdc.gov/vaccines/schedules/ and meeting tecommendations. CDC Web site. https://www.cdc.gov/vaccines/acip/index.html. Accessed November 19, 2023.

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FIGURE 8.2 — Catch-Up Schedule for Healthy Persons 4 mo-6 y, 2024

Vaccine	Minimum Age for Dose 1	Minimum Interval to…			
		Dose 2	Dose 3	Dose 4	Dose 5
HepB	Birth	4 wk	8 wk and ≥16 wk after Dose 1 (minimum age 24 wk)		
RV[a]	6 wk	4 wk	(4 wk)		
DTaP[b]	6 wk	4 wk	4 wk	6 mo	6 mo
Hib	6 wk	Dose 1 at <12 mo: 4 wk Dose 1 at 12-14 mo: 8 wk (final dose) Dose 1 at ≥15 mo: no further doses	Age <12 mo and Dose 1 at <7 mo: 4 wk Age <12 mo and Dose 1 at 7-11 mo: 8 wk (minimum age 12 mo; final dose) Age 12-59 mo and Dose 1 at <12 mo: 8 wk (minimum age 12 mo; final dose) Doses 1 and 2 were Hib-OMP at <12 mo: 8 wk (minimum age 12 mo; final dose) Any dose at ≥15 mo: no further doses	Age 12-59 mo and Doses 1, 2, and 3 were Hib-T at <12 mo with Dose 1 at <7 mo: 8 wk (final dose)	
PCV15 or PCV20[c]	6 wk	Dose 1 at <12 mo: 4 wk Dose 1 at ≥12 mo: 8 wk (final dose) Dose 1 at ≥24 mo: no further doses	Age <12 mo: 4 wk Age ≥12 mo: 8 wk (final dose) Any dose at ≥24 mo: no further doses	Age 12-59 mo and Doses 1, 2, and 3 at <12 mo: 8 wk (final dose)	
IPV[d]	6 wk	4 wk	Age <4 y: 4 wk Age ≥4 y: 6 mo (final dose)	6 mo (minimum age 4 y)	
MMR	12 mo	4 wk			
VAR	12 mo	3 mo			
HepA	12 mo	6 mo			

This schedule should be used for healthy children who start late or who are >1 mo behind (see **Figure 8.4** for special circumstances). Catch-up can be accomplished by giving all vaccines for which a person is eligible at each visit, keeping in mind the minimum intervals between doses (**Table 5.1**). Routine vaccine series do not need to be restarted, regardless of the time that has elapsed between doses. Combination vaccines may be used for catch-up, depending on the patient's age and dose number. Doses shown in parentheses may not be necessary, depending on which product is used.

[a] The maximum age for Dose 1 is 14 wk 6 d. The maximum age for the final dose is 8 mo 0 d.
[b] Dose 5 is not necessary if Dose 4 is given at ≥4 y.
[c] PCV 13 may be used if it is the only available vaccine.
[d] The minimum ages and intervals should only be used in the first 6 mo of life if imminent exposure to polio is expected. If ≥4 doses have been given before 4 y, an additional dose should be given at 4-6 y and ≥6 mo after the last dose. Dose 4 is not necessary if Dose 3 is given at ≥4 y and ≥6 mo after the last dose.

Adapted from Immunization schedules. CDC Web site. https://www.cdc.gov/vaccines/schedules/ and meeting recommendations. CDC Web site. https://www.cdc.gov/vaccines/acip/index.html. Accessed November 19, 2023.

FIGURE 8.3 — Catch-Up Schedule for Healthy Persons 7-18 y, 2024

Vaccine	Minimum Age for Dose 1	Minimum Interval to…			
		Dose 2	Dose 3	Dose 4	Dose 5
MenACWY[a]	—	8 wk			
Tdap/Td[b]	7 y	4 wk	Dose 1 of DTaP or DT at <12 mo: 4 wk Dose 1 of DTaP, DT, Tdap, or Td at ≥12 mo: 6 mo (final dose)	Dose 1 of DTaP or DT at <12 mo: 6 mo	
HPV9	9 y	5 mo if <15 y of age (final dose), 4 wk if ≥15 y of age (3-dose series needed)	12 wk and ≥24 wk after Dose 1 (3-dose series needed if initiation at ≥15 y of age)		
HepA	—	6 mo			
HepB	—	4 wk	8 wk and ≥16 wk after Dose 1		
IPV[c]	—	4 wk	6 mo[c]	*Footnote d*	
MMR	—	4 wk			
VAR	—	Age <13 y: 3 mo Age ≥13 y: 4 wk			
Dengue[e]	9 y	6 mo	6 mo		

This schedule should be used for healthy children and adolescents who start late or who are >1 mo behind (see **Figure 8.4** for special circumstances). Catch-up can be accomplished by giving all vaccines for which a person is eligible at each visit, keeping in mind the minimum intervals between doses (**Table 5.1**). Routine vaccine series do not need to be restarted, regardless of the time that has elapsed between doses. Combination vaccines may be used for catch-up, depending on patient's age and dose number.

[a] If Dose 1 is given at 13-15 y, Dose 2 should be given at 16-18 y and ≥8 wk after the last dose. If Dose 1 is given at ≥16 y, Dose 2 is not necessary.

[b] Persons in this age range who were not fully immunized with DTaP should receive Tdap as Dose 1 in the catch-up series (additional doses may be given as Tdap or Td). If a child receives a dose of Tdap at 7-10 y, Tdap or Td may be used for the routine booster dose at 11-12 y. Administration of >2 doses of Boostrix or Adacel is off-label.

[c] Persons ≥18 y who are known or suspected to be unvaccinated or incompletely vaccinated against polio should complete a primary series with IPV.

[d] Dose 4 is not necessary if Dose 3 is given at ≥4 y and ≥6 mo after the last dose. Dose 4 is indicated if all previous doses were administered at <4 y or if Dose 3 was administered <6 mo after Dose 2.

[e] Only indicated if 9-16 y, seropositive and living in an endemic area.

Adapted from Immunization schedules. CDC Web site. https://www.cdc.gov/vaccines/schedules/ and meeting recommendations. CDC Web site. https://www.cdc.gov/vaccines/acip/index.html. Accessed November 19, 2023.

FIGURE 8.4 — Special Vaccination Considerations for Children and Adolescents by Condition or Risk Factor, 2024

	Pregnancy	Immunocompromised	HIV infection (severe immune suppression)	HIV infection (no severe immune suppression)	CSF leak or cochlear implant	Asplenia, complement deficiency	Heart or chronic lung disease	Kidney failure, ESRD, hemodialysis	Chronic liver disease	Diabetes (types 1 and 2)	Homelessness, injecting drug use, MSM	Sexual abuse or assault	American Indian or Alaska Native	Receiving aspirin or salicylates
RSV-mAb														
HepB														
RV														
DTaP														
Hib														
PCV/PPSV														
IPV														
COV														
IIV														
LAIV														
MMR														
VAR														
HepA														
Tdap														
HPV9														
Men-ACWY														
MenB														
RSV (Pfizer)														
Dengue														
Mpox														

	Vaccination not recommended, not applicable, or no recommendation
	Contraindicated or not recommended
	Precautions, special recommendations, other considerations (see individual vaccine chapters and *Chapter 6: Vaccination in Special Circumstances*)
	Routinely recommended if age-eligible and unvaccinated or vaccination status incomplete
	Vaccination based on shared clinical decision-making (see *Chapter 2: Vaccine Infrastructure in the United States—Policy and Recommendations*)

CSF, cerebrospinal fluid; ESRD, end-stage renal disease; MSM, men who have sex with men; RSV-mAb, RSV monoclonal antibody

Adapted from Child and Adolescent Immunization Schedule by Medical Indication. CDC Web site. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-indications.html. Accessed November 19, 2023.

FIGURE 8.5 — Routine Immunization Schedule for Persons ≥19 y, 2024

Vaccine	Years of Age				
	19-21	22-26	27-49	50-64	≥65
COV	**Figures 12.6** and **12.7**				
Influenza	Annual				
RSV	Seasonal vaccination of pregnant women at 32-36 wks' gestation[a]				←60 y
IPV	Unvaccinated or incompletely vaccinated				
Tdap/Td	Tdap once, then Td or Tdap every 10 y; Tdap during each pregnancy; wound management				
MMR	If born in 1957 or later and not immune (**Table 22.2**)				67 y →
VAR	If born in 1980 or later and not immune (**Table 32.2**)			44 y →	
RZV					
HPV9	If not previously immunized			45 y →	
PCV15, PCV20, PPSV23	**Figure 6.1**				**Figure 6.1**
HepA					
HepB				60 y →	
MenACWY	**Figure 6.2**				
MenB	**Figure 6.2**				
	23 y →				
Hib					
Mpox (Jynneos)					

	Routine vaccination
	Vaccination based on shared clinical decision-making (see *Chapter 2: Vaccine Infrastructure in the United States—Policy and Recommendations*)
	Vaccination recommended for certain high-risk persons (see *Chapter 6: Vaccination in Special Circumstances*)
	Vaccination not recommended, not applicable, or no recommendation

See individual vaccine chapters for specific recommendations. See **Figure 8.6** for recommendations for adults with high-risk conditions.

[a] Vaccination with RSV (Pfizer) is recommended for pregnant women at 32-36 wks' gestation in order to provide passive immunity to their infants (there is no upper age limit for maternal vaccination).

Adapted from Immunization schedules. CDC Web site. https://www.cdc.gov/vaccines/schedules/ and meeting recommendations. CDC Web site. https://www.cdc.gov/vaccines/acip/index.html. Accessed November 19, 2023.

FIGURE 8.6 — Adult Immunization Schedule by Medical and Other Indications, 2024

Vaccine	Pregnancy	Immuno-compro-mised	HIV		Asplenia, comple-ment deficiency	ESRD, hemodi-alysis	Heart or lung disease, alcohol-ism	Chronic liver disease	Diabetes (types 1 and 2)	HCP	MSM
			CD4 <200/ mcL (<15%)	CD4 ≥200/ mcL (≥15%)							
RSV		≥60 y									
COV	**Figures 12.6** and **12.7**										
Influenza	Annual (LAIV is contraindicated in certain conditions[a])										
Tdap/Td	Tdap with each pregnancy	Tdap once, then Td or Tdap every 10 y									
MMR	*Footnote b*			If not immune (**Table 22.2**)							
VAR	*Footnote b*			*Foot-note c*	If not immune (**Table 32.2**)						
RZV		≥19 y			≥50 y						
HPV9	*Footnote b*	≤26 y									
		27-45 y									
PCV15, PCV20, PPSV23		**Figure 6.1**									**Figure 6.1**
HepA											
HepB[d]	<60 y										
	≥60 y	≥60 y		≥60 y	≥60 y	≥60 y	≥60 y				
	Persons ≥60 y without risk factors may be vaccinated										
Men-ACWY	**Figure 6.2**					**Figure 6.2**					
MenB	Precaution	**Figure 6.2**				**Figure 6.2**					
Hib		3 doses for HCT		1 dose if never immunized							
Mpox (Jynneos)											

	Contraindicated or not recommended
	Vaccination recommended
	Vaccination based on shared clinical decision-making (see *Chapter 2: Vaccine Infrastructure in the United States—Policy and Recommendations*)

Continued

FIGURE 8.6 — *Continued*

	Vaccination recommended for persons with additional high-risk conditions or situations (see *Chapter 6: Vaccination in Special Circumstances*).
	Vaccination not recommended, not applicable, or no recommendation

ACIP, Advisory Committee on Immunization Practices; ESRD, end-stage renal disease; HCP, health care personnel; MSM, men who have sex with men

See individual vaccine chapters for specific recommendations.

[a] LAIV is contraindicated in pregnant women, close contacts of severely immunosuppressed patients, and persons with immunodeficiency or immunosuppression, HIV infection, functional or anatomic asplenia, cerebrospinal fluid leak, and cochlear implants. Precautions may exist as well.

[b] Vaccinate after pregnancy if indicated.

[c] Vaccination of persons who are not immune (**Table 32.2**) may be considered.

[d] High-risk conditions in addition to those shown in the columns that are indications for vaccination of persons ≥60 y include sex partners and household contacts of chronic carriers; sexually active persons who are not in a long-term, mutually monogamous relationship; persons seeking evaluation or treatment for a sexually transmitted infection; persons at risk for infection by percutaneous or mucosal exposure to blood; persons with injection drug use; residents and staff members of facilities for persons with developmental disabilities; public safety personnel with risk for exposure to blood or blood-contaminated body fluids; international travelers to countries with high or intermediate levels of endemic hepatitis B; persons with hepatitis C virus infection; persons who are incarcerated.

Adapted from Immunization schedules. CDC Web site. https://www.cdc.gov/vaccines/schedules/ and meeting recommendations. CDC Web site. https://www.cdc.gov/vaccines/acip/index.html. Accessed November 19, 2023.

TABLE 8.1 — Immunization Platforms

Platform	Age	Special Immunization Tasks	Examples of Other Age-Specific Issues
Infant-toddler	Birth-2 y	Primary immunity for childhood diseases Set childhood immunization as the norm	Physical growth and development Establishment of a medical home
School-aged	4-6 y	Boosters for childhood diseases	Cognitive and social development Behavioral and emotional health
Early adolescent	11-12 y	Boosters for childhood diseases Primary immunity for "adolescent" diseases	Onset of puberty Sexuality, substance abuse, injury, mental health
Late adolescent	16 y	Boosters for "adolescent" diseases Catch-up	Independence and identity Intimacy, ownership of personal health issues
Young adult	19-26 y	Set adult immunization as the norm Assessment of immunization status	Family, work, and social life Reproductive health
Maternal	Child-bearing years	Protection of pregnant women Protection of infants	Motherhood Postpartum depression
Middle-aged	50 y	Protection against herpes zoster High-risk conditions	Colorectal and breast cancer screening Parenting, empty nest, aging parents
Senior	≥65 y	Protection against diseases of immune senescence and mitigation of disease severity	Retirement, economic insecurity, physical deterioration Fall prevention, depression

Adapted from Recommendations for preventive pediatric health care. American Academy of Pediatrics Web site. https://downloads.aap.org/AAP/PDF/periodicity_schedule.pdf. Accessed August 3, 2023; Swenson PF, et al. *Amer Fam Phys*. 2016;93:738-740.

Adenovirus

The Pathogen

Adenovirus is a nonenveloped, double-stranded DNA virus in the Adenoviridae family. The viral capsid consists of 240 hexons that form the faces of an icosahedron, and 12 pentons that form the vertices; each penton has a projecting fiber, giving the virion a satellite-like appearance. The fibers interact with surface ligands on epithelial cells, including CD46 (a complement regulatory protein) and CAR (the coxsackie virus and adenovirus receptor) to initiate infection, and antibodies to the fibers and pentons are neutralizing. After acute infection, latency is established (probably in mucosa-associated lymphoid cells)[1]; subsequent reactivation and shedding contribute to endemicity in populations. Over 50 serotypes of human adenovirus are described; most cause respiratory disease and some cause gastroenteritis. The virion is very stable and can survive in the environment for long periods of time, facilitating transmission.

Clinical Features

Adenovirus is most commonly associated with respiratory disease.[2] Types 1, 2, 3, 5, and 7 cause *nasopharyngitis, pharyngitis, tonsillitis, acute laryngotracheitis*, and *bronchitis*. Respiratory symptoms, which last 5 to 7 days, may be accompanied by fever, cervical adenopathy, headache, malaise, myalgia, chills, and rash. Rare extrapulmonary manifestations include hepatitis, splenomegaly, nephritis, myocarditis, seizures, meningitis, and encephalitis, and permanent sequelae such as *bronchiolitis obliterans* can occur. Types 4 and 7 cause *epidemic acute respiratory disease*, classically seen in military installations and characterized by high attack rates and high rates of hospitalization.[3] Types 3, 4, 7, and 21 rank third behind respiratory syncytial virus and parainfluenza virus as causes of *pneumonia* in young children. Some strains, particularly type 5, can cause a *pertussis-like illness* in infants and young children with paroxysmal cough, whoop, post-tussive emesis, cyanosis, and lymphocytosis. Other syndromes caused by adenovirus include *pharyngoconjunctival fever* (types 3, 4 and 7), *epidemic keratoconjunctivitis* (types 8 and 37), *hemorrhagic conjunctivitis* (type 11), *hemorrhagic cystitis*

(type 11), and *acute gastroenteritis* (types 31, 40, and 41). Mortality rates are high in immunocompromised persons.[4]

Epidemiology and Transmission

Infection rates peak between 6 months and 5 years of age such that by school age, most children have been infected with several serotypes. Epidemic respiratory disease is seen more often in winter and spring, but sporadic disease occurs throughout the year. Epidemics of pharyngoconjunctival fever typically occur during the summer and have been associated with camps and swimming pools. Epidemics that occur during basic training may involve over 90% of military recruits in the first 8 weeks. From 2003 to 2016, the most commonly reported adenovirus types in the US were 3 (23% of isolates), 2 (20%), 1 (17%), 4 (12%), 7 (9%), and 14 (6%).[5]

Transmission occurs by close physical contact with respiratory secretions, small droplet aerosols, and fomites or, in the case of enteric adenoviruses, by the fecal-oral route. Inoculation takes place at mucosal surfaces such as the conjunctiva, nose, and throat. In the military setting, contamination of environmental surfaces and prolonged shedding facilitate outbreaks.[6]

Immunization Program

Despite the significance of adenoviral disease in children, there has not been a concerted effort to develop a vaccine for generalized use in this population. In contrast, the heavy burden of disease among military recruits provided justification for vaccine development. Beginning in 1971, an adenovirus types 4 and 7 vaccine manufactured by Wyeth was routinely administered to recruits at US military training centers. Wyeth stopped producing the vaccine in 1994, and by 1997 outbreaks of adenovirus-associated acute respiratory disease were again occurring at training posts.[7] In 2001, the Department of Defense awarded a contract to Barr Laboratories (now part of Teva Pharmaceutical Industries) to remanufacture the vaccine, which was relicensed and deployed in 2011.[8]

Vaccines

Characteristics of the adenovirus vaccine licensed in the US are given in **Table 9.1**. This is a live vaccine that consists of lyophilized viruses embedded in enteric-coated tablets. The viruses are not attenuated; rather, because they are given enterically rather than in the respiratory tract, they are capable of inducing immunity without causing disease. The enteric coating allows the vaccine to bypass the stomach, where it might be inactivated, and establish infection in the small intestine.

TABLE 9.1 — Adenovirus Vaccine

Trade Name	—
Abbreviation	—
Manufacturer/distributor	Teva Pharmaceutical Industries
Type of vaccine	Live, not attenuated
Composition	Non-attenuated, lyophilized adenovirus types 4 and 7 in enteric-coated tablets (white and peach, respectively)
	Propagated in human diploid lung fibroblast (WI-38) cells
	At least 32,000 tissue-culture infective doses per tablet
Adjuvant	None
Preservative	None
Excipients and contaminants	Monosodium glutamate
	Sucrose
	D-mannose
	D-fructose
	Dextrose
	Human serum albumin
	Potassium phosphate
	Plasdone C
	Anhydrous lactose
	Microcrystalline cellulose
	Polacrilin potassium
	Magnesium stearate
	Cellulose acetate phthalate
	Alcohol
	Acetone
	Castor oil
	FD&C Yellow #6 aluminum lake dye
Latex	None
Labeled indications	Prevention of febrile acute respiratory disease in military populations[a]
Labeled ages	17-50 y
Dose	1 tablet of each type (swallowed whole)
Route of administration	Oral
Labeled schedule	1 dose
Recommended schedule	Same
How supplied (number in package)	100-dose bottles (1 bottle of type 4 and 1 bottle of type 7)
Reference package insert	October 2019

[a] The vaccine is not licensed for use in civilians.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Field trials of the previously licensed vaccine in military settings demonstrated over 90% effectiveness in preventing hospitalization.[9-11] During the years that the vaccine was used, except for a period when vaccine potency was compromised in the 1970s, there was never an outbreak of acute adenovirus type 4 or 7 respiratory disease in any vaccinated group.

The relicensed vaccine was studied in 4041 military recruits who were randomized to receive vaccine or placebo in a 3:1 ratio. Efficacy against febrile respiratory disease caused by adenovirus type 4 was 99% and seroconversion rates were 95%. The seroconversion rate for type 7 was 94% (there was not enough type 7 disease to allow for an efficacy assessment). After resumption of the vaccination program for military trainees (approximately 200,000 per year), adenovirus disease burden decreased 100-fold; it was estimated that 13,000 febrile illnesses, 1100 to 2700 hospitalizations, and 1 death were averted each year.[12]

Safety

Approximately 30% of vaccinees shed type 4 in the stool and 60% shed type 7, but this only occurs in the first 28 days. Vaccine virus is not detectable in the throat. Solicited adverse events include headache (30%), nasal congestion (15%), nausea (14%), sore throat (13%), cough (12%), and diarrhea (10%). Fever is reported in 1% of vaccinees. A postmarketing study among 100,000 military recruits showed no increase in prespecified medical events in the 42 days after vaccination when compared to a similarly-sized cohort of unvaccinated persons.[13] Psoriasis and serum reactions occurred more frequently in vaccinated persons, but causality could not be established because of confounding. Reports of serious adverse events in the Vaccine Adverse Event Reporting System from 2011 to 2018 were higher than expected, but there was no concerning pattern and attribution was difficult because most patients had received other vaccines, as well as penicillin, at the same time as the adenovirus vaccine.[14]

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)
- Pregnancy (theoretical risk to the fetus of live-virus vaccine or attribution of birth defects to vaccination). Vaccinees should avoid pregnancy for 6 weeks.
- Inability to swallow an entire tablet whole without chewing

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- Vomiting and/or diarrhea (potential interference with effectiveness or difficulty distinguishing illness from vaccine reaction)
- Immunodeficiency or immunosuppression (risk of disease caused by live virus)
- Breast-feeding (risk of disease caused by live virus)

Recommendations

Adenovirus vaccine is routinely given to all enlisted basic trainees 17 to 50 years of age as soon as they arrive at the accession site.[15] There are no booster doses. The vaccine is not used in civilians.

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Anthrax

The Pathogen

Bacillus anthracis is a large, aerobic, spore-forming, toxin-producing gram-positive rod with a "jointed bamboo-rod" appearance and "Medusa's head" colony morphology. Pathogenicity is mediated by two secreted virulence factors, lethal toxin and edema toxin.

Clinical Features

Inhalational anthrax is characterized by a flu-like illness, dyspnea, and hemorrhagic thoracic lymphadenitis and mediastinitis.[1] *Cutaneous anthrax* is characterized by a painless ulcer with extensive surrounding edema, eschar formation, and regional adenopathy. Both of these forms of disease would be seen after a bioterrorism attack and either can lead to meningitis. The *gastrointestinal* (bloody diarrhea, hemorrhagic mesenteric adenitis) and *oropharyngeal* (oral or esophageal ulcers and regional adenopathy) forms of anthrax result from ingestion of large numbers of vegetative bacilli (usually in poorly cooked meat) and would be unlikely to result from an attack. After the spores are ingested by phagocytes, they are transported to regional lymph nodes, where they germinate into vegetative cells after variable (and potentially extended) periods of time. Replicating cells then elaborate toxins that lead to massive hemorrhage, edema, necrosis, and cytokine release. Early therapy for symptomatic disease is essential, but the effects of local tissue damage and systemic toxinosis may be irreversible.[2]

Epidemiology and Transmission

Anthrax spores are found in soil worldwide and may remain viable for years. Infection occurs in grazing animals that ingest the spores, and natural human infection occurs almost exclusively after contact with infected animals and animal products (a classic example is *woolsorter's disease*—inhalational anthrax linked to the processing of hides and wool in closed spaces). Up to 20,000 annual cases of anthrax are estimated to occur worldwide, but disease was rare in the US until 2001. In September and October of that year, letters containing high-grade Ames strain anthrax spores were mailed through the US

postal service from Trenton, NJ, to sites in Florida, New York City, and Washington, DC.[3] One letter was known to contain 2 g of powder and between 100 billion and 1 trillion spores. A total of 22 anthrax cases occurred in seven eastern states between September 22 and November 16; 11 were inhalational (five deaths) and 11 were cutaneous (no deaths). Twelve victims were mail handlers. Cross-contamination was evidenced by the isolation of anthrax from over 100 environmental samples along the path of the letters.

Anthrax is a potential bioterrorism agent because infection can be lethal, natural immunity does not exist, the organism can be engineered into antibiotic resistance, and the infectious dose of spores is very low. It is easily grown in the laboratory, and the spores can be weaponized into a highly concentrated powder with uniform small particle size and low electrostatic charge, features that facilitate aerosol dispersal. Aerosols are odorless and invisible, can spread over large areas, and would probably not be detected until cases occurred. The lethality of aerosolized weapons-grade anthrax was demonstrated after the accidental release of anthrax spores (possibly as little as 1 g) on April 2, 1979, from a Soviet bioweapons facility in Sverdlovsk (now called Ekaterinburg, a city of over 1 million people).[4] Nearly 100 cases and over 60 deaths occurred downwind of the release, mostly from inhalational disease. Most cases occurred within 10 days, although some occurred 6 weeks later. While the majority of victims were exposed in a narrow 4-km band extending from the military facility to the southern city limit, cases did occur many miles away and livestock in several towns downwind of the release were affected.

A release of 100 kg of spores over Washington, DC would result in as many as 3 million deaths. Unlike smallpox, all cases occurring after an attack would result from primary exposure, because the infection is not transmitted from person to person. However, secondary aerosolization of particles that settle after a primary release could continue to cause disease for some time.

Immunization Program

Recommendations for civilian use of AVA were published in 2000.[5] Bioterrorism-related recommendations were released in 2002,[6] and updated civilian recommendations were published in 2010 and 2019.[7,8]

Antibiotic therapy after exposure can prevent inhaled spores from germinating. In fact, there were no cases of anthrax among over 10,000 people who took antibiotics (primarily ciprofloxacin or doxycycline) for at least 60 days following the 2001 attacks. Antibiotic therapy in conjunction with vaccination is considered optimal for exposed persons.

Pre-exposure vaccination is based on the risk of exposure and is not recommended for the general public. Although a vaccine has

been licensed since 1970, it was in limited use until 1991, when the US military immunized 150,000 service members deployed for the Gulf War. The Anthrax Vaccine Immunization Program was started in 1998 with the routine immunization of personnel deployed to high-risk areas. In 2002, the Department of Defense reintroduced the program (which had slowed because of dwindling vaccine supplies) because of intelligence assessments indicating possible risk of exposure of military personnel; updated guidelines have been maintained since then.[9] AVA was approved for postexposure prophylaxis in 2015.

Vaccines

Characteristics of the anthrax vaccine licensed in the US are given in **Table 10.1**. This is a non-live vaccine composed of proteins released by the bacterium into the medium during growth in culture. It contains no intact bacteria, live or dead.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

From 1955 to 1959, a controlled trial of a vaccine similar to the one that is currently licensed was conducted among 1249 mill workers (379 were immunized); efficacy was 92.5%. Case surveillance data from 1962 to 1974 suggest that anthrax in mill workers or those living near mills occurred exclusively in unvaccinated or incompletely vaccinated persons. In a controlled trial conducted from 2002 to 2008 involving 1564 adults, the intramuscular route of administration was found to be noninferior to the subcutaneous route in terms of immunogenicity, and nearly all vaccinees demonstrated a ≥4-fold increase in antibody titer.

Safety

In an open-label safety study, 15,907 doses of BioThrax were administered subcutaneously to 7000 at-risk persons. Mild local reactions occurred after 8.6% of doses administered, moderate reactions after 0.9%, and severe reactions after 0.15%. There were only four reports of systemic reactions such as fever, chills, nausea, and general body aches.

Intramuscular administration causes less local reactogenicity than subcutaneous administration. Most local and systemic reactions are mild or moderate in severity. Injection site reactions are more common in women, especially with subcutaneous administration. There were 44 pregnancies during the 2002 to 2008 study; the majority of outcomes were good, although there was a spontaneous abortion and a clubbed foot abnormality among infants born to 15 women vaccinated in the first trimester. In a study of infants born to US military service women from 1998 to 2004, birth defects were

TABLE 10.1 — Anthrax Vaccine Adsorbed

Trade Name	BioThrax
Abbreviation	AVA
Manufacturer/distributor	Emergent BioDefense Operations Lansing
Type of vaccine	Non-live, subunit, purified
Composition	Cell-free filtrate of microaerophilic cultures of an avirulent, noncapsulated *Bacillus anthracis* strain
	Includes 83 kDa protective antigen
Adjuvant	Aluminum hydroxide (0.6 mg aluminum)
Preservative	Benzethonium chloride (12.5 mcg)
	Formaldehyde (50 mcg)
Excipients and contaminants	Sodium chloride (0.85%)
Latex	Vial stopper contains latex
Labeled indications	Pre- and postexposure prophylaxis
Labeled ages	18-65 y
Dose	0.5 mL
Route of administration	Intramuscular or subcutaneous
Labeled schedule	
Pre-exposure	Subcutaneous[a]: doses at 0, 2, 4 wk and 6, 12, and 18 mo, then yearly booster doses
	Intramuscular: doses at 0, 1, 6, 12, and 18 mo, then yearly booster doses
Postexposure	Postexposure: doses at 0, 2, and 4 wk subcutaneously, combined with antimicrobial therapy
Recommended schedule	
Pre-exposure	Intramuscular doses at 0, 1, 6, 12, and 18 mo, then yearly booster doses[b]
Postexposure	Subcutaneous doses at 0, 2, and 4 wk, combined with antimicrobial therapy[c]
How supplied (number in package)	10-dose vial (1)

Continued

TABLE 10.1 — *Continued*

Trade Name	BioThrax
Cost per dose (USD, 2023)	
Public	—
Private	236.99
Reference package insert	November 2015

[a] Indicated for persons at risk for hematoma formation after intramuscular injection.
[b] Booster doses may be given every 3 y in persons who are not at high risk but want to maintain protection.
[c] During a large-scale emergency response, the intramuscular route may be used if the subcutaneous route poses challenges that might delay or preclude vaccination. Persons who experienced adverse events from AVA that was administered subcutaneously may elect to receive subsequent doses intramuscularly. Dose-sparing regimens may be recommended if vaccine supply is insufficient to cover all exposed persons.

slightly more common among the 3465 infants born to women who were vaccinated during the first trimester when compared with the 33,675 infants whose mothers were vaccinated outside of the first trimester (most of these were vaccinated before pregnancy or after delivery).[10]

In a study involving >4300 service personnel in Korea, 2% of persons reported limitation in work performance after Dose 1 or Dose 2 but <1% lost a day or more of work. In 2002, an Institute of Medicine (now known as the National Academy of Medicine) study concluded that the anthrax vaccine is safe.[11] Approximately 6 million doses of AVA were administered from 1998 to 2007, generating just over 4700 reports to the Vaccine Adverse Event Reporting System; no unexpected risks were seen and there was no distinctive pattern of serious events or death.[12]

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- Pregnancy (vaccine can cause fetal harm, so use only if the potential benefits outweigh the potential risks)
- Previous anthrax disease (risk of more severe adverse events)

Recommendations

Routine pre-exposure use of AVA in civilians is limited to nonpregnant persons 18 to 65 years of age in the following categories: 1) laboratory workers with potential exposure to spores, including those who handle pure cultures and environmental samples associated with anthrax investigations (this does not include workers who use standard Biosafety Level 2 practices in routine processing of clinical or environmental samples); and 2) persons who work with potentially infected animals (examples include certain animals in research settings and animals known to have a high incidence of enzootic anthrax) or animal products (examples include imported animal hides, furs, bone meal, wool, animal hair, and bristles).

Vaccination is mandatory for all uniformed personnel, emergency essential designated civilians, contractor personnel performing mission-essential services, some Naval Forces afloat, and civilian and contact mariners traveling or assigned to the Central Command area of responsibility or Korean Peninsula for ≥15 consecutive days, as well as certain special units. Vaccination is voluntary for other Department of Defense service members, government civilian employees of the Department of Defense, adult family members, and other contractors. AVA is typically administered up to 120 days before deployment to or arrival in higher threat areas.

Prophylaxis is recommended after suspected or known exposure to aerosolized *B anthracis* spores; the only exception may be persons who have already received 5 appropriately-timed doses of AVA plus annual boosters. The postexposure regimen depends on vaccination status and includes both vaccination and antimicrobial therapy for some period of time. In some situations, monoclonal antibody products that neutralize *B anthracis* toxin—raxibacumab (Emergent Biosolutions) or obiltoxaximab (Anthim; Elusys Therapeutics)—may be indicated, and public health authorities may recommend vaccination of persons <18 or >65 years of age (off-label recommendation). More information is available at the Centers for Disease Control and Prevention Web site (https://www.cdc.gov/anthrax/index.html; accessed August 3, 2023).

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Cholera

The Pathogen

Vibrio cholerae is a noninvasive, gram-negative bacterium found in costal and estuarial waters, often associated with zooplankton and shellfish.[1] There are over 200 serogroups based on the somatic O antigen; only serogroups O1 and O139 cause epidemic disease, and most cases worldwide are caused by serogroup O1. Orally ingested bacteria colonize the small intestine and elaborate *cholera toxin*, which consists of an A subunit associated with 5 B subunits. The B pentamer binds to ganglioside GM1 on epithelial cells, leading to translocation of the A subunit, activation of adenylate cyclase, increased intracellular cAMP levels and ultimately chloride secretion through apical channels. This leads to massive *secretory diarrhea.*

Clinical Features

While most infected people are asymptomatic, 2% to 5% experience severe gastrointestinal disease. Diarrhea begins abruptly and may be accompanied by vomiting. Profuse, painless watery diarrhea and massive fluid and electrolyte losses can progress rapidly—some patients lose one liter of water per hour—to shock and death (this is referred to as *cholera gravis*). The intestinal output is characterized as *rice water* in consistency, referring to the cloudy water that remains after rice has been washed. Patients may have decreased skin turgor, dry mucus membranes, sunken eyes, rapid pulse, tachypnea, decreased urine output, lethargy, weakness, and altered mental status. Complications include hypotension, hypoglycemia, hypokalemia, seizures, intestinal ileus, cardiac arrhythmias, renal failure, acidosis, aspiration, and pneumonia. Children are especially susceptible to hypoglycemia and resultant seizures.

Epidemiology and Transmission

Cholera persists around the Indian subcontinent and pandemics probably originate there. There were 6 pandemics between 1817 and 1923, all caused by serogroup O1 organisms. Two main serotypes—Inaba and Ogawa—and two biotypes—classical and El Tor—are described (all combinations of serotypes and biotypes can occur). The current pandemic,

caused by the El Tor biotype, began in 1961 in Indonesia. By 1991, it had spread through Asia, Africa, and Europe to Latin America. In 1992, a new epidemic caused by toxigenic *V cholerae* serogroup O139 Bengal spread rapidly throughout the Indian subcontinent and southeast Asia. The World Health Organization estimates that there are 3 to 5 million cases of cholera per year, mostly in Asia and Africa. However, explosive outbreaks can occur when the organism is introduced into impoverished populations, as occurred in the wake of the Haitian earthquake in 2010.[2]

The organism is acquired through ingestion of water contaminated with feces; brackish surface water may remain contaminated for long periods of time due to persistence of the organism in invertebrates. A high inoculum (10^8 to 10^{10} organisms) is necessary from environmental sources, but organisms acquire *hyperinfectivity* after passage through humans, such that the infectious dose of recently shed organisms is much lower. Secondary spread is exacerbated by poor sanitation conditions, where contaminated water may be used for drinking, cooking, bathing, and washing. Raw or undercooked shellfish are sources of infection because they are harvested from or washed with contaminated water and may be handled by infected individuals. Long-term human carriers are rare and probably not important in transmission of disease. Persons with achlorhydria and blood group O are more likely to develop severe disease. Natural infection confers long-term protection against disease.

Immunization Program

A phenol-inactivated, parenterally administered vaccine was available in the US until 2000. Standing recommendations at that time, citing the low risk of cholera for US travelers, focused on satisfaction of entry requirements for persons traveling to certain countries.[3] Oral vaccines have been available outside the US for some time. Vaxchora, a live attenuated vaccine redeveloped from a previous product that was available until 2003, was licensed in the US in 2016.[4] Recommendations for adults traveling to areas with active cholera transmission were published in 2017[5] and comprehensive recommendations for adults and children were published in 2022.[6]

Vaccines

Characteristics of the cholera vaccine licensed in the US are given in **Table 11.1**. This vaccine consists of *V cholerae* strain CVD 103-HgR, which was derived from a serogroup O1 classical Inaba strain by deletion of the genes encoding the cholera toxin A subunit, thus preventing the synthesis of functional cholera toxin (the strain still produces the B subunit, which is immunogenic but not toxic). A marker was also inserted into the hemolysin gene locus to allow for differentiation of the vaccine strain from the wild type.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

An observational study of mass vaccination in Micronesia with the previously manufactured version of CVD 103-HgR showed 79% protection,[7] while an earlier single-dose efficacy trial in nearly 70,000 subjects in Indonesia had demonstrated no protection.[8] Given the safety profile and efficacy in challenge studies, the product was licensed as a traveler's vaccine but not for use in endemic settings.[9] The new version of the vaccine was studied in 197 adults who were randomized to receive 1 dose of the vaccine or placebo; protection against moderate-to-severe diarrhea was 90% after challenge 10 days later with a wild-type *V cholerae* O1 El Tor Inaba strain. Efficacy after challenge 3 months postvaccination was 80%.[10] In a subsequent study, seroconversion was seen in 94% of 2795 vaccinees within 10 days.[11] Efficacy among persons 2 to 17 years of age has not been directly assessed; however, seroconversion rates were >98% in randomized controlled trials involving approximately 500 children.[12,13]

Safety

In prelicensure trials involving a total of 3235 adult vaccinees, solicited adverse reactions included tiredness (31%), headache (29%), abdominal pain (19%), nausea or vomiting (18%), and lack of appetite (17%). These rates were similar to those in placebees. Diarrhea occurs in about 4% of vaccinees and fever is rare. The safety profile is similar in children to that in adults. Fecal shedding occurs in about 11% of vaccinees in the first 7 days after vaccination.

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)
- Phagocyte disorders (risk of disease caused by live bacterium)

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- Pregnancy and breast feeding (theoretical risk to the fetus, attribution of birth defects to vaccination, transmission to infant). The vaccine is not systemically absorbed, and maternal use is not expected to result in fetal exposure, although perinatal transmission from fecal shedding is a theoretical possibility.
- Concomitant antibiotic or chloroquine therapy (inactivation of live bacterial vaccine). The package insert cautions against vaccination of persons who have received antibiot-

TABLE 11.1 — Cholera Vaccine

Trade Name	Vaxchora
Abbreviation	—
Manufacturer/ distributor	Emergent Travel Health[a]
Type of vaccine	Live, attenuated, engineered
Composition	*V cholerae* strain CVD 103-HgR, consisting of serogroup O1 classical Inaba strain 569B with deletion of the catalytic domain of both copies of the *ctxA* gene (does not produce active cholera toxin, but does produce the B subunit, which is immunogenic but not toxic), 4×10^8 -2 $\times 10^9$ colony forming units
Adjuvant	None
Preservative	None
Excipients and contaminants	Vaccine
	Sucrose (≤165.37 mg)
	Hydrolyzed casein (≤17.11 mg)
	Ascorbic acid (≤8.55 mg)
	Anhydrous lactose (≤2.09 gm)
	Buffer
	Sodium bicarbonate (2.16-2.41 gm)
	Sodium carbonate (0.24-0.49 gm)
	Ascorbic acid (1.5-1.8 gm)
	Anhydrous lactose (0.18-0.22 gm)
Latex	None
Labeled indications	Prevention of cholera caused by serogroup O1
Labeled ages	2-64 y
Dose	2-5 y: entire packet of active component mixed in 50 mL of reconstituted buffer solution 6-64 y: entire packet of active component mixed in 100 mL of reconstituted buffer solution
Route of administration	Oral (avoid eating and drinking for 1 h before and after)[b]
Labeled schedule	One dose ≥10 d before potential exposure
Recommended schedule	Same
How supplied (number in package)	Carton containing 1 packet of buffer and 1 packet of active component (buffer packet is reconstituted in 100 mL of purified bottled or spring bottled water (1)

Continued

TABLE 11.1 — *Continued*

Trade Name	Vaxchora
Cost per dose (USD, 2023)	
Public	—
Private	337.99
Reference package insert	December 2022

[a] Previously manufactured by PaxVax Bermuda. Manufacture was suspended from May 2021 to May 2023 due to decreased demand during the COVID-19 pandemic.

[b] The vaccine may be mixed with table sugar (1/4 to 1 teaspoon) or stevia sweetener (1 gm or 1 packet) to improve palatability.

ics in the previous 14 days, but the Advisory Committee on Immunization Practices considers this acceptable in certain situations when travel cannot be avoided. Administer ≥10 days before beginning chloroquine for malaria prophylaxis.

Recommendations

Vaccination is recommended for persons 2 to 64 years of age who are traveling to areas with active transmission of toxigenic *V cholerae* O1. A list of areas with active cholera transmission can be found at https://wwwnc.cdc.gov/travel/page/cholera-travel-information (accessed August 3, 2023). No country or territory requires cholera vaccination as a condition for entry.

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COVID-19

The Pathogen

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a large, enveloped, single-stranded RNA virus in the Coronaviridae family.[1] It is closely related to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), both of which emerged after 2000 and caused severe but circumspect outbreaks of respiratory illness. The viral particle has a spherical shape, and the surface is studded with a transmembrane "spike" or S-protein, giving it the appearance of a crown. The receptor-binding domain (RBD) of the S-protein, present on the S1 subunit, associates with human angiotensin converting enzyme 2 (ACE2).[2] Binding causes a conformational change that exposes the cleavage domain; host cell enzymes act on this region to remove S1, exposing S2, which initiates infection by mediating fusion of the viral and cellular membranes. The Omicron variant, which has dominated since late 2021, enters cells efficiently through the endosomal pathway, expanding its cellular range and contributing to its high infectivity.[3]

Several virologic characteristics of SARS-CoV-2 contribute to its success as a pathogen. The S-protein has a high affinity for ACE2[4] and the virus replicates to high titer in the nasopharynx[5]; this helps explain efficient contagion. In addition, the virus mutates frequently, has a large genome that can accommodate changes, and generates sub-genomic RNAs during replication that increase the rate of homologous recombination.[6] These factors help explain the emergence of variants (*see below*).

ACE2, which is involved in regulation of blood pressure, is widely distributed in human tissues and is especially prominent on endothelial cells; this helps explain the endothelial damage, microvascular injury, hypercoagulability, and micro- and macrothrombosis that can be seen in severe coronavirus disease-2019 (COVID-19).[7] The initial phase of illness is marked by viral replication in the upper respiratory tract, high mucosal viral loads, and innate antiviral immune responses.[8] This can progress to lower respiratory tract infection and marked systemic inflammation, cytokine storm, immune dysregulation, and endothelial activation, leading to more tissue damage. Severe disease is associated with polymorphisms in genes that are involved in the control of viral replication, pulmonary inflammation, and intravascular coagulation.[9]

Antibodies to the RBD are neutralizing, and T-cell responses are important in controlling infection and providing long-lasting immunity.[10-12] Natural immunity to SARS-CoV-2 infection can be short-lived but protection against severe or fatal disease is preserved.[13,14]

Clinical Features

The incubation period for early variants was about 5 days but has been as short as 3 to 4 days for later variants.[15] About half of infections are asymptomatic, and children and young people are more likely to be asymptomatic than older adults.[16] Symptoms that do occur (**Figure 12.1**) include fever, myalgia, and cough; while rhinorrhea is unusual, loss of taste and smell is a distinctive feature. Overall, about 80% of cases are mild and self-limited. Severe COVID, as was seen frequently early in the pandemic, is characterized by fever and respiratory distress, lymphopenia, thrombocytopenia, elevated inflammatory markers, coagulopathy, bilateral lower lobe infiltrates on chest X-ray, and peripheral ground-glass opacities and/or consolidation on computed tomography.[17] Complications include pneumonia, acute respiratory distress syndrome, myocarditis, multiorgan failure, thromboembolic events, macrophage activation and cytokine storm, impaired consciousness, acute cerebrovascular disease, encephalitis, and shock.

Both hospitalization rate and death rate are highly correlated with age (**Figure 12.2**); risk factors for mortality in addition to increasing age include male gender, smoking, chronic obstructive pulmonary disease, cardiovascular disease (including hypertension), diabetes, cancer, and acute kidney injury.[18] Serious illness is much less common among children than it is among adults.[19,20]

Symptoms may last for weeks, and most patients gradually improve. However, many develop *post-acute sequelae of COVID-19*[21] (PASC; synonymous terms include long COVID and long-haul syndrome), with symptoms persisting for long periods of time. As many as half of hospitalized patients may still be affected 6 months out, with problems ranging from abnormal chest imaging to functional impairment, fatigue or muscle weakness, generalized anxiety, and difficulty concentrating (sometimes referred to as "brain fog").[22] A pooled data analysis of 1.2 million individuals with symptomatic SARS-CoV-2 infection from 22 countries showed that just over 6% experienced 1 of 3 symptom clusters (persistent fatigue with bodily pain or mood swings; cognitive problems; or ongoing respiratory problems) 3 months later,[23] and a prospective, population-based, observational cohort study in the Netherlands estimated that 1 out of 8 people with COVID experienced PASC.[24] Importantly, patients with asymptomatic or mildly symptomatic infection may develop PASC.[25]

Multisystem inflammatory syndrome (MIS) may develop 2 to 5 weeks after infection, especially in children (MIS-C)[26]; this occurs after viral clearance and affects organ systems (eg, cardiovascular and gastrointestinal) that were not clinically affected during the acute infection. MIS-C may resemble Kawasaki disease and is marked by profound elevation of C-reactive protein, D-dimer, and troponin, and myocardial dysfunction can occur.[27] While MIS-C may be severe, the prognosis is good,[28] and the condition has been seen less frequently with sequential variants.[29] An adult form of the condition (MIS-A) has also been described.[30]

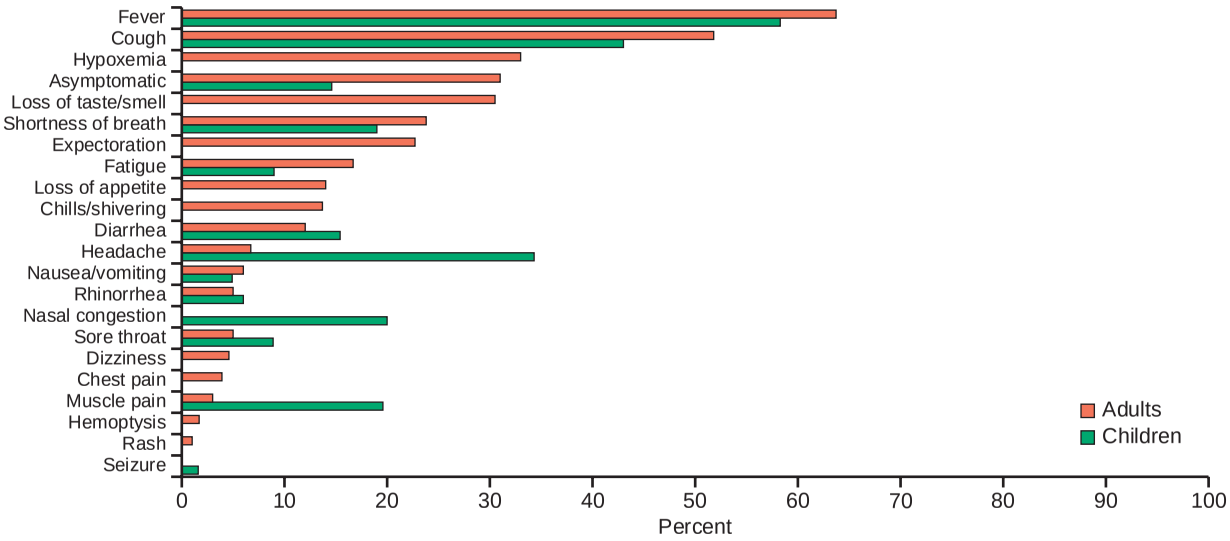
Epidemiology and Transmission

SARS-CoV-2 most likely originated in bats, which harbor a rich pool of coronaviruses.[31] Most scientific evidence points to a jump to humans through multiple zoonotic events at the Huanan Seafood Market in Wuhan, China.[32-35] The first known hospitalization occurred on December 12, 2019, and widespread disease occurred in Wuhan in early January 2020. By early February the virus had been fully characterized.[36,37] On March 11, 2020, the World Health Organization (WHO) declared that COVID-19 was a pandemic.[38] Approximately 1 year later there had been 152 million cases reported globally, with 3.2 million deaths[39] (the true number of cases may have been 5 to 20 times higher than that[40])—this despite social distancing measures, mask-wearing, hand hygiene, and lockdowns. The lockdowns themselves were unprecedented; in fact, human activity decreased to such an extent that anthropogenic seismic noise was reduced up to 50% for months.[41] Health care resources were strained to the breaking point; auto parts plants were retooled to help produce ventilators, and refrigerated trucks were enlisted in some cities to store dead bodies in preparation for burial in make-shift graves.

Between January 2020 and December 2021, an estimated 18.2 million people died of COVID-19[42]; there were 53.2 million incremental cases of major depressive disorder and 76.2 million cases of anxiety disorder in 2020 alone,[43] and between March 2020 and April 2021, 1 million children became orphans.[44] The global social and economic impact of the COVID-19 pandemic was enormous: the deepest recession since World War II, with a decline of >4% in gross domestic product; upwards of 736 million people pushed into poverty; and, at the peak of the pandemic, 1.5 billion students out of the classroom.[45] In the US alone, the economic welfare losses due to COVID-19 exceeded $4 trillion.[46]

By the end of 2021, 60% of people had antibodies to SARS-CoV-2, either by virtue of natural infection or vaccination[47]; after the Omicron wave in early 2022, it is fair to say that almost all people on the planet had some degree of COVID-19 immunity. This fact, in the context of lower disease burden, decreased impact

FIGURE 12.1 — Symptoms of Acute COVID-19



The graph shows the proportion of adults and children with the indicated symptoms. Data are from a systematic review of reviews published through August 2021 providing pooled estimates of the prevalence of clinical features of COVID-19 diagnosed by polymerase chain reaction or antigen detection in the general population. The primary studies covered in the analysis were mostly from China, Europe, and the US, and most cohorts were derived from hospitalized patients.

Adapted from Lee B, et al. *J Glob Health*. 2022;12:05012.

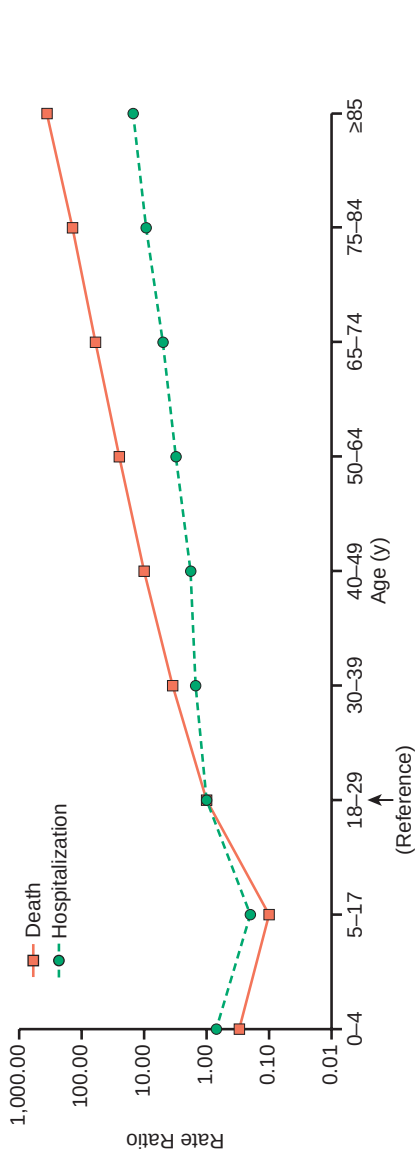


FIGURE 12.2 — COVID-19 Hospitalizations and Deaths by Age in the United States

The graph shows the ratio of hospitalization rate and death rate in the given age group compared to persons 18-29 y. Note that the y-axis scale is logarithmic. Data are through May 2023.

Adapted from COVID-19 hospitalization and death by age. CDC Web site. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html. Accessed June 20, 2023.

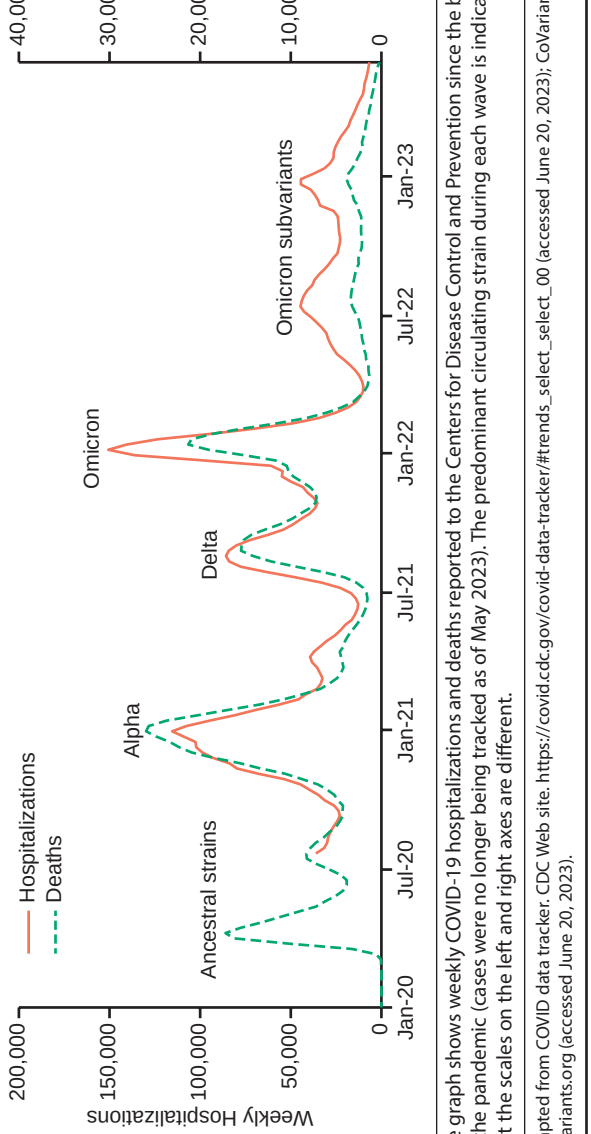
on health care resources, and a return to normal social and economic activities, suggests that COVID-19 had evolved towards endemicity, during which the disease is expected to occur at a steady state with surges caused by new variants and fueled by waning of immunity and the accumulation of new susceptible children.[48]

SARS-CoV-2 is spread primarily by respiratory droplets. Shedding peaks on or before the onset of symptoms,[49] and transmission can occur as early as 2 days before symptoms develop.[50] Asymptomatic individuals account for more than half of all transmissions,[51] which in part explains rapid spread through communities. The basic reproduction number (R_0) of the ancestral strains was estimated at 2.4 to 3.4,[52] and the virus was highly overdispersed, meaning that a majority of the cases came from a minority of infected individuals (see *Chapter 1: Introduction to Vaccinology—Epidemiological Concepts*).[53] Spread through communities was rapid, especially when physical containment measures were not fully implemented; in one urban sentinel population of >2 million, >70% were infected within 7 months.[54] The herd immunity threshold was estimated to be 60% to 70%[55]; as the pandemic progressed, estimates of the herd immunity threshold increased to around 85%, and some wondered whether herd immunity was, in fact, achievable.[56] A unique feature of the pandemic was its punctuation by "super-spreader" events—the prototype was an international business conference in Boston on February 26 and 27, 2020, where a single case is estimated to have led to approximately 300,000 cases around the world over the subsequent 9 months.[57]

The strains that initially circulated were versions of the ancestral Wuhan virus that had acquired the G614 mutation (aspartate at position 614 changed to glycine), which increased transmissibility and led it to dominate worldwide within one month—March of 2020.[58] Successive waves (**Figure 12.3**) were dominated by new strains[59] that retained the original G614 mutation but acquired others that conferred increased receptor affinity, replicative fitness, and/or antigenic escape[60-63] (see **Table 12.1** for the current schema by which new strains are classified). In general, R_0 for each new strain was higher than the previous one; for example, estimates of R_0 for Delta ranged from 3.2 to 8.0[64] and for Omicron from 5.5 to 24.0.[65] Of note, ancestral and early variants, including Alpha, Beta, Gamma, and Delta, were no longer detected in humans as of 2023.

Environmental factors contributed to disease resurgences, including colder weather (which brought people into close quarters with one another), social gatherings (especially at holiday time), and pandemic restriction fatigue. Various segments of the population were affected differently during each wave. For example, the first wave caused disproportionate morbidity and mortality among the elderly, especially in nursing homes.[66] Subsequent waves were sustained by transmission among young adults—persons in this age group have more contact with other people, are mobile, and engage

FIGURE 12.3 — COVID-19 Disease Burden in the United States



The graph shows weekly COVID-19 hospitalizations and deaths reported to the Centers for Disease Control and Prevention since the beginning of the pandemic (cases were no longer being tracked as of May 2023). The predominant circulating strain during each wave is indicated. Note that the scales on the left and right axes are different.

Adapted from COVID data tracker. CDC Web site. https://covid.cdc.gov/covid-data-tracker/#trends_select_select_00 (accessed June 20, 2023); CoVariants. https://covariants.org (accessed June 20, 2023).

TABLE 12.1 — Working Definitions for SARS-CoV-2 Variants—August 2023[a]

Designation	Working Definition
Variant under monitoring (VUM)	Genetic changes that are suspected to affect virus characteristics and early signals of growth advantage relative to other circulating variants, but evidence of phenotypic or epidemiological impact remains unclear (includes variants with an unusually large number of antigenic mutations but with very few sequences and/or whose relative growth advantage cannot be estimated)
Variant of interest (VOI)	Genetic changes that are predicted or known to affect transmissibility, virulence, antibody evasion, susceptibility to therapeutics or detectability, and growth advantage over other circulating variants in more than one WHO region with increasing relative prevalence and number of cases or other apparent epidemiological impacts to suggest an emerging risk to global public health
Variant of concern (VOC)	A VOI that meets at least one of the following criteria: ■ Detrimental change in clinical disease severity ■ Change in COVID-19 epidemiology causing substantial impact on the ability of health systems to provide care and therefore requiring major public health interventions ■ Significant decrease in the effectiveness of available vaccines to protect against severe disease

WHO, World Health Organization

[a] WHO in began assigning Greek letters (eg, Delta and Omicron) to VOIs and VOCs in May 2021. In March 2023, WHO announced that Greek letters will only be assigned to VOCs, while VOIs will be referred to using established scientific nomenclature systems such as those used by Nextstrain (eg, 19A/28688C; https://nextstrain.org) and Pango (eg, XBB.1.5; https://www.pango.network).

Adapted from Updated working definitions and primary actions for SARS-CoV-2 variants, 17 August 2023. WHO Web site. https://www.who.int/docs/default-source/coronaviruse/annex1_updated_working_definitions_17-08-2023.pdf?sfvrsn=2cde3a06_6&download=true. All Web sites accessed September 3, 2023.

in behaviors that favor transmission.[67] Delta was the first wave to substantially impact children,[68] and COVID-19 was the leading cause of death due to infectious or respiratory diseases among children and young people from August 2021 to July 2022.[69] Omicron was characterized by exceptionally high transmission rates (note the very high, narrow peak in cases in **Figure 12.3**), proportionately less morbidity and mortality (especially in adults[70]), high rates of infection in children,[71] and less robust and durable protection against reinfection.[72] Throughout the pandemic, ethnic minorities shouldered a disproportionate share of the disease burden,[73] driven largely by social and structural vulnerabilities.[74]

Immunization Program

Emergency Use Authorization (EUA) was initially granted for monovalent (Wuhan strain) vaccines as follows: COV-mRNA (Pfizer-BioNTech) on December 11, 2020; COV-mRNA (Moderna) on December 18, 2020; COV-Ad26 (Janssen) on February 27, 2021; and COV-aPS (Novavax) on July 13, 2022 (some of these products were later granted full approval in certain age groups).[75] Millions of doses were available for distribution as soon as the first approvals were granted. The movement from a novel, highly contagious, virulent pathogen to safe and effective vaccines in tens of millions of arms in less than a year was a crowning human achievement that saved millions of lives (in fact, the 2023 Nobel Prize in Physiology or Medicine was awarded to Katalin Karikó and Drew Weissman, scientists whose discoveries made vaccination with mRNA possible). The success of vaccination against COVID-19 was driven by a solid scientific and technological foundation; billions of dollars in funding; tens of thousands of study volunteers; deep collaboration between academia, industry, government, and public health authorities; and herculean effort by countless people, from laboratory technicians to delivery truck drivers. In the context of widespread COVID-19 vaccine hesitancy,[76] it is critical to understand that, despite the "warp speed"[77] with which these vaccines were developed, no corners were cut in terms of the methodologic rigor and the thorough, systematic assessments that were made before (and after) approval was granted.

The initial vaccine roll-out used a phased, risk-based approach.[78] Within months, tens of millions of people in the US had been vaccinated, although vaccination rates began to trail off in the summer of 2021 (**Figure 12.4**). Recommendations for each vaccine were made after the respective EUA was issued or amended and as the formulations and dosing regimens were updated; this led to a succession of vaccination schemata that encompassed broader groups of people and an increasing number of permutations, which were updated on the Centers for Disease Control and Prevention (CDC) Web site. The first bivalent boosters were authorized in

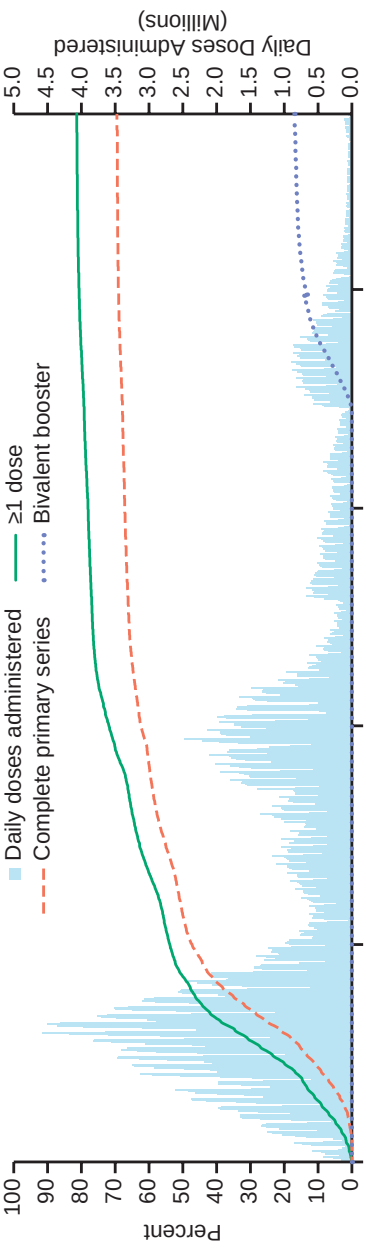


FIGURE 12.4 — COVID-19 Vaccination in the United States

The graph shows the coverage rates for at least 1 dose of COVID-19 vaccine, complete primary series, and at least 1 dose of bivalent booster. As of May 9, 2023, a total of 676,728,782 doses of COVID-19 vaccine had been administered in the US.

Adapted from COVID vaccine tracker. CDC Web site. https://covid.cdc.gov/covid-data-tracker/#vaccination-trends. Accessed June 20, 2023.

August 2022, and the first seasonally updated (2023-2024) vaccines were authorized in September 2023. As of the fall of 2023, only the seasonally updated vaccines were authorized for use in the US.

Vaccination against COVID-19 is estimated to be cost-saving for persons ≥65 years of age; the incremental cost-effectiveness ratio for persons 50 to 64 years of age is about $26,000 per quality-adjusted life year (QALY) gained, and for persons 18 to 49 years of age about $116,000 per QALY gained (2023 dollars).[79]

From December 2020 through September 2023, vaccination was offered free of charge by the US Government, and providers needed to be enrolled in the CDC COVID-19 Vaccination Program. That program ended on September 12, 2023,[80] after which the standard pathways of procurement, distribution, and payment in both public and private sectors were reimplemented.[81]

Vaccines

Characteristics of the COVID-19 vaccines authorized or approved for use in the US as of October 2023 are given in **Table 12.2**. The mRNA-based vaccines use nucleic-acid to direct host cells to make the S-protein; advantages of this approach are discussed in *Chapter 1: Introduction to Vaccinology—In Vivo-Expressed Subunits*. In a sense, the vaccines operate in the same way as live attenuated viral vaccines, which infect cells and utilize host cell machinery to produce viral proteins. They are, however, not "live" in the sense that they cannot create copies of themselves in the inoculated host. This is a little confusing when it comes to vectored vaccines (*see COV-Ad26 [Janssen], below*), which *can* replicate—but only in vitro, in special cells designed for manufacturing.

mRNA vaccines direct synthesis of a full-length S-protein containing 2 proline substitutions in the S2 domain, which lock the protein in the prefusion conformation, preserving exposure of the RBD to immune effectors, improving immunogenicity, preventing membrane fusion, and retaining the ability of the protein to be anchored in the cell membrane.[82,83] The original monovalent vaccines employed the S-protein sequence from the ancestral Wuhan strain, which does not contain the G614 substitution (*see above*); the later bivalent vaccines used the Wuhan sequence plus the sequence from Omicron BA.4/BA.5, and the 2023-2024 updated vaccines used the sequence from Omicron XBB.1.5. The mRNA sequences are modified to enhance translation efficiency and stability and reduce reactogenicity,[84] and the mRNA is packaged in proprietary lipid nanoparticles that protect it from degradation and deliver it to the cytoplasm, where it can be translated into protein (the lipids also stimulate innate immune responses, enhancing immunogenicity[85]). COVID-19 vaccines were the first mRNA-based vaccines approved for use in the US, but it is important to note that research on similar vaccines had been ongoing for decades.[86]

COV-aPS (Novavax) consists of full-length S-protein (initially Wuhan but updated to Omicron XBB.1.5 for 2023-2024) containing the 2 stabilizing proline substitutions in the S2 domain as well as a mutated furin cleavage site, assembled into nanoparticles and co-formulated with an adjuvant.[87] Protein nanoparticles stimulate innate immunity, promote antigen uptake, and generate strong humoral and cellular responses.[88]

COV-Ad26 (Janssen) consists of adenovirus type 26 (Ad26) in which the E1 and E3 genes have been deleted and the modified SARS-CoV-2 S-protein gene has been inserted.[89] The E1/E3 deletion renders the virus incapable of replicating in vivo; the recombinant Ad26 particle binds to host cells and delivers the transgene to the nucleus for transcription into mRNA, which is then translated into protein. Vaccine virus is manufactured in cells that constitutively express the adenovirus E1 protein, which allows for replication.[90] The vaccine was effective in clinical trials[91,92] but was ultimately linked to *vaccine-induced immune thrombotic thrombocytopenia* (VITT)[93] (also referred to as *thrombosis with thrombocytopenia syndrome*), an autoimmune condition wherein platelets are activated by antibodies, leading to thrombosis, consumptive coagulopathy, and thrombocytopenia. In January 2022, the Advisory Committee on Immunization Practices issued a preferential recommendation for mRNA-based vaccines, and on June 1, 2023, the EUA for COV-Ad26 (Janssen) was revoked. The reporting rate for VITT following administration of COV-Ad26 (Janssen) was estimated at about 11 per million in women 30 to 39 years of age.[94]

In May 2023, the WHO recommended that new vaccine formulations induce antibodies that neutralize XBB descendent lineages, and that new formulations not contain the S-protein from the index virus.[95] In June 2023, the US Food and Drug Administration advised manufacturers to make monovalent vaccines based on the Omicron XBB.1.5 S-protein for the fall of 2023.[96] In September 2023, the corresponding vaccines from Pfizer and Moderna were approved for persons ≥12 years of age and authorized under EUA for persons 6 months to 11 years of age, and in October 2023 the updated vaccine from Novavax was authorized under EUA for persons ≥12 years of age.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Clinical Trials

For each of the vaccines available in the US, large, randomized, placebo-controlled trials demonstrated efficacy and safety.

- COV-mRNA (Pfizer-BioNTech)—In a multinational study, 43,584 (mostly adult) subjects were randomized 1:1 to receive 2 doses (30 mcg each) of vaccine or placebo 21 days apart.[97] Eight

TABLE 12.2 — COVID-19 Vaccines in Use in the United States as of October 2023[a]

Manufacturer/Distributor	Pfizer-BioNTech	Moderna	Novavax
Phone number	1-877-829-2619	1-866-663-3762	1-844-668-2829
Trade name of licensed product (age indication)	Comirnaty (≥12 y)	Spikevax (≥12 y)	—
Name of product granted EUA (age indication)	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula) (6 mo-11 y)	Moderna COVID-19 Vaccine (2023-2024 Formula) (6 mo-11 y)	Novavax COVID-19 Vaccine (2023-2024 Formula), Adjuvanted (≥12 y)
Abbreviation	COV-mRNA (Pfizer-BioNTech)	COV-mRNA (Moderna)	COV-aPS (Novavax)[b]
Type of vaccine	Non-live, subunit, in vivo-expressed	Non-live, subunit, in vivo-expressed	Non-live, subunit, in vitro-expressed
Composition	Nucleoside-modified mRNA encoding prefusion-stabilized spike (S) protein of SARS-CoV-2, Omicron lineage XBB.1.5	Nucleoside-modified mRNA encoding prefusion-stabilized spike (S) protein of SARS-CoV-2, Omicron lineage XBB.1.5	Nanoparticles composed of purified full-length prefusion-stabilized spike (S) protein of SARS-CoV-2, Omicron lineage XBB.1.5, expressed using baculovirus in an insect cell line derived from Sf9 cells
Adjuvant	None	None	Matrix-M (Fraction-A [42.5 mcg] and Fraction-C [7.5 mcg] of *Quillaja saponaria* Molina extract)
Preservative	None	None	None
Excipients and contaminants[c]	((4-hydroxybutyl)azanediyl) bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (0.43 mg)	SM-102, polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC] (total lipid content 1.01 mg)	Cholesterol, phosphatidylcholine, potassium dihydrogen phosphate (3.85 mcg)
	2-(polyethylene glycol 2000)-N,N-ditetradecylacetamide (0.05 mg)	Tromethamine (0.25 mg)	Potassium chloride (2.25 mcg)
	1,2-distearoyl-sn-glycero-3-phosphocholine (0.09 mg)	Tromethamine hydrochloride (1.2 mg)	Disodium hydrogen phosphate dihydrate (14.7 mcg)
	Cholesterol (0.19 mg)	Acetic acid (0.021 mg)	Disodium hydrogen phosphate heptahydrate (2.465 mg)
	Tromethamine (0.06 mg)	Sodium acetate trihydrate (0.1 mg)	Sodium dihydrogen phosphate monohydrate (0.445 mg)
	Tromethamine hydrochloride (0.4 mg)	Sucrose (43.5 mg)	Sodium chloride (8.766 mg)
	Sucrose (31 mg)		Polysorbate 80 (0.050 mg)
			Baculovirus and Sf9 cell proteins (≤0.96 mcg)

Continued

TABLE 12.2 — *Continued*

Manufacturer/Distributor	Pfizer-BioNTech	Moderna	Novavax
Excipients and contaminants[c] (*continued*)	Sucrose (31 mg) (*continued*)		Baculovirus and cellular DNA (≤0.00016 mcg)
			Lentil lectin (<0.025 mcg)
			Methyl-α-D-mannopyranoside (2 mcg)
			Simethicone (<0.92 mcg)
			Pluronic F-68 (<2.19 mcg)
			Triton X-100 (<0.025 mcg)
			Tergitol (NP9) (<0.05 mcg)
Latex	None	None	None
Labeled indications	Prevention of COVID-19	Prevention of COVID-19	Prevention of COVID-19
Route of administration	Intramuscular	Intramuscular	Intramuscular
Recommended schedule	See **Figures 12.6** and **12.7**	See **Figures 12.6** and **12.7**	*Footnote d*
How supplied (number in package)	30 mcg/0.3 mL ■ 1-dose vial, gray cap and gray label border (10)	50 mcg/0.5 mL ■ 1-dose vial, blue cap and blue label border (10)	5 mcg/0.5 mL ■ 5-dose vial, blue cap (2)
	■ Prefilled syringe (10) 10 mcg/0.3 mL ■ 1-dose vial, blue cap and blue label border (10) 3 mcg/0.3 mL ■ 3-dose vial, yellow cap and yellow label border (10)[e]	■ 5-dose vial, blue cap and blue label border (10) ■ Prefilled syringe (10) 25 mcg/0.25 mL ■ 1-dose vial, blue cap and green label border (10)	
Cost per dose (2023)[f]	—	—	—
Reference package insert	September 2023	September 2023	—
Reference EUA fact sheet	September 2023	September 2023	October 2023

EUA, Emergency Use Authorization; FDA, US Food and Drug Administration

[a] COV-Ad26 (Janssen) was removed from the US market, and its EUA was revoked, in June 2023. For updated guidance, see Interim Clinical Considerations for Use of COVID-19 Vaccines in the US. CDC Web site. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html. Accessed October 3, 2023.

[b] *aPS* stands for "adjuvanted protein subunit".

[c] The table shows data for the products that are FDA-approved (Pfizer-BioNTech and Moderna) or approved under EUA (Novavax). Providers should be aware of the potential for mix-ups between the various formulations and doses of COVID-19 vaccine.

[d] COV-aPS (Novavax) 2023-2024 Formula was authorized on October 3, 2023 as a 2-dose primary series at ≥12 y and as a single dose in persons ≥12 y who previously received any COV. See Regan JJ, et al. *MMWR*. 2023; doi: 10.15585/mmwr.mm7242e1 and check the CDC Web site for updated recommendations for use of this vaccine.

[e] Dilution with 1.1 mL of 0.9% Sodium Chloride Injection, USP is necessary before use.

[f] Vaccines were provided free of charge to the public until September 2023, after which they were commercialized.

cases of COVID-19 occurred ≥7 days after Dose 2 in the vaccine group, compared to 162 in the placebo group, for an efficacy of 95%. Four cases of severe disease occurred among placebees ≥7 days following Dose 2 versus 1 among vaccinees, and there were no COVID-19 deaths in the study. During 6 months of follow-up, efficacy against COVID-19 was 91% and against severe disease was 97%.[98]

In a study of adolescents 12 to 15 years of age without prior infection who were followed for several months after 2 doses (30 mcg each) of the vaccine, there were 16 cases of COVID-19 among 978 placebees (none were severe) and no cases among 1005 vaccinees, for an estimated vaccine efficacy of 100%.[99] Immunogenicity in a subset of these adolescents was non-inferior to that in older adolescents and young adults. Studies of children 5 to 11 years of age[100] and 6 months to 4 years of age[101] demonstrated safety, immunogenicity, and efficacy of various dosing regimens.

- COV-mRNA (Moderna)—In a US study, 30,415 adult subjects were randomly assigned 1:1 to receive 2 doses of vaccine (100 mcg each) or placebo 28 days apart.[102] At a median follow-up of about 5 months, there were 55 cases of COVID-19 in the vaccine group compared to 744 in the placebo group, for an efficacy of 93%. One hundred and six severe cases and 3 deaths occurred among placebees versus 2 severe cases and no deaths among vaccinees. Efficacy about 6 months out was 90%.[103]

  In a study of adolescents 12 to 17 years of age, 2480 received 2 doses of vaccine (100 mcg each) and 1222 received placebo.[104] Non-inferiority immunogenicity criteria were met as compared to young adult vaccinees, in whom efficacy had been demonstrated. No cases of COVID-19 occurred in the vaccine group and 4 cases occurred in the placebo group (efficacy was difficult to assess because of the low number of cases). Studies of children 6 to 11 years of age[105] and 6 months to 5 years of age[106] have demonstrated safety, immunogenicity, and efficacy of various dosing regimens.

- COV-aPS (Novavax)—In a study conducted in the United Kingdom, 15,187 adults were randomized 1:1 to receive 2 doses of vaccine (5 mcg each) or placebo 21 days apart.[107] Ten cases of COVID-19 occurred ≥7 days after Dose 2 in the vaccine group, compared to 96 in the placebo group, for an efficacy of 90% (per-protocol analysis); severe disease occurred in 5 placebees and in no vaccinees. At about 5 months out, efficacy against COVID-19 was 83% and against severe disease was 100%.[108] In a second study conducted in the US and Mexico, 29,949 adults were randomized 2:1 to receive 2 doses of vaccine or placebo 21 days apart.[109] In the 3 months following vaccination, there were 14 cases of COVID-19 among vaccinees and 63 among placebees, for an efficacy of 90% (per-protocol analysis). There were 14 moderate or severe cases of COVID-19 among placebees and none among vaccinees, for an efficacy of 100% against moderate-to-severe disease.

  In a study of adolescents 12 to 17 years of age, 1487 received 2 doses of vaccine and 745 received placebo.[110] Safety and immunogenicity was demonstrated, and efficacy against COVID-19 was 80%.

In general, clinical trials of updated bivalent booster vaccines demonstrated continued safety, improved neutralizing antibody responses against circulating strains, and efficacy.[111] Analogous to seasonal influenza vaccines, the updated 2023-2024 COV formulas were not tested for efficacy before approval, but they were made in the same way as the monovalent and bivalent vaccines.

Real-World Evidence

Large scale, robust effectiveness data initially came from Israel, which initiated a public vaccination campaign in December 2020 and by February 2021 had immunized 75% of individuals ≥16 years of age with ≥1 dose of COV-mRNA (Pfizer-BioNTech). In a study comparing almost 600,000 people who had been vaccinated to 600,000 who had not been vaccinated, the estimated effectiveness after Dose 2 was 92% against infection, 94% against symptomatic COVID-19, and 92% against severe COVID-19.[112] Protection was seen even though the Alpha variant had come to predominate during the study period and the vaccine, as discussed above, is based on the ancestral strain. In a nationwide surveillance study, the effectiveness of 2 doses of COV-mRNA (Pfizer-BioNTech) was 95% against infection and 97% against hospitalization.[113] A historical cohort study that included approximately 1.2 million vaccinees looked at infection and illness in the 1 to 7 days after Dose 1 (before vaccine-induced immunity would have developed) and then again during the 7 to 27 days after Dose 2 (when vaccine-induced immunity would have been robust); effectiveness against infection and illness was 90% and 94%, respectively.[114] Subsequent studies demonstrated the effectiveness of 3 (during the Delta wave) and even 4 (during the Omicron wave) doses.[115-117]

A wealth of data has now accumulated from around the world supporting the effectiveness of COVID-19 vaccination, especially against severe disease, despite changes in circulating strains and in the context of various multiple-dose regimens and updates in vaccine composition. For example, during the Delta wave in the US, the risk of death was 53-fold higher among unvaccinated persons as compared to those who were fully vaccinated and boosted,[118] the effectiveness in adolescents was 94% against hospitalization and 98% against intensive care unit admission.[119] During the Omicron

wave, effectiveness among adolescents was 40% against hospitalization and 79% against critical illness; among children 5 to 11 years of age, effectiveness against hospitalization was 68%.[120] The effectiveness of bivalent boosters, first offered in the US in September 2022, against hospitalization was 48% compared to monovalent-only regimens with the last dose being ≥11 months earlier.[121] However, meta-analyses and systematic reviews point to lower protection rates and faster waning of immunity against Omicron compared to earlier variants, underscoring the need for updated boosters.[122-125]

The estimated real-world impact of the US COVID-19 vaccination program is shown in **Table 12.3**. Globally, vaccination prevented as many as 20 million premature deaths from December 2020 to December 2021.[126] There are many benefits of vaccination beyond protection of the vaccinated individual from severe COVID-19. For example, vaccination decreases transmission,[127,128] prevents MIS-C,[129,130] reduces the risk of long COVID,[131] and protects infants when their mothers are vaccinated.[132]

Persistence of Immunity

Neutralizing antibody wanes in the first 6 months after vaccination.[133] One study suggested that effectiveness against symptomatic disease wanes by about 25% to 30% over 6 months and against severe disease by about 10%, regardless of vaccine used[134]; another estimated the half-life of monovalent vaccine effectiveness against symptomatic infection with Omicron to be 87 days.[135] It is not surprising that serum from immunized persons might have diminished neutralizing activity against emerging variants, since these arise, in part, through antigenic escape.[136,137] The extent to which S-protein–based vaccines will be able to protect against disease caused by SARS-CoV-2 variants depends on many factors.[138] Despite waning antibody, effectiveness against severe disease remains high,[139,140] likely due to the robust, broadly reactive T-cell responses induced by vaccination.[141]

The technologies used to develop the first COVID-19 vaccines can be leveraged to respond to variants quickly, safely and at scale; one could envision, for example, periodic boosters that include S-proteins from the prevailing strains, approved through a pathway much like that used for seasonal influenza vaccines. However, there is concern that *immunological imprinting* due to previous vaccination with the "old" S-protein could modulate the response to the "new" one.[142]

TABLE 12.3 — Impact of the COVID-19 Vaccination Program in the United States—December 12, 2020 to March 31, 2022

Outcome Averted	Estimate	Credible Interval
Hospitalizations	17,003,960	15,680,556-18,250,413
Deaths	2,265,222	2,051,041-2,467,683
Years of life lost	16,641,801	15,083,113-18,112,780
Costs (2021 USD)		
Direct health care	$895.4 billion	$611.9 billion-$1191.2 billion
Indirect	$26.9 billion	$19.5 billion-$34.2 billion

Adapted from Sah P, et al. *J Glob Health*. 2022;12:03062.

Safety

Surveillance

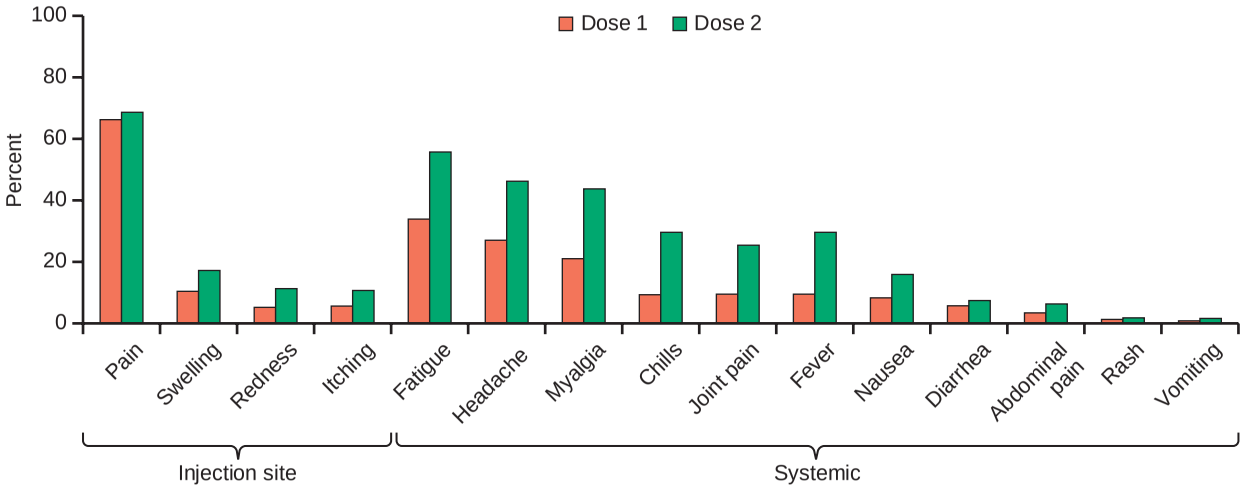
Safety monitoring during the rollout of COVID-19 vaccines was the most comprehensive in US history. Robust safety databases for each vaccine were available at the time of EUA because tens of thousands of people had been enrolled in the pivotal efficacy trials. Systems modeled after those deployed during the influenza A(H1N1) pandemic of 2009 were established to monitor safety after approval (see *Chapter 2: Vaccine Infrastructure in the United States—The Vaccine Safety Net*).[143] Enhanced passive surveillance was implemented through linkage of the Vaccine Adverse Event Reporting System to COVID-19 vaccine administration tracking systems; use of smartphone and web-based reporting; and initiatives of the National Healthcare Safety Network, Department of Defense, and Indian Health Service. Active surveillance was implemented through the Vaccine Safety Datalink (VSD), the Veterans Administration, and the Centers for Medicare & Medicaid Services. In addition, the vaccine manufacturers instituted routine pharmacovigilance programs.

As of May 2023, 677 million doses of vaccine had been administered in the US and 13.4 billion had been administered worldwide.[144] The unprecedented number of people vaccinated, the depth of surveillance for adverse events, and the rarity of serious side effects should be very reassuring to those who are concerned about the safety of the vaccines (see *Chapter 7: Addressing Concerns About Vaccines—COVD-19 Vaccines* for discussion of COVID-19 vaccine hesitancy).

Reactogenicity

Local and systemic reactions are common (**Figure 12.5**). In general, reactogenicity is higher in younger people, and Dose 2 of a series is more reactogenic than Dose 1. Increased reporting of low-severity adverse events has been seen after Dose 3, with no increase in reporting of severe adverse events as compared to the standard 2-dose regimen.[145] Most reported adverse events are mild and of short duration; serious adverse events are extremely rare. In a VSD study

FIGURE 12.5 — Adverse Reactions to COVID-19 Vaccines



The graph shows the proportion of vaccinees reporting the indicated reactions in the first 7 d following Dose 1 and Dose 2. Data are from *v-safe*, a smartphone-based monitoring system in the US operated by the Centers for Disease Control and Prevention, collected between December 2020 and June 2021. About 6.8 million participants reported after Dose 1 and 5.7 million after Dose 2, split approximately equally between COV-mRNA (Pfizer-BioNTech) and COV-mRNA (Moderna). Reactogenicity was greater after Dose 2 and among recipients of COV-mRNA (Moderna), persons <65 y, and females (data not shown). Adverse reactions to a single dose of COV-Ad26 (Janssen) reported in clinical trials were similar: redness, 5%-9%; swelling, 3%-7%; pain, 33%-59%; fever, 3%-13%; headache, 30%-44%; fatigue, 30%-44%; myalgia and/or arthralgia, 24%-39%; nausea and/or vomiting, 12%-16% (https://www.cdc.gov/vaccines/covid-19/info-by-product/janssen/reactogenicity.html; accessed November 20, 2023). Adverse reactions to COV-aPS (Novavax) reported in one large clinical trial (Dunkle LM, et al. *N Engl J Med*. 2022;386:531-543) included redness, 1-7%; swelling, 1-6%; pain, 34%-60%; tenderness, 52%-73%; fever, 0%-6%; headache, 25-44%; fatigue, 26-50%; myalgia and/or arthralgia, 8-48%; nausea and/or vomiting, 6%-11%, fatigue, 26%-50%; malaise, 15%-39%.

Adapted from Rosenblum HG, et al. *Lancet Infect Dis*. 2022;22:802-812.

of about 12 million doses of mRNA-based COVID-19 vaccine, the incidence of confirmed anaphylaxis was around 5 per million doses; most cases occurred in persons with a history of allergies.[146]

Myocarditis

Myocarditis, in some cases accompanied by pericarditis, has been reported after receipt of mRNA-based COVID-19 vaccines[147] (early data suggested a possible association with COV-aPS [Novavax],[148] but this has yet to be borne out in large epidemiologic studies). Symptoms include chest pain, fever, shortness of breath, and systemic complaints; troponin and acute inflammatory markers are elevated, and patients may have an abnormal electrocardiogram, decreased ejection fraction, and late gadolinium enhancement of the myocardium on magnetic resonance imaging.[149] A systematic review and meta-analysis that included 854 patients found that just over 1% of patients had severe left ventricular dysfunction; 90% were hospitalized (23% requiring an intensive care unit stay), the length of stay was about 3 days, and no patients died or required mechanical support.[150] Patients respond well to treatment with non-steroidal anti-inflammatory drugs and the prognosis is excellent.

The risk is highest in adolescent and young adult males after Dose 2, of the order of 1 in 6600 to 1 in 17,000[151-155]; cases have rarely been reported in children 5 to 11 years of age,[156] but the risk in children ≤5 years of age does not appear to be elevated.[157] Some studies suggest that the risk is higher after receipt of COV-mRNA (Moderna) than COV-mRNA (Pfizer-BioNTech).[158-160]

The pathogenesis is unclear but could involve innate immune responses or pre-existing immune dysregulation triggered by vaccination[161]; high levels of free circulating S-protein have been detected in post-vaccination myocarditis patients but not controls,[162] although molecular mimicry between the S-protein and myocarditis-associated antigens seems unlikely.[163] Recent evidence points to autoantibodies that neutralize the endogenous interleukin-1 receptor antagonist, an inhibitor of inflammation.[164]

Importantly, the risk of myocarditis after SARS-CoV-2 infection is substantially higher than the risk after vaccination.[165,166]

Guillain-Barré Syndrome (GBS)

The incidence of GBS (see *Chapter 7: Addressing Concerns About Vaccines—Guillain-Barré Syndrome*) following receipt of COV-Ad26 (Janssen) is significantly above the background rate, at an unadjusted incidence rate of 32 cases per 100,000 person-years in the first 1 to 21 days.[167]

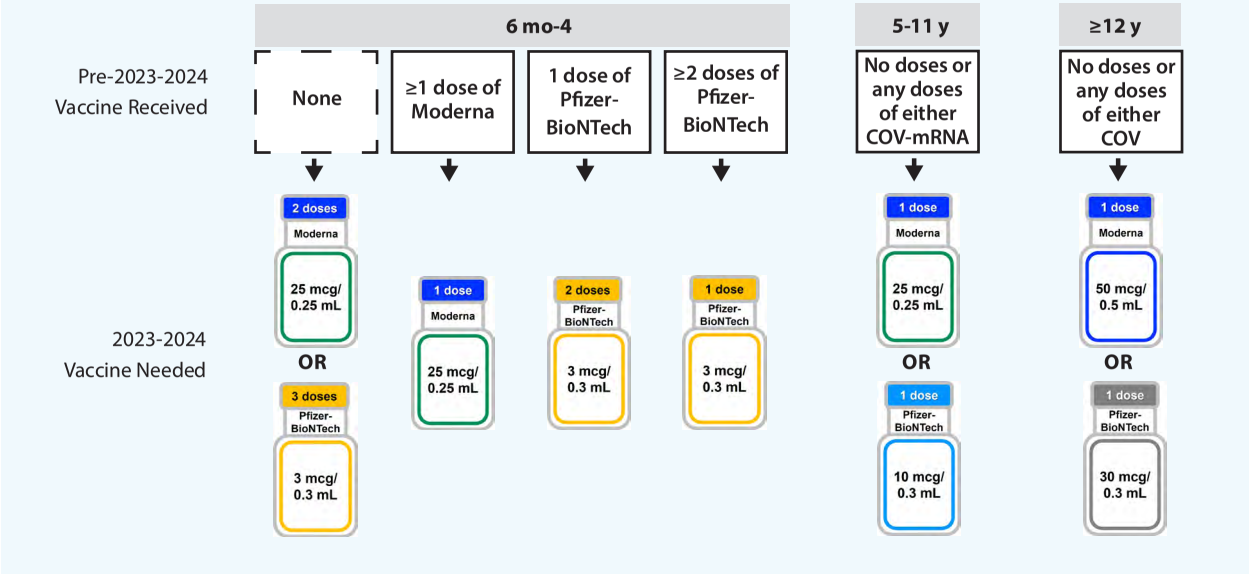
Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (this includes polyethylene glycol for COV-mRNA and polysorbate 80 for COV-aPS) (risk of recurrent allergic reaction). If one COV-mRNA product is contraindicated on this basis, the other one is as well.
- History of allergy to a vaccine component

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- Anaphylaxis after any vaccine other than COV (risk of recurrent allergic reaction)
- Anaphylaxis after any injectable therapy, except for subcutaneous allergy immunotherapy (risk of recurrent allergic reaction)
- Allergy-related contraindication to one type of COV is a precaution for another type (risk of recurrent allergic reaction). Thus, an allergy-related contraindication to either COV-mRNA product is a precaution for COV-aPS, and vice-versa.
- Immediate (within 4 hours) non-severe allergic reaction (urticaria beyond the injection site, angioedema that does not involve the airway) to previous dose of vaccine (risk of recurrent allergic reaction). A reaction to one of the COV-mRNA products is a precaution for both of the COV-mRNA products. Subsequent doses of the same type of vaccine should occur in a setting where severe allergic reactions can be managed appropriately.
- History of MIS-C or MIS-A (risk of recurrent MIS-C or MIS-A). Vaccination should be delayed until the patient has clinically recovered, and it has been ≥90 days since diagnosis. Any theoretical risk of recurrence of MIS-C or MIS-A due to vaccination must be balanced against the risks of COVID-19 and the risk of recurrence of MIS-C or MIS-A after reinfection.
- History of myocarditis or pericarditis after previous dose of any COV (risk of recurrent myocarditis or pericarditis). Vaccination should generally be avoided. If after a risk assessment the decision is made to continue vaccination, administration of vaccine should occur after resolution of symptoms, when ongoing myocardial inflammation and cardiac sequelae have been ruled-out, and when cleared by the patient's clinical team. Considerations for subsequent vaccination include the possibility that the episode of myocarditis or pericarditis had an alternative explanation, the personal risk of severe acute COVID-19, and the timing of any immunomodulatory therapies.
- Persons who have a history of myocarditis or pericarditis unrelated to COVID-19 vaccination may receive COVID-19 vaccines after their clinical illness resolves.

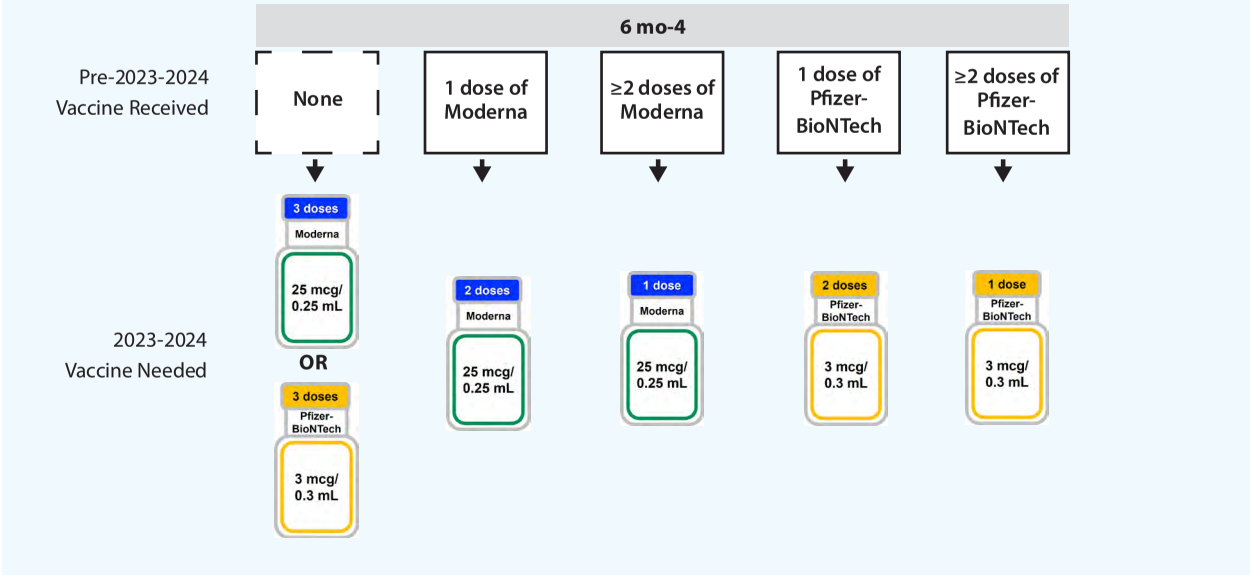
FIGURE 12.6 — COV Regimens for Persons Who Are Not Moderately or Severely Immunocompromised



The graphic shows dosing regimens by age and by previous vaccine doses received. The color of the cap on the icon corresponds to the color of the vial cap; the color of the rounded rectangle on the icon corresponds to the color of the vial label. In general, people should receive the appropriate vaccine product and dose based on their age on the day of vaccination. Doses given to children 6 mo-4 y should be from the same manufacturer. There are 2 options for children who transition from 4 to 5 y during the Pfizer-BioNTech series: complete the 3-dose series with updated (2023–2024 Formula) Pfizer-BioNTech vaccine for ages 6 mo-4 y (3 mcg/0.3 mL, yellow cap and yellow label), or administer 1 dose of the updated (2023–2024 Formula) Pfizer-BioNTech vaccine for ages 5-11 y (10 mcg/0.3 mL, blue cap and blue label). Children who transition from 4 to 5 y during the Moderna series should complete the 2-dose series with the same vaccine (25 mcg/0.25 mL). For multidose series of (2023–2024 Formula) Pfizer-BioNTech vaccine, the interval between Dose 1 and Dose 2 is 3-8 wk and between Dose 2 and Dose 3 is ≥8 wk. For multidose series of (2023–2024 Formula) Moderna vaccine, the interval between Dose 1 and Dose 2 is 4-8 wk and between Dose 2 and Dose 3 is ≥8 wk. For more details on dosing intervals, see Table 1 in Interim Clinical Considerations for Use of COVID-19 Vaccines in the United States (CDC Web site; https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html [accessed October 3, 2023]). See *Footnote d* in **Table 12.2** regarding COV-aPS (Novavax) 2023-2024 Formula.

Adapted from COVID-19 Vaccination recommendations infographic. CDC Web site. https://www.cdc.gov/vaccines/covid-19/downloads/COVID19-vaccination-recommendations-most-people.pdf. Accessed October 3, 2023.

FIGURE 12.7 — COV Regimens for Persons Who Are Moderately or Severely Immunocompromised



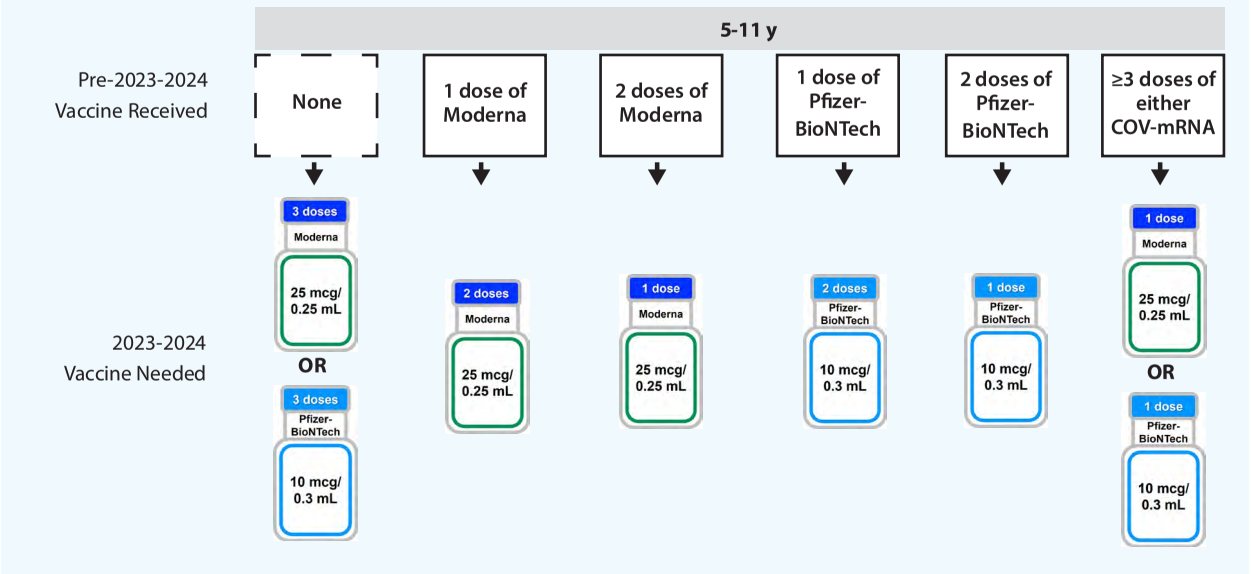


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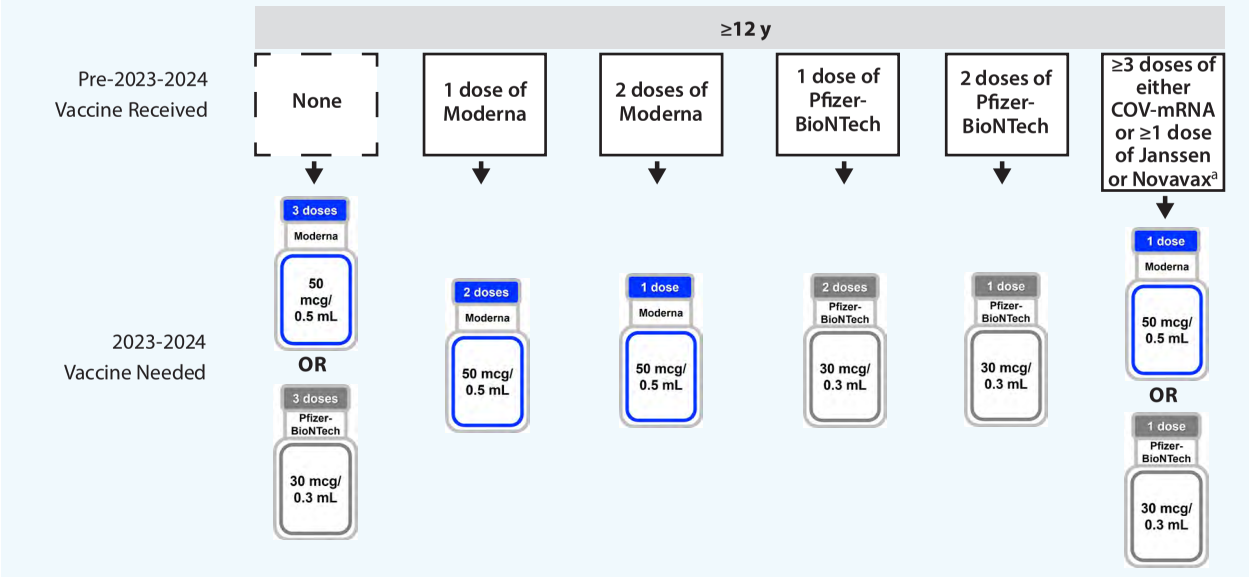
FIGURE 12.7 — *Continued*



The graphic shows dosing regimens by age and by previous vaccine doses received. The color of the cap on the icon corresponds to the color of the vial cap; the color of the rounded rectangle on the icon corresponds to the color of the vial label. In general, people should receive the appropriate vaccine product and dose based on their age on the day of vaccination. In general, doses given to immunosuppressed persons should be from the same manufacturer. There are 2 options for children who transition from 4 to 5 y during the Pfizer-BioNTech series: complete the 3-dose series with updated (2023–2024 Formula) Pfizer-BioNTech vaccine for ages 6 mo-4 y (3 mcg/0.3 mL, yellow cap and yellow label), or use the updated (2023–2024 Formula) Pfizer-BioNTech vaccine for ages 5-11 y (10 mcg/0.3 mL, blue cap and blue label) for all doses after turning 5 y. Children who transition from 4 to 5 y during the Moderna series should complete all doses with the same vaccine (25 mcg/0.25 mL). Children 5-11 y have the option to receive 1 additional dose of the age-appropriate 2023-2024 formula vaccine ≥2 mo after the last dose. Children who received Moderna or Pfizer and transition from 11 to 12 y may complete the respective 3-dose series with the lower dose vaccine or with the respective higher dose vaccine (for persons ≥12 y).

For multidose series of (2023–2024 Formula) Pfizer-BioNTech vaccine, the interval between Dose 1 and Dose 2 is 3 wk and between Dose 2 and Dose 3 is ≥4 wk. For multidose series of (2023–2024 Formula) Moderna vaccine, the interval between Dose 1 and Dose 2 is 4 wk and between Dose 2 and Dose 3 is ≥4 wk. For more details on dosing intervals, see Table 2 in Interim Clinical Considerations for Use of COVID-19 Vaccines in the United States (CDC Web site; https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html [accessed October 3, 2023]). See *Footnote d* in **Table 12.2** regarding COV-aPS (Novavax) 2023-2024 Formula.

Moderate or severe immunocompromise includes the following: active treatment for solid tumor or hematologic malignancy; hematologic malignancy associated with poor vaccine response regardless of current treatment (eg, chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia); solid-organ or islet transplant receiving immunosuppressive therapy; chimeric antigen receptor (CAR)-T-cell therapy or hematopoietic cell transplant within 2 years of transplantation or taking immunosuppressive therapy; primary immunodeficiency (eg, common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome); advanced (eg, CD4 cell count less than 200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations

Continued

FIGURE 12.7 — *Continued*

of symptomatic HIV) or untreated HIV infection; high-dose corticosteroids (20 mg or more of prednisone or equivalent per day for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, severely immunosuppressive cancer chemotherapeutic agents, tumor necrosis factor (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (eg, B-cell-depleting agents). Patients can self-attest to their immune competency status.

See *Footnote d* in Table 12.2 regarding COV-aPS (Novavax 2023-2024 Formula.

[a] Includes COV-Ad26 (Janssen) or COV-aPS (Novavax) given in combination with any COV-mRNA.

Adapted from COVID-19 Vaccination Recommendations Infographic (Immunocompromised). CDC Web site. https://www.cdc.gov/vaccines/covid-19/downloads/COVID19-vaccination-recommendations-immunocompromised.pdf. Accessed October 3, 2023.

Recommendations

All persons ≥6 months of age should be vaccinated. The recommended regimens are shown in **Figure 12.6** (persons who are not moderately or severely immunocompromised) and **Figure 12.7** (persons who are moderately to severely immunocompromised). The formulation, number of doses, and timing of doses depends on age, immune competency status, and previous vaccination history.

The standard observation period after vaccination is 15 minutes, but this may be extended to 30 minutes for persons with an allergy-related contraindication to a different type of COV, a history of non-severe, immediate (within 4 hours) allergic reaction to a previous dose of COV, or anaphylaxis after other vaccines or injectable therapies. Routine prophylaxis with acetaminophen or non-steroidal anti-inflammatory agents is not recommended, but these drugs may be used after vaccination if medically indicated.

Note the following:

- Vaccination is recommended regardless of history of SARS-CoV-2 infection. Vaccination after natural SARS-CoV-2 infection provides *hybrid immunity*[168] and added protection against disease. While people with current SARS-CoV-2 infection can be vaccinated as soon as isolation is discontinued, patients who had acute COVID-19 may consider deferring vaccination for 3 months after symptoms started (or 3 months after a positive test if the infection was asymptomatic)—they are likely well protected during that time and are more likely to develop robust immunity if they wait. Unvaccinated people who were exposed to COVID-19 should generally defer vaccination until the quarantine period is over.
- COVID-19 vaccines may be administered at the same time, or at any interval, with respect to other vaccines (see *Chapter 5: General Recommendations—Rule 1*, including the caution about co-administration with orthopoxvirus vaccines).
- The 4-day grace period (see *Chapter 3: Standards, Principles, and Regulations—Mandates and Exemptions*) applies to COVID-19 vaccination.
- If possible, vaccination should take place 2 weeks before initiation or resumption of immunosuppressive therapies. For patients who receive B-cell-depleting therapies (eg, rituximab), vaccination should occur approximately 4 weeks before the next scheduled therapy.
- Anti-SARS-CoV-2 antibody testing is not recommended, either before or after vaccination.
- In cases where sequential doses of any COV are called for—as, for example, in an unvaccinated 4-year-old receiving COV-mRNA, or a previously-vaccinated young adult receiving COV-aPS (Novavax)—an 8-week interval between Doses 1 and 2 should be

considered for some people, as this might reduce the very small risk of myocarditis and pericarditis associated with vaccination.

Answers to frequently asked questions about COV are given in **Table 12.4**. See *Chapter 7: Addressing Concerns About Vaccination—The COVID-19 Vaccine Misinformation Pandemic* for a discussion of COV hesitancy.

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TABLE 12.4 — Frequently Asked Questions About COVID-19 Vaccination[a]

Question	Answer
Can patients be vaccinated before a scheduled surgery or procedure?	Because vaccination can cause fever, and fever after a procedure can raise concern about infection, vaccination should occur ≥1 wk before a scheduled procedure.
Can a patient have a mammogram or MRI shortly after vaccination?	Regional lymphadenopathy may occur near the injection site, which could interfere with interpretation of the results. Some centers recommend that patients not be vaccinated in the 4-6 wk before certain imaging studies.
Are the recommendations for masking and other precautions the same for vaccinated and unvaccinated people?	Yes.
Can vaccination improve long COVID-19 symptoms?	There are anecdotal reports that patients feel better after vaccination,[b] but preliminary data are conflicting.[c,d]
How should providers handle patients who were vaccinated outside the US?	Vaccination with a product that is approved or authorized by the FDA or listed for emergency use by the WHO is considered valid.[e] Vaccination with any other product is considered invalid, and a US-approved or -authorized series should be given (starting ≥28 days after the last dose of the invalid vaccination). White CDC COVID-19 vaccination cards were only issued to people vaccinated in the US; those vaccinated outside the US should keep the documentation they received at the time of vaccination.
What should be done if a patient loses their CDC COVID-19 vaccination card?	Patients should keep the card in a safe place and consider making a copy. Cards were no longer being distributed by the CDC as of October 2023.
Can vaccination be mandated?	States, local governments, employers, and institutions can require certain vaccinations, including those approved under EUA (see *Chapter 3: Standards, Principles, and Regulations—Mandates and Exemptions*). Some colleges continued their COV mandate after the public health emergency declaration expired in May 2023.[f] It is unclear how many employers will do the same, and applicable regulations vary from state to state.[g]
Is compensation available for severe adverse reactions?	Compensation is available for certain injuries and with certain restrictions (see *Chapter 3: Standards, Principles, and Regulations—Public Readiness and Emergency Preparedness [PREP] Act*).

CDC, Centers for Disease Control and Prevention; EUA, Emergency Use Authorization; FDA, US Food and Drug Administration; WHO, World Health Organization

[a] Updates may be found at Frequently Asked Questions About COVID-19 Vaccination. CDC Web site. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html; COVID-19 Vaccine FAQ. National Foundation for Infectious Diseases Web site. https://www.nfid.org/infectious-diseases/covid-19/covid-vaccine-faq/; and Questions and Answers About COVID-19 Vaccines. Children's Hospital of Philadelphia Web site. https://www.chop.edu/centers-programs/vaccine-education-center/making-vaccines/prevent-covid. See **Table 7.10** for concerns about COVID-19 vaccines frequently expressed by patients.

[b] Some long-haul COVID-19 patients say their symptoms are subsiding after getting vaccines. The Washington Post Web site. https://www.washingtonpost.com/health/long-haul-covid-vaccine/2021/03/16/6effcb28-859e-11eb-82bc-e58213caa38e_story.html.

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Dengue

The Pathogen

Dengue virus (DENV) is an enveloped, single-stranded RNA virus in the Flaviviridae family that has four serotypes.[1] The envelope-embedded E protein mediates binding to a variety of receptors on diverse host cell types, and antibodies against it are neutralizing.[2] The virus is tropic for myeloid cells, but, interestingly, not endothelial cells[3]; the capillary leak that is characteristic of severe dengue is caused, at least in part, by direct effects of non-structural protein 1 (NS1), which circulates in high quantities during acute infection, on the endothelial glycocalyx.[4]

Severe disease is classically seen with second infections. This is, in part, explained by *antibody-dependent enhancement* (ADE), whereby cross-reactive, sub-neutralizing antibodies induced by the first infection bind a heterologous infecting serotype, facilitating uptake by monocytes, macrophages, and dendritic cells via their Fc receptors. This process, which is more efficient than viral entry through cognate receptor-mediated endocytosis, leads to a high burden of infection and consequent systemic inflammation. Pathogenesis also involves the induction of anti-NS1 antibodies that have pro-inflammatory effects and can induce apoptosis; strain-to-strain genomic variation; inhibition of host defense mechanisms by sub-genomic RNA; cross-reactive T-cells; dysregulated cytokine production; and the generation of immune complexes.[5]

Clinical Features

The incubation period is 4 to 7 days. Most infected people remain asymptomatic, although 25% experience a relatively minor, self-limited febrile illness. A small proportion of patients progress further through the clinical phases shown in **Table 13.1**. Those who manifest the abrupt onset of high fever, severe headache, retro-orbital pain, musculoskeletal pain, nausea, vomiting, lymphadenopathy, and rash are classified as having *dengue*.[6] Those who develop complications—plasma leakage severe enough to cause shock or respiratory distress, severe bleeding, or severe organ impairment—are classified as having *severe dengue* (the terms *dengue fever* and *dengue hemorrhagic fever* are no longer favored). Warning signs of severe dengue include severe abdominal pain, persistent vomiting, tachypnea, bleeding gums, fatigue restless-

TABLE 13.1 — Clinical Phases of Dengue

Febrile Phase	Critical Phase	Recovery Phase
Sudden onset 4-7 d after infection Duration 3-7 d High fever, chills headache, malaise, retro-orbital pain, arthralgia, myalgia, bone pain, nausea, vomiting, altered taste sensation Rash, flushed appearance, conjunctival or pharyngeal injection, mild bleeding, generalized lymphadenopathy, palpable liver Leukopenia, thrombocytopenia, atypical lymphocytosis, elevated hepatic transaminases	Coincides with cessation of fever and escalation of host immune response Duration 2-3 d *Vascular leakage* • Intravascular volume depletion • Hypoproteinemia • Hemoconcentration • Serosal effusions • Respiratory distress • Cardiovascular collapse • Hypovolemic shock *Bleeding* • Coagulopathy • Petechiae, bruising, epistaxis • Mucosal, uterine, intracranial (rare) *Liver impairment* • Hepatomegaly • Liver dysfunction • Acute liver failure (rare) *Central nervous system impairment* • Seizures • Encephalitis • Encephalopathy • Neuropathies • Guillain-Barré syndrome • Transverse myelitis	1-2 wk after onset of illness Some symptoms persist for months Fatigue Weakness Myalgia Depression Macular rash with "islands of white" Bacterial superinfection Hemophagocytic lymphohistiocytosis

Continued

ness, and hematemesis. *Dengue shock syndrome* occurs when vascular leakage leads to profound hypovolemia and progressively narrowing pulse pressure. Management focuses on recognizing early signs of severe dengue, aggressive fluid resuscitation, and cardiopulmonary

TABLE 13.1 — *Continued*

Febrile Phase	Critical Phase	Recovery Phase
	Cardiac impairment • Sinus bradycardia • Minor arrhythmias • Myocarditis (rare) *Ocular manifestations* • Retinal hemorrhage and edema • Macular ischemia • Optic neuritis *Renal* • Microscopic hematuria • Renal failure due to profound shock or rhabdomyolysis	

Adapted from Simmons CP, et al. *N Engl J Med*. 2012;366:1423-1432; Wilder-Smith A, et al. *Lancet*. 2019;393:350-363.

support. The case fatality rate in the Americas has fallen to 0.04%,[7] due largely to early recognition and supportive care; the case-fatality rate for untreated severe dengue is about 10%.

Epidemiology and Transmission

Dengue is spreading faster throughout the world than any other arthropod-borne viral disease; not surprisingly, in 2019 the World Health Organization (WHO) listed dengue as one of the top ten threats to global health.[8] A reservoir of DENV is maintained by a sylvatic transmission cycle involving *Aedes* mosquitos and non-human primates in Southeast Asia and West Africa. Human-to-human transmission occurs in urban settings from the bite of peridomiciliary mosquitos, principally *Aedes aegypti* and *Aedes albopictus*.[9] The global disease burden as estimated in 2017 was 105 million cases, a 4.5-fold increase since 1990; during the same period of time, the number of deaths increased from 17,000 to 40,000.[10] Increases in disease incidence are attributed to global warming, which has led to wider geographic reach of *Aedes* mosquitos,[11] as well as international travel to and from endemic areas.[12] High infection rates are found in South Asia, Southeast Asia, Latin America, and the Caribbean; in fact, approximately 10% of febrile illnesses among children in Southeast Asia and Latin America are caused by DENV.[13] From 2010 to 2020, Puerto Rico reported the highest

number of dengue cases (29,862) in the US, but the incidence was highest (10.2 cases per 1,000) in American Samoa. Approximately half of all US cases occurred in persons aged <20 years of age.[14]

Dengue is a leading cause of fever in returned travelers; in fact, during peak season in the epidemic years 1998 to 2002, dengue accounted for >200 cases per 1000 ill travelers returning from Southeast Asia.[15]

Immunization Program

Dengvaxia was first licensed outside the US in 2015. In 2016, the WHO recommended that countries in which the disease is highly endemic consider vaccination of children ≥9 years of age.[16] Shortly thereafter, it became apparent that the vaccine could increase disease severity in seronegative persons, likely mimicking the effect of primary infection by inducing enhancing antibodies (*see above*). Countries like the Philippines, where 830,000 children had already been vaccinated, quickly suspended their programs, and there was a significant public backlash.[17] The WHO position changed in 2018 to include the recommendation for prevaccination serological testing, with vaccination of seropositive persons only.[18] Recommendations for use of dengue vaccine in the US, which also call for testing, were published in 2021.[19] In a simulation model, routine vaccination of 9-year-olds in Puerto Rico over a 10-year period—assuming 50% seroprevalence, prevaccination screening with 80% sensitivity and 95% specificity, and considering direct medical costs only—would cost $16,000 per hospitalization prevented and $122,000 per quality-adjusted life year gained (2019 dollars).[20]

Vaccines

Characteristics of the dengue vaccine licensed in the US (CDY-TDV) are given in **Table 13.2**. This consists of the live attenuated yellow fever virus strain 17D-204 (see *Chapter 33: Yellow Fever—Vaccine*) in which sequences encoding the pre-membrane and envelope proteins were substituted with homologous sequences from each of the 4 DENV serotypes. The resultant chimeric viruses are replication competent, attenuated, and express immunogenic dengue proteins. Preclinical studies demonstrated that the chimeric viruses are genetically and phenotypically stable; that the expressed proteins undergo appropriate post-translational modification; and that the vaccine viruses have a very low risk of being transmitted by arthropods, reverting to virulence, or recombining.[21]

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Licensure of CYD-TDV was based on two large Phase 3 trials. Study CYD14 was conducted among children 2 to 14 years of age in five Asian-Pacific countries in 2011.[22] In the per-protocol analysis, 6710 vaccinees were compared to 3350 placebees; efficacy was 57% against virologically confirmed dengue, and there were no significant safety signals. Study CYD15 was conducted among children 9 to 16 years of age in five Latin American countries in 2011 and 2012.[23] The per-protocol analysis included 12,574 vaccinees and 6261 placebees; efficacy was 61% against virologically confirmed dengue, 80% against hospitalization, and 96% against severe dengue. Importantly, while efficacy in both studies was higher in subjects with positive baseline serology, more severe disease was not detected in vaccinees. Combined data from both studies showed the highest efficacy (77%) against serotype 4 and lowest (43%) against serotype 2.[24] Pooled analyses showed efficacy of 81% against hospitalization among those ≥9 years of age and 56% among those <9 years of age; at the time, the reasons for this difference were not clear.[25]

Baseline serostatus in the above studies was determined by plaque reduction neutralization in a small subset of subjects. In a post-hoc study, a new assay for anti-DENV NS1 antibody—a marker for DENV infection rather than vaccination—and other methods were used to impute baseline subject serostatus from postvaccination sera in studies CDY14 and CDY15, as well as another clinical trial conducted in Thailand.[26] Efficacy against symptomatic virologically confirmed dengue among subjects who were 9 to 16 years of age was 76% for seropositives and 39% for seronegatives; among seropositives, vaccination was about 80% protective against severe dengue and hospitalization over a 5-year period. Importantly, the risks of hospitalization and severe dengue were elevated among seronegative children who had been vaccinated as compared to those who had received placebo; this confirmed that in seronegatives, vaccination mimicked primary infection in its ability to enhance disease (*see above*).

Safety

Injection site reactions among children 9 to 16 years of age include pain (32%), erythema (4%), and swelling (4%); systemic reactions include headache (40%), myalgia (29%), asthenia (25%), malaise (25%), and fever (7%). Most reactions are low-grade. Serious adverse events in the month following vaccination were rare (0.6%) and occurred with approximately equal frequency in placebees. No cases of viscerotropic or neurotropic illness related to the yellow fever component of the vaccine (see *Chapter 33: Yellow Fever—Safety*) have been reported.

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)

TABLE 13.2 — Dengue Vaccine

Trade name	Dengvaxia
Abbreviation	CYD-TVD[a]
Manufacturer/distributor	Sanofi
Type of vaccine	Live, attenuated, engineered
Composition	Chimeric yellow fever virus (strain 17D-204) constructs, each expressing the pre-membrane and envelope proteins of one of the 4 DENV serotypes (1, 2, 3, 4)
	Propagated in Vero (African green monkey kidney) cells
	4.5 $\log_{10}$ - 6.0 $\log_{10}$ 50% cell culture infective dose of each chimeric virus
Adjuvant	None
Preservative	None
Excipients and contaminants	Sodium chloride (2 mg)
	Essential amino acids, including L-phenylalanine (0.56 mg)
	Non-essential amino acids (0.2 mg)
	L-arginine hydrochloride (2.5 mg)
	Sucrose (18.75 mg)
	D-trehalose dihydrate (13.75 mg)
	D-sorbitol (9.38 mg)
	Trometamol (0.18 mg)
	Urea (0.63 mg)
Latex	None
Labeled indications	Prevention of dengue due to virus serotypes 1, 2, 3, and 4
Labeled ages	9-16 y with laboratory-confirmed previous dengue infection and living in endemic areas (*see text*)
Dose	0.5 mL
Route of administration	Subcutaneous
Labeled schedule	Doses at 0, 6, and 12 mo
Recommended schedule	Same
How supplied (number in package)	1-dose vial (1), lyophilized, with diluent
Cost per dose (USD, 2023)[b]	
Public	95.93
Private	100.98
Reference package insert	January 2023

[a] CYD-TDV stands for "chimeric yellow fever dengue-tetravalent dengue vaccine".
[b] Dengvaxia is not available in areas where dengue is not endemic, including the continental US. The vaccine can be ordered from the manufacturer by calling 1-800-822-2463.

Continued

- No history of laboratory-confirmed dengue or current seronegative status (risk of severe dengue with subsequent natural infection)
- Severe immunodeficiency or immunosuppression, including children with HIV infection whose CD4 count is <200 cells/mcL (risk of disease caused by live virus)

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- HIV infection without evidence of severe immunosuppression (risk of disease caused by live virus)
- Pregnancy (theoretical risk to the fetus of live-virus vaccine or attribution of birth defects to vaccination)

Recommendations

Children 9 to 16 years of age who have evidence of previous DENV infection and live in endemic areas should be vaccinated. Endemic areas in the US include Puerto Rico, American Samoa, the US Virgin Islands, the Federated States of Micronesia, the Republic of Marshall Islands, and the Republic of Palau.[27] The vaccine is not approved or recommended as a travel vaccine.

Evaluation for evidence of previous DENV infection is required before vaccination. Patients must have met the 2015 case definition of laboratory-confirmed dengue[28] in the past or have a positive highly-accurate serodiagnostic screening test at the time of vaccination (testing and vaccination should be delayed for ≥12 months after receipt of antibody-containing blood products due to the risk of

detecting passively-acquired antibodies and erroneously concluding that the patient has had prior DENV infection). For updated guidance on dengue vaccination, see www.cdc.gov/dengue/vaccine/hcp/index.html (accessed August 8, 2023).

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Diphtheria, Tetanus, and Pertussis

The Pathogens

Diphtheria

Corynebacterium diphtheriae is an aerobic, nonencapsulated, nonspore-forming, pleomorphic gram-positive bacillus that has a club-like appearance on Gram stain.[1] Infection occurs on mucous membranes of the upper respiratory tract or in the skin, where the organism elaborates a potent exotoxin that works by inactivating tRNA transferase, preventing amino acids from being added to nascent polypeptide chains during protein synthesis. On respiratory surfaces like the throat, necrotic cells, inflammatory exudate, bacteria, and fibrin coalesce into adherent *pseudomembranes.* Local effects of the toxin include paralysis of the palate and hypopharynx; distant effects can be seen in the kidneys, liver, heart, and nervous system.

Tetanus

Clostridium tetani is a nonencapsulated, gram-positive, obligately anaerobic bacillus that has a drumstick or tennis racket appearance on Gram stain because of terminally located spores.[2] Initial infection usually takes place in a deep, penetrating wound, where the organism elaborates *tetanospasmin*, a potent neurotoxin. The toxin spreads via the bloodstream and lymphatics to distant sites, where it is taken up into nerves through the neuromuscular junction and transported to the central nervous system. There it prevents the release of neurotransmitters at inhibitory synapses, causing unopposed lower motor-neuron activity, with resultant spasms and rigidity.

Pertussis

Bordetella pertussis is a tiny, aerobic, gram-negative coccobacillus that is tropic for ciliated respiratory epithelium.[3] Attachment is mediated by *filamentous hemagglutinin* (FHA), *fimbriae* (FIM), and *pertactin* (PRN), among other proteins. The major virulence factor is *pertussis toxin* (PT), a complex molecule that causes increased intracellular levels of cAMP and disruption of cellular function. PT also facilitates adherence, promotes lymphocytosis, inhibits phagocytosis, increases insulin

production (causing hypoglycemia), and increases sensitivity to histamine (causing vascular permeability and hypotension). PT and other toxins, including *tracheal cytotoxin* and *adenylate cyclase toxin*, are involved in the genesis of protracted cough.

Clinical Features

Diphtheria

The disease most often presents as *membranous nasopharyngitis* or *obstructive laryngotracheitis* associated with low-grade fever. Less commonly, cutaneous, vaginal, conjunctival, or otic infection can occur. Serious complications include upper airway obstruction caused by extensive membrane formation, myocarditis, and peripheral neuropathy. The case fatality rate is as high as 10% but is higher in young children and older adults. Treatment includes antibiotics as well as equine antitoxin (available through the Centers for Disease Control and Prevention), which neutralizes circulating toxin and prevents disease progression.

Tetanus

Most cases occur within 14 days of injury. Shorter incubation periods have been associated with more heavily contaminated wounds, more severe disease, and worse prognosis. *Generalized tetanus* (lockjaw) initially manifests as trismus, followed quickly by neck stiffness, dysphagia, rigidity of the abdominal muscles, and generalized muscle spasms. Severe spasms, often aggravated by external stimuli, persist for 3 to 4 weeks, and complete recovery may take months. *Neonatal tetanus* results from contamination of the umbilical stump. *Localized tetanus* manifests as muscle spasms in areas contiguous with an infected wound. *Cephalic tetanus* refers to cranial nerve dysfunction associated with infected wounds on the head and neck. Treatment includes tetanus immune globulin (TIG), which neutralizes unbound toxin. The case fatality rate is about 10%.

Pertussis

Classic *whooping cough* begins with mild upper respiratory tract symptoms (*catarrhal stage*) that last for 1 to 2 weeks. This progresses to severe paroxysms of cough (*paroxysmal stage*), often followed by a characteristic inspiratory whoop, that last for 4 to 6 weeks. Posttussive emesis is common and the cough can be forceful enough to cause injury (rib fractures and even carotid artery dissection have been reported). Fever is usually absent and symptoms wane gradually (*convalescent stage*) over 6 to 10 weeks, giving rise to the colloquial term "the hundred-day cough." Complications include seizures, pneumonia, and encephalopathy. Pertussis is most severe during the first year of life and almost all deaths occur in young infants. Disease in infants <6 months of age may be atypical, with prominent apnea and absent whoop. Older children and adults may also have atypical disease, manifested only as persistent cough, making recognition and treatment difficult.

Epidemiology and Transmission

Diphtheria

Humans are the only known reservoir of *C diphtheriae*. Patients excrete the organism for 2 to 6 weeks in nasal discharge, from the throat, or from eye or skin lesions. Antibiotic treatment shortens the period of communicability. Transmission results from intimate contact, and illness is more common in crowded living situations. Although *infection* can still occur in immunized persons, *disease* generally does not because any elaborated toxin is neutralized by antibody. Respiratory diphtheria is seen in winter and spring; summer epidemics can occur in warm, moist climates where skin infections are prevalent. While there are only two or three cases reported each year in the US, toxigenic *C diphtheriae* can still be found in some populations. Diphtheria continues to be a significant cause of morbidity and mortality in developing countries.

Tetanus

Tetanus is not transmissible from person to person. Spores of *C tetani* are ubiquitous in the environment, especially where there is soil contaminated with excreta. The organism infects wounds and elaborates toxin; soil-contaminated wounds, those that result from deep puncture, and those with devitalized tissue are at greatest risk. Disease occurs worldwide but is more frequent in warmer climates and during warmer months, in part because contaminated wounds are more common. Just over 30 cases of tetanus are reported in the US each year. Neonatal tetanus is rare in the US but common in developing countries, where pregnant women may not be fully immunized and nonsterile umbilical cord-care practices are followed.

Pertussis

Humans are the only known hosts for *B pertussis.* Transmission occurs through respiratory droplets and direct contact with respiratory secretions, and acquisition rates approach 80% in susceptible household contacts. Patients are most contagious during the catarrhal stage, before the onset of paroxysms; communicability then diminishes but may persist for ≥3 weeks after onset of cough. Antibiotic therapy decreases infectivity and may limit spread. Asymptomatic infection may be common among household contacts of cases and may have a role in transmission.[4]

Pertussis is a common cause of prolonged cough illness. One study showed that 26% of university students with cough for ≥6 days had pertussis.[5] Many cases go unrecognized and untreated, and chemoprophylaxis of contacts does not take place, facilitating

persistence and spread through communities. People in the immediate environment—like older siblings and parents—are the most important source of transmission to young infants.[6] From 2000 to 2016, there were 20,000 reported cases of pertussis per year in the US.[7] The highest incidence was in infants, and infants accounted for about 90% of deaths. Baseline incidence doubled over that period of time, due in large part to an increase in cases among school-aged children and adolescents, groups that had been primed earlier in life with acellular vaccines.

Immunization Program

Diphtheria

Diphtheria has been rare in the US since the 1940s, when vaccines were introduced; most cases today occur in unvaccinated or inadequately vaccinated persons. However, immunization does not completely eliminate the potential for transmission because it does not prevent carriage of the organism. The consequences of inadequate population immunity were demonstrated by the massive resurgence of diphtheria in the former Soviet Union during the 1990s.[8]

Tetanus

The incidence of tetanus declined rapidly after the introduction of vaccines in the 1940s. The majority of cases today occur in persons who have not completed a 3-dose primary series. Because naturally acquired immunity to tetanus toxin does not occur, universal primary vaccination with appropriately timed boosters is the only way to protect persons in all age groups.

Pertussis

Figure 14.1 shows the evolution of pertussis immunization recommendations in the US. Several things are worth highlighting. First, the Tdap booster, introduced in 2006 for adolescents, adults, and postpartum women, became part of a "cocooning" strategy intended to protect young infants (see *Chapter 4: Vaccine Practice—Improving Delivery*). Second, periodic revaccination of adults with Tdap was initially recommended against, given the rarity of pertussis hospitalizations and deaths among older persons, the rapid waning of antibody, and a lack of data to support indirect effects from Tdap. However, in 2020, citing incremental safety data and evidence that Tdap was widely being used in place of Td, the Advisory Committee on Immunization Practices recommended either Td or Tdap for the decennial tetanus and diphtheria boosters, for tetanus prophylaxis in wound management, and for additional doses in a catch-up series for persons ≥7 years of age, including those who are pregnant. A model published in 2020 suggested that under favorable assumptions and

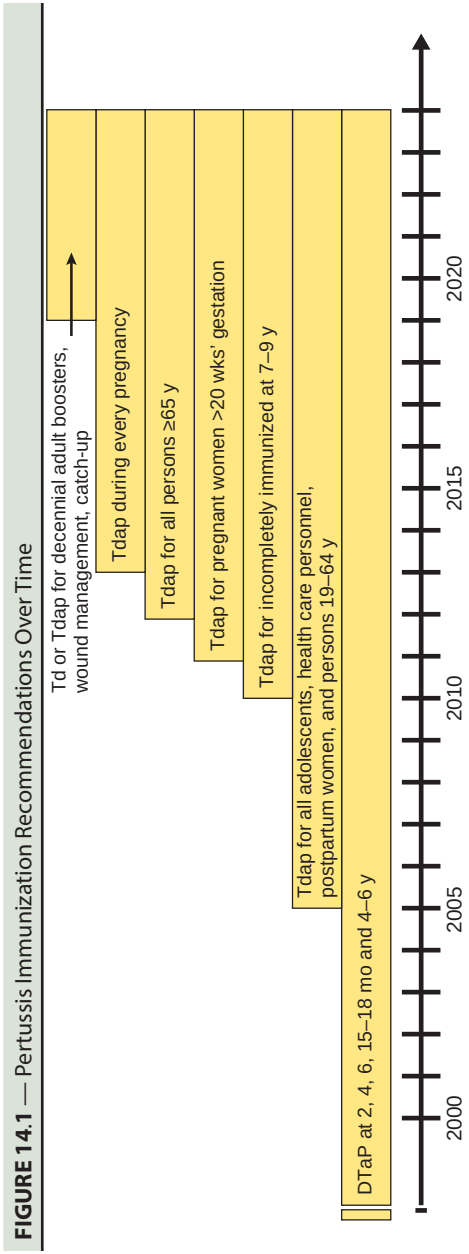

FIGURE 14.1 — Pertussis Immunization Recommendations Over Time

The figure shows major steps in the evolution of pertussis immunization recommendations in the US. Note that pertussis antigens have essentially always been combined with diphtheria and tetanus toxoids. Around 1997, DTaP replaced DTwP, which had been recommended for all infants since the 1940s.

Adapted from DTaP/Tdap/Td ACIP vaccine recommendations. Centers for Disease Control and Prevention Web site. http://cdc.gov/vaccines/hcp/acip-recs/vacc-specific/dtap.html. Accessed August 8, 2023.

excluding programmatic considerations, decennial doses of Tdap for adults becomes cost-saving when the incidence of pertussis is above 250 per 100,000 person-years.[9]

Third, because it had become apparent that cocooning was not enough to protect young infants from pertussis,[10,11] routine vaccination of pregnant women was recommended starting in 2011; the idea was that transplacental antibodies would protect the youngest infants. Updated comprehensive recommendations for prevention of diphtheria, tetanus and pertussis were released in 2018[12]; importantly, several conditions (unexplained fever ≥105°F [40.5°C], collapse or shock-like state, inconsolable crying, seizure with or without fever) were removed as precautions for DTaP. Updated recommendations for prevention of pertussis in health care personnel were published in 2011.[13]

Vaccines

Characteristics of the diphtheria, tetanus, and pertussis vaccines licensed in the US are given in **Table 14.1** and **Table 14.2**. These vaccines contain diphtheria, tetanus, and pertussis toxins that are chemically treated to render them nontoxic but still immunogenic, as well as other physically purified bacterial subunits, such as PRN, FHA, and FIM, some of which are also chemically modified.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Essentially all persons who receive a series of any of the available diphtheria or tetanus toxoid-containing vaccines achieve protective antibody levels, and one model predicts that 95% of the population remains protected for ≥30 years.[14] The acellular pertussis vaccines have not been compared directly in head-to-head clinical trials, but efficacy estimates overlap enough so as to consider the products equivalent in terms of protection.

Infanrix was tested in an Italian trial that enrolled 15,601 infants, 4481 of whom received 3 doses. Efficacy against typical pertussis (≥21 days of cough) was 84% and efficacy against milder disease (>7 days of cough) was 71%. In a German household contact study involving 22,000 children, Infanrix was 89% effective against typical pertussis and 81% effective against disease with ≥7 days of paroxysmal cough. Daptacel was tested in a Swedish trial involving 9829 infants, 2587 of whom received 3 doses. Efficacy against typical pertussis was 85%, and efficacy against milder disease (≥1 day of cough) was 78%.

Tdap vaccines were licensed on the basis of immunogenicity rather than efficacy. For each product, the antibody response to pertussis antigens after a single dose was noninferior to the analogous infant DTaP vaccine, for which efficacy had been previously demonstrated. In a randomized, double-blind trial among adolescents and adults, 1391 subjects received an acellular pertussis vaccine containing the same antigens as Boostrix and 1390 received HepA as a control.[15] Efficacy against pertussis was 92%, although there was no difference in the incidence of prolonged cough illness. In a study involving 1104 subjects, Boostrix was found to be immunogenic in persons ≥65 years of age.[16]

Reported pertussis cases began to increase after 1980. While incidence rates decreased after introduction of the Tdap booster for adolescents in 2005, they rose sharply again after 2010, corresponding directly to the aging of cohorts that had received acellular vaccines during early childhood.[17] Immunity from DTaP wanes with time; in fact, a case-control study estimated the loss of protection to be 27% per year following 5 doses of DTaP.[18] However, modeling data from Massachusetts suggest that the resurgence of pertussis was set in motion before the switch to acellular vaccines, and that current vaccines are effective in reducing circulation of the organism.[19] Immunity also wanes after Tdap in adolescents who were primed with DTaP as children.

A meta-analysis placed the efficacy of acellular pertussis vaccines at 84% and whole-cell vaccines at 94%.[20] The risk of pertussis is much lower in persons who ever received a dose of DTwP as compared to those who only received DTaP.[21] In fact, during the California outbreak of 2010 it was found that adolescents who had received 4 doses of whole-cell vaccine as infants were 6-fold less likely to get pertussis than those who had received DTaP as infants.[22] While DTwP may have been more immunogenic, the trade-off was more reactogenicity, which is what prompted the migration to acellular vaccines in the first place. Even though immunity after DTaP wanes, disease is decidedly less severe in those who were vaccinated compared to those who were not.[23]

Vaccinating pregnant women with Tdap during the third trimester protects their infants from pertussis (see *Chapter 6: Vaccination in Special Circumstances—Pregnancy, Postpartum, and Breast-Feeding*), and there is evidence that the incidence of pertussis among infants <2 months of age declined significantly after Tdap was recommended routinely during pregnancy.[24]

There is evidence that under the selective pressure of populations immunized with PRN containing vaccines, pertactin-deficient strains can emerge.[25] However, efficacy against these strains appears to be preserved.[26]

Safety

Local pain, swelling, and erythema are common after DTaP administration, reported in up to 40% of vaccinees during the primary series. The rate of local reactions is higher with Doses 4 and 5, and swelling of the entire limb, sometimes accompanied by fever,

TABLE 14.1 — Diphtheria, Tetanus, and Pertussis Vaccines[a]

Trade name	Adacel	Boostrix	Daptacel[b]	Infanrix[c]
Abbreviation	Tdap	Tdap	DTaP	DTaP
Manufacturer/distributor	Sanofi	GSK	Sanofi	GSK
Type of vaccine	Non-live, subunit, toxoid and purified	Non-live, subunit, toxoid and purified	Non-live, subunit, toxoid and purified	Non-live, subunit, toxoid and purified
Composition				
Diphtheria toxoid	2 Lf units	2.5 Lf units	15 Lf units	25 Lf units
Tetanus toxoid	5 Lf units	5 Lf units	5 Lf units	10 Lf units
Inactivated pertussis toxin	2.5 mcg	8 mcg	10 mcg	25 mcg
Filamentous hemagglutinin	5 mcg	8 mcg	5 mcg	25 mcg
Pertactin	3 mcg	2.5 mcg	3 mcg	8 mcg
Fimbriae types 2 and 3	5 mcg	—	5 mcg	—
Adjuvant	Aluminum phosphate (0.33 mg aluminum)	Aluminum hydroxide (≤0.3 mg aluminum)	Aluminum phosphate (0.33 mg aluminum)	Aluminum hydroxide (≤0.5 mg aluminum)
Preservative	None	None	None	None
Excipients and contaminants				
Formaldehyde	≤5 mcg	≤100 mcg	≤5 mcg	≤100 mcg
Glutaraldehyde	≤50 ng	—	<50 ng	—
2-phenoxyethanol	3.3 mg[d]	—	3.3 mg[d]	—
Polysorbate 80	—	≤100 mcg	—	≤100 mcg
Sodium chloride	—	4.4 mg	—	4.4 mg
Latex	None	Tip cap of prefilled syringe contains latex[e]	None	Tip cap of prefilled syringe contains latex[e]
Labeled indications	Booster immunization against diphtheria, tetanus, and pertussis	Booster immunization against diphtheria, tetanus, and pertussis	Prevention of diphtheria, tetanus, and pertussis	Prevention of diphtheria, tetanus, and pertussis
	Immunization during the third trimester of pregnancy to prevent pertussis in infants <2 mo	Immunization during the third trimester of pregnancy to prevent pertussis in infants <2 mo		
Labeled ages	10-64 y	≥10 y	6 wk-6 y	6 wk-6 y
Dose	0.5 mL	0.5 mL	0.5 mL	0.5 mL
Route of administration	Intramuscular	Intramuscular	Intramuscular	Intramuscular
Labeled schedule	1 dose	1 dose	2, 4, 6, 15-20 mo, and 4 -6 y of age	2, 4, 6, 15-20 mo, and 4-6 y of age
	A second dose may be administered ≥8 y after Dose 1	A second dose may be administered ≥9 y after Dose 1		

Continued

TABLE 14.1 — *Continued*

Trade name	Adacel	Boostrix	Daptacel[b]	Infanrix[c]
Recommended schedule (age)	11-12 y	11-12 y	2, 4, 6, 15-18 mo, and 4-6 y	2, 4, 6, 15-18 mo, and 4-6 y
	May be used for decennial boosters, wound management, and catch-up series[f]	May be used for decennial boosters, wound management, and catch-up series[f]		
How supplied (number in package)				
1-dose vial	5, 10	10	1, 5, 10	10
Prefilled syringe	5	10	—	10
Cost per dose (USD, 2023)				
Public	35.68 (pediatric) 27.91 (adult)	36.01 (pediatric) 27.21 (adult)	20.76	21.09
Private	52.41	46.08	35.75	28.02
Reference package insert	January 2023	November 2022	July 2022	November 2022

[a] Tripedia (Sanofi), which contained diphtheria and tetanus toxoids, inactivated pertussis toxin, and filamentous hemagglutinin, was discontinued in 2012.
[b] Daptacel is available in combination with Hib-T and IPV (Pentacel; Sanofi); IPV alone (Quadracel; Sanofi); and HepB, IPV, and Hib-OMP (Vaxelis; Merck and Sanofi). See *Chapter 35*: *Combination Vaccines*.
[c] Infanrix is available in combination with HepB and IPV (Pediarix; GSK) and IPV alone (Kinrix; GSK). See *Chapter 35*: *Combination Vaccines*.
[d] Not present as a preservative.
[e] The vial stopper does not contain latex.
[f] Administration of >2 doses of Boostrix or Adacel is off-label.

TABLE 14.2 — Diphtheria and Tetanus Vaccines[a]

Trade name	Tenivac	TdVax
Abbreviation	Td	Td
Manufacturer/distributor	Sanofi	MassBiologics/Grifols[b]
Type of vaccine	Non-live, subunit, toxoid	Non-live, subunit, toxoid
Composition		
Diphtheria toxoid	2 Lf units	2 Lf units
Tetanus toxoid	5 Lf units	2 Lf units
Adjuvant	Aluminum phosphate (0.33 mg aluminum)	Aluminum phosphate (≤0.53 mg aluminum)
Preservative	None	None
Excipients and contaminants		
Formaldehyde	≤5 mcg	<100 mcg
Sodium chloride	—	—
Thimerosal	—	≤0.3 mcg mercury[c]
Latex	Tip cap of prefilled syringe contains latex	None
Labeled indications	Prevention of diphtheria and tetanus	Prevention of diphtheria and tetanus
Labeled ages	≥7 y	≥7 y
Dose	0.5 mL	0.5 mL
Route of administration	Intramuscular	Intramuscular
Labeled schedule	2 doses 2 months apart; Dose 3, 6-8 mo after Dose 2	2 doses 4-8 wk apart; Dose 3, 6-12 mo after Dose 2
	Booster doses	Booster doses
Recommended schedule	Same	Same
How supplied (number in package)	1-dose vial (10)	1-dose vial (10)
	Prefilled syringe (10)	
Cost per dose (USD, 2023)		
Public	23.42 (pediatric) 21.55 (adult)	18.51 (pediatric) 17.28 (adult)
Private	39.74	27.99
Reference package insert	December 2019	September 2018

[a] Decavac (Td; Sanofi) was discontinued in 2012. Diphtheria and Tetanus Toxoids Adsorbed USP for Pediatric Use (DT; Sanofi) was discontinued in 2012. Tetanus Toxoid Adsorbed (TT; Sanofi) was discontinued in 2013. Diphtheria and Tetanus Toxoids Adsorbed (DT; Sanofi) was discontinued in 2023.
[b] Manufactured by MassBiologics (formerly Massachusetts Public Health Biologic Laboratories) and distributed by Grifols.
[c] Not present as a preservative.

has been reported. Such reactions are self-limited, resolve without sequelae, and are not contraindications to further doses.[27] Clinically significant fever is reported in <5% of DTaP recipients.

Tdap appears to be slightly more painful than Td, with local pain and/or tenderness in up to 75% of vaccinees; swelling and erythema occur in around 20% of recipients and fever occurs in <5%. In a large Vaccine Safety Datalink (VSD) study, the risk of medically attended local reactions was 2.6 per 10,000 vaccinations[28]; a subsequent VSD study that included nearly 120,000 Tdap recipients ≥65 years of age showed similar postvaccination events to those seen after Td, although there was a small increase in medically attended inflammatory or allergic events 1 to 6 days after vaccination.[29] A postmarketing study of Boostrix involving 13,427 adolescents showed no increases in medically attended neurologic, allergic, or hematologic events, and no increased risk of new onset chronic illness.[30] The reporting rate to the Vaccine Adverse Event Reporting System for serious events after Tdap is <1 per 100,000 doses distributed.[31] In a VSD study of more than 29,000 women who had previously received a tetanus-containing vaccine and then received Tdap during pregnancy, there was no association with adverse events in the mothers or infants.[32] Data from the VSD also show no increase in adverse events with repeated doses of Tdap.[33]

DTaP

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)
- Encephalopathy within 7 days of receiving a pertussis-containing vaccine (risk of recurrent encephalopathy [causality not established] and difficulty distinguishing illness from vaccine reaction)

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, and progressive encephalopathy (risk of neurologic deterioration [causality not established] and difficulty distinguishing illness from vaccine reaction)
- Personal history of Guillain-Barré syndrome (GBS) within 6 weeks of receiving a tetanus toxoid-containing vaccine (risk of recurrent GBS; family history not relevant)
- Severe local (Arthus-type) reaction to previous dose of tetanus and/or diphtheria toxoid-containing vaccine (this includes MenACWY-D) in the last 10 years (risk of recurrent reaction)

Tdap

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)
- Encephalopathy within 7 days of receiving a pertussis-containing vaccine (risk of recurrent encephalopathy [causality not established] and difficulty distinguishing illness from vaccine reaction)

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- Progressive or unstable neurologic disorder, uncontrolled seizures, or progressive encephalopathy (risk of neurologic deterioration [causality not established] and difficulty distinguishing illness from vaccine reaction)
- Personal history of GBS within 6 weeks of receiving a tetanus toxoid-containing vaccine (risk of recurrent GBS; family history not relevant)
- Severe local (Arthus-type) reaction to previous dose of tetanus and/or diphtheria toxoid-containing vaccine (this includes MenACWY-D) in the last 10 years (risk of recurrent reaction)

DT, Td

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- GBS within 6 weeks of receiving a tetanus toxoid-containing vaccine (risk of recurrent GBS; family history not relevant)
- Severe local (Arthus-type) reaction to previous dose of tetanus and/or diphtheria toxoid-containing vaccine (this includes MenACWY-D) in the last 10 years (risk of recurrent reaction)

Recommendations

All persons should be vaccinated against diphtheria, tetanus, and pertussis, and immunity should be maintained through booster immunization. The primary series of DTaP consists of doses at 2,

4, 6, and 15 to 18 months of age; Dose 4 may be given at 12 to 14 months of age if ≥6 months have elapsed since Dose 3 and the child is unlikely to return at 15 to 18 months of age. A booster dose of DTaP is given at 4 to 6 years of age (this is optional if Dose 4 was given at ≥4 years of age), and while there is a preference to use the same brand of DTaP for all 5 doses, any brand may be used if this is not feasible. Tdap is given at 11 to 12 years of age, and Td or Tdap boosters are given every 10 years throughout adulthood (administration of >2 doses of Boostrix or Adacel is off-label, as is use of Adacel in persons >64 years of age). There is no minimum interval between the last dose of DTaP, DT or Td and a dose of Tdap, and Tdap may be given at the same time as MenACWY and HPV9.

If contraindications to pertussis immunization exist, DT may be used for children and Td may be used for adolescents. However, if pertussis vaccination is deferred during the first year of life because of the possibility of an evolving neurologic condition, DT should not be given because the risk of diphtheria or tetanus is very low. By 1 year of age, if the neurologic condition is deemed to be non-progressive, the DTaP series may be initiated; if the condition is progressive, the series should be given as DT.

Tdap should be given to children 7 to 10 years of age who are not fully immunized against pertussis (5 doses of DTaP or 4 doses if the last dose was given at ≥4 years of age; use of Tdap at 7 to 9 years of age is off-label). If a dose of Tdap is received at 10 years of age, this counts as the routine dose recommended at 11 to 12 years of age. For persons 7 to 18 years of age who were not fully immunized with DTaP, Tdap should be the first dose in the catch-up series, with subsequent doses given as Td or Tdap. For adults who did not receive a primary series of diphtheria, tetanus, and pertussis immunization, Tdap should be given, followed by a dose of Td or Tdap ≥4 weeks later and another dose of Td or Tdap 6 to 12 months after the last dose. They should then receive Td or Tdap every 10 years.

Tdap should be used in place of Td for wound management for all persons ≥11 years of age if they have not previously had a dose; if they have had a previous dose of Tdap, either Td or Tdap may be used.

Children who have had well-documented pertussis (ie, laboratory confirmed, or typical symptoms and epidemiological link to a confirmed case) do not need further pertussis immunization until they reach adolescence and become eligible for Tdap. Patients who have had diphtheria or tetanus should still be immunized because natural infection does not confer immunity (the amount of toxin is too small to induce effective immune responses).

Women should receive a dose of Tdap during each pregnancy (see *Chapter 6: Vaccination in Special Circumstances—Pregnancy, Postpartum, and Breast-Feeding*). The preferred timing is early in the period from 27 to 36 weeks' gestation (this may coincide with other

procedures during pregnancy, such as the oral glucose tolerance test). Postpartum women who have never received Tdap should receive a dose before discharge from the hospital. Doses of Tdap given during or shortly after pregnancy "reset the clock" for the next decennial dose of Td or Tdap. Tdap should be used in pregnant women if tetanus immunization is indicated for wound management. Pregnant women who need primary immunization against tetanus should receive 3 doses of a tetanus and diphtheria toxoid-containing vaccine on a schedule of 0, 4 weeks, and 6 to 12 months; Tdap should replace at least one dose of Td, preferably early between 27- and 36-weeks' gestation, but Tdap may also be used for all doses in the catch-up series.

The use of tetanus toxoid-containing vaccines and TIG for wound management is summarized in **Table 14.3**.

TABLE 14.3 — Tetanus Prophylaxis in Wound Management

Tetanus Toxoid Vaccine	Age (y)	Last Dose	Clean, Minor Wounds		Tetanus-Prone Wounds[a]	
			Vaccine	TIG[b]	Vaccine	TIG[b]
Primary series complete[c]	≤6[d]	<5 y ago	None	No	None	No
		≥5 y ago	DTaP[e,f]	No	DTaP[f]	No
	7-10	<5 y ago	None[g]	No	None[g]	No
		≥5 y ago	None[g]	No	Tdap or Td[h]	No
	≥11	<5 y ago	None[g]	No	None[g]	No
		≥5 y ago	None[g]	No	Tdap or Td[g]	No
Unimmunized, unknown, or incomplete	≤6[d]	Not relevant	DTaP[e,f]	No	DTaP[f]	Yes
	7-10		Tdap or Td[h]	No	Tdap or Td[h]	Yes
	≥11		Tdap or Td[g]	No	Tdap or Td[g]	Yes

TIG, tetanus immune globulin

[a] Includes puncture, avulsion, crush, necrotic, and burn wounds; frostbite; and wounds contaminated with dirt, feces, soil, or saliva. Wounds should be cleaned, necrotic tissue debrided, and foreign material removed.

[b] TIG (HyperTET [Grifols]) is used for postexposure tetanus prophylaxis. It consists of IgG derived from pooled plasma of human donors who have been immunized with tetanus toxoid; TIG is therefore polyclonal (contains a variety of antibodies, including antibodies to other organisms). Various procedures are used to purify the immune globulin and reduce the potential for transmission of blood-borne pathogens, and the product is formulated for intramuscular administration. Patients with selective IgA deficiency may be at increased risk for anaphylactic reactions to TIG because it may contain minute amounts of IgA. The dose of TIG is 250 units given intramuscularly. Immune globulin intravenous can be used if TIG is not available. Equine tetanus antitoxin is not available in the US. Vaccine and TIG should be given at separate sites.

[c] The primary series is considered complete if the patient has received ≥3 doses of an adsorbed (not fluid) tetanus toxoid. A healthy person who has received a valid primary series of tetanus-containing vaccines never needs TIG in wound management, no matter what type of wound is sustained, no matter how long the interval has been since the last vaccination, and regardless of whether or not the person has received tetanus boosters in the past. HIV-infected persons should be considered *unimmunized* even if they have received the vaccine series; therefore, they should be vaccinated and given TIG for tetanus-prone wounds, regardless of immunization history.

[d] For infants <6 months of age who have not received the 3-dose primary series, decisions about the use of TIG are based on the mother's vaccination history and the gestational age at birth. So, for example, a 3-month-old term infant with a tetanus-prone wound whose mother had a complete primary series plus a booster dose in the last year does not need TIG—he should have received plenty of protective antibody before birth (transplacental transfer of maternal IgG to the fetus occurs in the third trimester). On the other hand, if the same baby was born prematurely (<32 weeks' gestation), he might not have received enough transplacental antibody to protect him, and TIG would be indicated. Likewise, if the mother received a primary series many years ago but no booster, the baby would need TIG, even if he was born at term—in this scenario, whereas the *mother* would not need TIG for a tetanus-prone wound (see *Footnote c*), the *baby* would (he may have been born with little transplacental antibody and he himself has no memory B-cells specific for tetanus).

[e] A booster dose of DTaP is routinely indicated for all children at 4-6 y, so a dose should be given to children who have not received a routine booster, even for clean, minor wounds (vaccination here is for catch-up, not wound management).

[f] Use DT if pertussis immunization is contraindicated.

[g] In situations where tetanus vaccination is not necessary for wound management, Tdap should be given anyway if otherwise indicated. For example, a child 7-10 y whose pertussis immunization is incomplete should receive Tdap, even if tetanus immunization is not indicated (use of Tdap at 7-9 y is off-label). Another example would be any adolescent or adult who has not yet received a dose of Tdap. If a patient ≥11 years of age qualifies for tetanus vaccination for wound management and Tdap has never been given, it should be used instead of Td. If Tdap has previously been given, Td or Tdap may be used, and if pertussis immunization is contraindicated, Td should be used. Use of Adacel at >64 years of age is off-label.

[h] Tdap should be used at 7-10 y if pertussis immunization is incomplete (use of Tdap at 7-9 y is off-label). Otherwise, Td is preferred (only adsorbed products are indicated).

Adapted from Liang JL, et al. *MMWR*. 2018;67(RR-2):1-44.

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Ebola

The Pathogen

Ebola virus (EBOV) is an enveloped, single-stranded RNA virus in the Filoviridae family (technically, the abbreviation "EBOV" refers to the species *Zaire ebolavirus)*.[1] The viral particle has a characteristic filamentous appearance, the surface of which is studded with a transmembrane glycoprotein (GP) that mediates viral entry by binding to a variety of host cell receptors. Once internalized through macropinocytosis, GP is cleaved, allowing binding to NPC intracellular cholesterol transporter 1 (Neimann-Pick C1 receptor); this initiates membrane fusion and entry of the viral genome into the cytosol, where transcription, translation, and virion assembly take place. Antibodies to GP are neutralizing. Mononuclear phagocytes and dendritic cells are primary targets and allow for dissemination to regional lymph nodes, liver, and spleen.[2] Infected, activated macrophages secrete pro-inflammatory cytokines that recruit additional susceptible cells the site of infection and lead to breakdown of the endothelial barrier; the resultant third-spacing contributes to hypovolemic shock caused by fluid losses. EBOV encodes a variety of factors that suppress the antiviral immune response. Disease progression is characterized by lymphocyte depletion, cytokine dysregulation, disseminated intravascular coagulation, and multiple organ dysfunction. After recovery, the virus can persist in immunologically privileged compartments (eg, central nervous system, eye, urogenital system, placenta and possibly breast milk) for months, and in some cases, years.

Clinical Features

The incubation period is 2 to 21 days.[3] Illness begins abruptly and is initially nonspecific, evolving from "dry symptoms" like fever, headache, myalgia, and arthralgia to "wet symptoms" like nausea, vomiting, and diarrhea (**Table 15.1**). EBOV is one of the most lethal viral infections known, with an overall case-fatality rate of 40% to 50%. Survivors may have persistent symptoms like headache, arthralgia, myalgia, memory loss and fatigue lasting for months or years,[4] and mortality risk is increased 5-fold during the first year after the acute illness.[5]

TABLE 15.1 — Clinical Stages of Ebola Virus Disease

Early Febrile or Mild Stage	Gastrointestinal Stage	Complicated Stage
Days 0-3	Days 3-10	Days 7-12
High fever, weakness, lethargy, malaise, myalgia	Early-stage symptoms plus diarrhea and/or vomiting or abdominal pain	Gastrointestinal stage symptoms plus hemorrhage, shock, organ failure, and neurological complications
Ambulatory and able to compensate for fluid losses	Difficulty compensating for fluid losses (which may reach 5-10 L/d) because of emesis or large volume losses	Critically ill, hypovolemic shock, confusion, seizures, delirium, systemic inflammatory response, hemorrhagic events
Anemia, leukopenia, thrombocytopenia		Elevated creatine phosphokinase
Decreased renal function		Elevated amylase
Hypokalemia, hyponatremia, hypocalcemia		Coagulopathy
Elevated hepatic transaminases		Metabolic acidosis

Adapted from Malvy D, et al. *Lancet*. 2019;393:936-948.

Epidemiology and Transmission

EBOV was first identified in 1976 in the Democratic Republic of the Congo (then called Zaire). It was considered an exotic, circumspect pathogen until 2013 to 2016, when an unprecedented outbreak occurred in West Africa, ultimately involving nearly 29,000 infections and >11,000 deaths. It is thought that every case in this outbreak could be traced back to a single zoonotic transmission in Guinea, with subsequent person-to-person transmission.[6] Circumspect outbreaks occurred in the Democratic Republic of the Congo until 2018, when a sustained outbreak began; by 2020, there had been a total of >3300 cases.[7] Only 11 cases were known to have been treated in the US during the West African outbreak; 9 had acquired the disease in West Africa and 2 were health care personnel (HCP) who had cared for an imported case in the US.

The natural reservoir of EBOV is unknown, although bats are suspected because they are tolerant of infection; most other species, including humans, non-human primates, and other large mammals develop disease and are dead-end hosts.[8] Outbreaks are thought to arise from singular spillover events that occur by unknown means, after which human-to-human transmission occurs via direct contact with body fluids or infected tissues (EBOV has been detected in almost every body fluid). Certain activities are particularly high-risk, including handling dead bodies during funeral rituals and caring for the sick. Sexual transmission has been reported. EBOV is highly contagious—even 1 plaque-forming unit is capable of causing disease in animal models.[9] The basic reproduction number (R_0) (see *Chapter 1: Introduction to Vaccinology—Epidemiological Concepts*) during the West African outbreak was estimated at 2.0,[10] but simple infection control measures such as isolation and safe burial practices ultimately lowered this substantially and controlled the outbreak. Infected persons are not contagious during the asymptomatic incubation period, and transmission via aerosol, droplets, food, water, and fomites are not thought to contribute significantly to community spread.[11]

Immunization Program

Ervebo was licensed in 2019; recommendations for use were published in 2021[12] and updated in 2022.[13]

Vaccines

Characteristics of the Ebola vaccine licensed in the US are given in **Table 15.2**. This consists of vesicular stomatitis virus (an arbovirus that infects cattle, horses and pigs and is naturally attenuated for humans) in which the gene encoding the native envelope glycoprotein is substituted with the gene encoding the envelope GP of EBOV.[14] The substitution further attenuates the virus but maintains replication competence. The recombinant virus is genetically stable and expresses GP on its surface in the native conformation. The likelihood of reversion to virulence, recombination events, person-to-person transmission, and transmission by hematophagous insects is considered to be extremely low.[15]

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Ervebo was tested in a two-part, open-label, cluster-randomized, controlled ring vaccination trial in Guinea in 2015, during the West African outbreak. New cases were identified and confirmed as part of a national surveillance system. Clusters of contacts, including contacts of contacts, were defined and those who were ≥18 years of age were randomized 1:1 to immediate vaccination or vaccination 21 days later.[16] At the time of a planned interim analysis, 48 clusters (4123 people) had been assigned to immediate vaccination and 42 clusters (3528 people) to delayed vaccination. No cases of disease occurred ≥10 days after vaccination among eligible and vaccinated subjects in the immediate vaccination group, whereas 16 cases

TABLE 15.2 — Ebola Vaccine

Trade name	Ervebo
Abbreviation	rVSVΔG-ZEBOV-GP[a]
Manufacturer/distributor	Merck[b]
Type of vaccine	Live, attenuated, engineered
Composition	Vesicular stomatitis virus (Indiana strain) with the native envelope glycoprotein gene substituted by the envelope glycoprotein gene from *Zaire ebolavirus* (Kikwit 1995 strain)
	Propagated in Vero (African green monkey kidney) cells
	≥72 million plaque forming units
Adjuvant	None
Preservative	None
Excipients and contaminants	Tromethamine (Tris) (10 mM)
	Rice-derived recombinant human serum albumin (2.5 mg)
	Residual host cell DNA (≤10 ng)
	Benzonase (≤15 ng)
	Rice protein (trace)
Latex	None
Labeled indications	Prevention of disease caused by *Zaire ebolavirus*
Labeled ages	≥1 y
Dose	1 mL
Route of administration	Intramuscular
Labeled schedule	1 dose
Recommended schedule	Same
How supplied (number in package)	1-dose vial (10)
Cost per dose (USD, 2023)[c]	
Public	—
Private	—
Reference package insert	July 2023

Continued

TABLE 15.2 — *Continued*

[a] rVSVΔG-ZEBOV-GP stands for "recombinant vesicular stomatitis virus, (envelope) G-glycoprotein deleted-Zaire (strain) Ebola virus (envelope) GP-glycoprotein (expressing)".

[b] The original vaccine construct was developed by the Public Health Agency of Canada, licensed to NewLink Genetics (now part of Lumos Pharma), then sublicensed to Merck.

[c] The vaccine is not commercially available but is supplied to civilians at no cost through the US government. For information on how to obtain the vaccine, contact Viral Special Pathogens Branch of the Centers for Disease Control and Prevention (spathvax@cdc.gov).

occurred among eligible subjects in the delayed group, for a vaccine efficacy of 100%. Effectiveness at the cluster level (including all eligible and non-eligible persons) was estimated at 76%. The delayed arm was discontinued after the interim analysis, and final results were published in 2017.[17] In total, there were 117 contact clusters; no cases of Ebola virus disease (EVD) occurred ≥10 days after vaccination among immediately vaccinated subjects (N=3775) compared to 23 cases among those eligible for delayed vaccination or eligible for immediate vaccination but not vaccinated (N=4507). Vaccine efficacy was estimated to be 100%.

In a study conducted in Guinea, Liberia, Mali, and Sierra Leone in 2018, Ervebo was shown to be safe in children and to elicit higher antibody responses than those in adults.[18]

Safety

Over 15,000 adults received Ervebo during the clinical development program. In an early controlled clinical trial, a total of 1051 adults received Ervebo; the rate of injection site pain was 70%, swelling 17%, and redness 12%. Across all age groups in the 2015 study in Guinea, the most common adverse events were headache (25%), fatigue (19%), and muscle pain (13%). The vast majority of adverse events were judged to be mild or moderate, and only two serious adverse events (a febrile reaction and a case of anaphylaxis) were thought to be vaccine-related. Across six randomized trials, the incidence of arthralgia was 17%[19]; severe arthralgia was rarely reported. Vaccine virus RNA has been detected in blood, urine, saliva, synovial fluid, and skin vesicles after vaccination, but data on transmissibility of vaccine virus to others are not available.

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component, including rice protein (risk of recurrent allergic reaction)

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)

- Immunodeficiency or immunosuppression (risk of disease caused by live virus should be weighed against the risk of EVD)
- Pregnancy (theoretical risk to the fetus of live-virus vaccine or attribution of birth defects to vaccination should be weighed against the risk of EVD)
- Breast-feeding (risk of disease caused by live virus should be weighed against the risk of EVD)
- Measures to minimize transmission from vaccine recipients
  - Do not donate blood for 6 weeks
  - Avoid sharing needles, razors, eating utensils, toothbrushes; drinking from the same cup; and open-mouth kissing for 2 weeks (if oral sores develop, avoid these activities until the sores heal)
  - Use barrier protection for 2 months during any sexual encounter
  - Consider avoiding close association with high-risk persons (immunocompromised persons, pregnant or breast-feeding women, and children <1 year of age) for 6 weeks if exposure to blood and bodily fluids is possible
  - Avoid exposure of livestock to blood and body fluids for 6 weeks
  - Cover rashes with a bandage until healed (place contaminated bandages in a sealed plastic bag and dispose of in the trash; wash hands with soap and water)

Recommendations

Pre-exposure vaccination is recommended for persons ≥18 years of age in the following categories:

- Those responding to an EVD outbreak
- HCP at federally designated Ebola treatment centers
- Workers at biosafety level 4 facilities
- HCP involved in the care and transport of patients with suspected or confirmed EVD at special pathogens treatment centers (formerly known as state-designated Ebola treatment centers)
- Laboratorians and support staff at Laboratory Response Network facilities that handle specimens that might contain replication-competent EBOV (species *Zaire ebolavirus)*

In July 2023, the age indication for Ervebo was extended down to 1 year, but as of August 2023 recommendations for use of Ervebo in children had not yet been issued.

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Haemophilus influenzae type b

The Pathogen

H influenzae type b is an aerobic gram-negative bacterium that appears as pleomorphic coccobacilli on Gram stain. The organism produces a polysaccharide capsule (polyribosylribitol phosphate [PRP]) that contributes to virulence by inhibiting complement-mediated lysis and phagocytosis; antibodies to PRP are protective. Colonization of the nasopharynx is facilitated by factors that mediate adherence to respiratory epithelium and interfere with ciliary clearance, as well as immune evasion mechanisms such as IgA1 protease. Disease results from bacteremia and spread to distant sites like the meninges.

Clinical Features

The most common forms of invasive *H influenzae* type b disease are *meningitis, bacteremia, epiglottitis, pneumonia, arthritis, periorbital cellulitis,* and *buccal cellulitis.* Meningitis was the most common clinical manifestation in the prevaccine era, accounting for 50% to 65% of cases. Hallmark presenting features include fever, altered mental status, and stiff neck. The mortality rate is 2% to 5%, even with appropriate antimicrobial therapy, and neurologic sequelae occur in 15% to 30% of survivors. Osteomyelitis and pericarditis are less common. Infection with nontypeable (nonencapsulated) strains of *H influenzae*, commonly associated with otitis media and acute bronchitis, is not prevented by currently available vaccines.

Epidemiology and Transmission

Humans are the only natural hosts and transmission occurs by direct person-to-person contact or via respiratory droplets. The organism does not survive on fomites. Asymptomatic nasopharyngeal colonization was seen in 2% to 5% of children in the prevaccine era, but widespread use of Hib has resulted in much lower colonization rates. Invasive disease now is rare. *H influenzae* type b disease was more frequent in boys, African-Americans, Alaska Eskimos, Apache and Navajo Indians, child-care center attendees, children living in overcrowded conditions, and children who were not breast-fed. Sickle cell disease,

asplenia, HIV infection, certain immunodeficiency syndromes, and malignant neoplasms may predispose to invasive infection.

Immunization Program

Prior to the introduction of routine childhood immunization, *H influenzae* type b was a major cause of invasive bacterial infection in the US, with an estimated 12,000 cases of meningitis and 8000 other invasive syndromes annually. One out of every 200 children in the first 5 years of life developed invasive *H influenzae* type b infection, with peak incidence in infants 6 to 12 months of age. Disease rates were even higher in certain populations.

Universal infant immunization was introduced in 1991,[1] and comprehensive recommendations for Hib were published in 1993[2] and 2014.[3]

Vaccines

Characteristics of the Hib vaccines licensed in the US are given in **Table 16.1**. Each of these is a protein-polysaccharide conjugate made much the same way as MenACWY and PCV.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Efficacy of PedvaxHIB (Hib-OMP) was first demonstrated in Navajo infants. After a primary regimen given at 2 and 4 months of age, 91% of infants had anti-PRP antibody levels >0.15 mcg/mL (the so-called *short-term* correlate of protection) and 60% had levels >1 mcg/mL (the so-called *long-term* correlate of protection) (see *Chapter 1: Introduction to Vaccinology—Correlates of Protection*). Efficacy at 15 to 18 months of age was 93%. In infants drawn from the general US population who received the 2-dose primary series, 97% achieved anti-PRP antibody levels >0.15 mcg/mL and 80%, >1 mcg/mL; the proportions after a booster at 12 to 15 months were 99% and 95%, respectively. Hib-OMP is the only vaccine that induces significant antibody levels after a single injection in infants <6 months of age.

Licensure of ActHIB (Hib-T) was based on immunogenicity that was comparable to that of the other licensed products. Overall, about 90% of infants achieve anti-PRP antibody levels of ≥1 mcg/mL after the primary series of 3 doses, and 98% achieve this level after a booster dose.

Hiberix (Hib-T) had been used outside the US since 1996. Immunogenicity studies conducted in Germany and Canada involving slightly over 200 subjects led to US licensure for the booster dose in 2009. Hiberix was approved in 2016 for the primary series at 2, 4, and 6 months of age based on a multicenter study in the US

involving over 4000 infants, wherein noninferiority to ActHIB was demonstrated for the ≥0.15 mcg/mL (but not for the ≥1.0 mcg/mL) anti-PRP antibody endpoint.[4] In another study, 3 doses of Hiberix resulted in higher antibody levels than 3 doses of DTaP-IPV/Hib.

The incidence of invasive disease in infants and young children declined by >99% after the introduction of universal immunization in 1991. This was partly due to the ability of conjugate vaccines to reduce nasopharyngeal carriage, which led to reduced rates of exposure and infection (this is an example of herd immunity; see *Chapter 1: Introduction to Vaccinology—Epidemiological Concepts*). Today, invasive *H influenzae* type b disease, when it does occur, usually involves infants too young to have completed the primary series or children who were intentionally not immunized.[5]

Safety

Local reactions such as redness, swelling, and pain occur in 5% to 30% of recipients, but typically are mild and last <24 hours. Systemic reactions, such as high fever and irritability, are infrequent. A review of almost 30,000 cases reported to the Vaccine Adverse Event Reporting System from 1990 to 2013 failed to identify any unexpected safety concerns.[6]

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)
- Age <6 weeks (risk of induction of immune tolerance)

Precaution

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)

Recommendations

All infants should be vaccinated against *H influenzae* type b. The primary series for ActHIB and Hiberix consists of doses at 2, 4, and 6 months of age. The primary series for PedvaxHIB consists of doses at 2 and 4 months of age (PedvaxHIB is preferred for the primary series in American Indians and Alaska Natives because it provides earlier protection; this preference does not extend to Vaxelis, the Hib-OMP–containing combination vaccine). A booster dose using any product is given at 12 to 15 months of age. Previously unimmunized children 15 to 59 months of age should receive a single dose of any Hib product. Catch-up is not recommended for unimmunized persons >5 years of age who are not at high risk. Unimmunized (defined as no infant series plus booster and no dose after 14 months of age) *children* with functional or anatomic asple-

TABLE 16.1 — *H influenzae* type b Vaccines[a]

Trade name	ActHIB[b,c]	PedvaxHIB[b,d]	Hiberix[b,e]
Abbreviation	Hib-T	Hib-OMP	Hib-T
Manufacturer/distributor	Sanofi	Merck	GSK
Type of vaccine	Non-live, subunit, engineered	Non-live, subunit, engineered	Non-live, subunit, engineered
Composition	Polyribosylribitol phosphate (10 mcg) conjugated to tetanus toxoid (24 mcg)	Polyribosylribitol phosphate (7.5 mcg) conjugated to *N meningitidis* serogroup B (strain B11) outer membrane protein (125 mcg)	Polyribosylribitol phosphate (10 mcg) conjugated to tetanus toxoid (25 mcg)
Adjuvant	None	Aluminum hydroxyphosphate sulfate (0.225 mg aluminum)	None
Preservative	None	None	None
Excipients and contaminants	Sucrose (8.5%)	Sodium chloride (0.9%)	Lactose (12.6 mg)
	Residual formaldehyde (<0.5 mcg)		Residual formaldehyde (≤0.5 mcg)
	Sodium chloride (diluent; 0.4%)		Sodium chloride (diluent; 0.9%)
Latex	None	Vial stopper contains latex	None
Labeled indications	Prevention of invasive *H influenzae* type b disease	Prevention of invasive *H influenzae* type b disease	Prevention of invasive *H influenzae* type b disease
Labeled ages	2 mo-5 y	2 mo-5 y	6 wk-4 y
Dose	0.5 mL	0.5 mL	0.5 mL
Route of administration	Intramuscular	Intramuscular	Intramuscular
Labeled schedule (age)	2, 4, 6, and 15-18 mo	2, 4, and 12-15 mo[f]	2, 4, 6, and 15-18 mo
Recommended schedule (age)	2, 4, 6, and 12-15 mo	Same	2, 4, 6, and 12-15 mo
How supplied (number in package)	1-dose vial (5), lyophilized, with diluent	1-dose vial (10)	1-dose vial (10), lyophilized, with diluent
Cost per dose (USD, 2023)			
Public	10.78	15.66	10.76
Private	18.94	28.87	12.45
Reference package insert	October 2022	April 2023	May 2019

[a] ProHIBit (Hib-D; Connaught), HibTITER (Hib-CRM; Wyeth), and TriHIBit (Hib-T/DTaP; Sanofi) are no longer available.
[b] ActHIB, Hiberix, and PedvaxHIB are considered interchangeable. However, if either the 2-mo or 4-mo dose is given as ActHIB or Hiberix, a dose of either product must be given at 6 mo. If the first 2 doses are PedvaxHIB, the 6-mo dose is omitted.
[c] ActHIB is available in combination with DTaP and IPV (Pentacel; Sanofi). See *Chapter 35*: *Combination Vaccines*.
[d] Hib-OMP is available in combination with DTaP, HepB, and IPV (Vaxelis; Merck and Sanofi). See *Chapter 35*: *Combination Vaccines*. Hib-OMP in combination with HepB (Comvax; Merck) was discontinued in 2014.
[e] Hib-T in combination with *N meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine (HibMenCY-T [MenHibrix]; GSK) is no longer manufactured.
[f] The primary series for Hib-OMP consists of only 2 doses.

nia (including sickle cell disease and splenectomy), HIV infection, immunoglobulin deficiency (including IgG2 subclass deficiency), early complement component deficiency, and immunosuppression from cancer chemotherapy or radiation should receive one dose of Hib (use of ActHIB and PedvaxHIB >5 years of age, and use of Hiberix >4 years of age, is off-label). Unimmunized (same definition as above) *adults* with functional or anatomic asplenia, including those anticipating splenectomy, should receive one dose of Hib. Children and adults who have had hematopoietic cell transplantation should be reimmunized (**Table 6.3**).

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Hepatitis A

The Pathogen

Hepatitis A virus (HAV) is a small, nonenveloped, single-stranded RNA virus in the Picornaviridae family. There is only one known serotype. Initial infection occurs in the pharynx and lower gastrointestinal tract, with hematogenous spread to the liver, where the virus replicates in hepatocytes and Kupffer cells (resident macrophages). It is believed that most of the injury to the liver is immune mediated rather than the direct result of viral replication. Virus is excreted in the bile and ultimately shed in the stool. Unlike hepatitis B virus, HAV does not establish chronic infection and does not cause chronic liver disease.

Clinical Features

Ninety percent of children <5 years of age with HAV infection are asymptomatic, whereas 90% of adults experience symptoms. The incubation period ranges from 15 to 50 days. Onset is usually abrupt, with low-grade fever, myalgia, poor appetite, nausea, vomiting, malaise, and fatigue, followed by dark-colored urine, scleral icterus, pale stools, jaundice, and weight loss. Diarrhea is more common in children. Hepatomegaly, right upper quadrant tenderness, and occasionally splenomegaly or rash may be present. Symptoms generally subside within 3 to 4 weeks, although 10% to 15% of patients experience prolonged or relapsing disease for up to 6 months. Fulminant hepatitis is rare. Extrahepatic manifestations include arthralgia, pruritus, cutaneous vasculitis, cryoglobulinemia, hemophagocytic syndrome, and Guillain-Barré syndrome.

Epidemiology and Transmission

Humans are the only natural hosts and transmission occurs by the fecal-oral route. Peak infectivity occurs during the 2-week period before the onset of jaundice, and infants and children can shed the virus for several months. Since infants and young children often have clinically silent infection and exposure to their feces may be unavoidable, they are often the source of infection for adults in households or day care centers. Contaminated water and undercooked food (especially shellfish) are also common sources of transmission—often a food handler

somewhere up the line is infected.[1] Transient viremia in a donor occasionally leads to transmission through transfusion of blood products.

Hepatitis A is most prevalent in Southeast Asia, Africa, and Latin America. In countries with high endemicity, the infection is usually acquired in childhood, whereas in developed countries many adults have not yet been exposed. Childhood disease often correlates with overcrowding, poor sanitation, limited access to clean water, and inadequate sewage systems. Prior to the institution of a universal immunization program in the US, the incidence of *disease* was highest among children 5 to 14 years of age, but the incidence of *infection* was highest in those <4 years of age. Infection was more common among American Indians, Alaska Natives, and Hispanics. Disease rates were substantially higher in the western US; between 1987 and 1997, half of all cases occurred in 11 states west of the Mississippi. The majority of patients in the US in 2007 had no known risk factor for hepatitis A.[2] The most important *known* risk factor was international travel (18% of cases)[3]; other risk factors were contact with a case (17%), food- or water-borne outbreaks (7%), male homosexual activity (6%), contact with a day care employee or attendee (45%), employment or attendance at a day care center (4%), and injection drug use (1%). The epidemiology of hepatitis A began to change in 2016, such that by 2020 the most important risk factors were drug use and homelessness. Nearly 40,000 outbreak-associated cases occurred between 2016 and 2020, with approximately 400 deaths.[4]

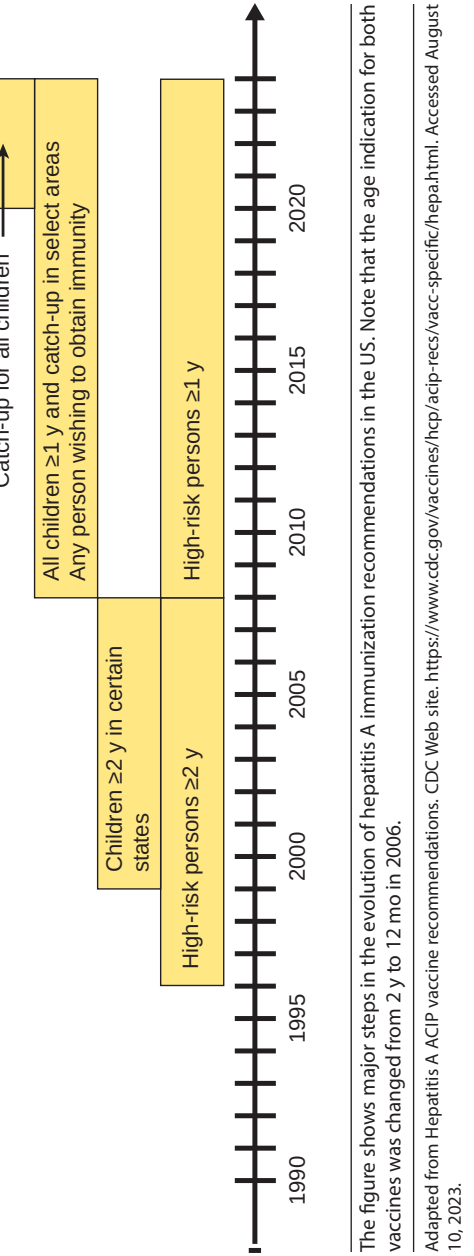
Immunization Program

Figure 17.1 shows the evolution of hepatitis A immunization recommendations in the US (comprehensive recommendations were published in 2020[5]). Notable incremental steps not depicted in the figure include recommendations for control of hepatitis A in correctional facilities in 2003[6]; updates on postexposure prophylaxis and international travel in 2007[7] and 2018[8]; and vaccination of contacts of international adoptees in 2009[9]. Vaccination of children, a foundational aspect of the program, led to dramatic declines in disease in all age groups, demonstrating the remarkable ability of childhood immunization to prevent disease in an entire population (see *Chapter 1: Introduction to Vaccinology—Epidemiological Concepts*). Herd immunity effects more than doubled the cost savings of the immunization program when compared with direct effects alone.[10]

Vaccines

Characteristics of the hepatitis A vaccines licensed in the US are given in **Table 17.1**. These are non-live, whole-virus vaccines, made much the same way as the Salk polio vaccine.

FIGURE 17.1 — HepA Immunization Recommendations Over Time



The figure shows major steps in the evolution of hepatitis A immunization recommendations in the US. Note that the age indication for both vaccines was changed from 2 y to 12 mo in 2006.

Adapted from Hepatitis A ACIP vaccine recommendations. CDC Web site. https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepa.html. Accessed August 10, 2023.

TABLE 17.1— Hepatitis A Vaccines

Trade name	Havrix[a]	Vaqta
Abbreviation	HepA	HepA
Manufacturer/ distributor	GSK	Merck
Type of vaccine	Non-live, whole agent	Non-live, whole agent
Composition[b]		
Virus strain	HM175	CR326F
Propagation	Human diploid (MRC-5) cells	Human diploid (MRC-5) cells
Inactivation	Formalin	Formalin
Antigen content		
Pediatric/ adolescent formulation	720 ELISA units/0.5 mL	25 U/0.5 mL
Adult formulation	1440 ELISA units/mL	50 U/mL
Adjuvant	Aluminum hydroxide (0.25 mg/0.5 mL aluminum)	Aluminum hydroxyphosphate sulfate (0.225 mg/0.5 mL aluminum)
Preservative	None	None
Excipients and contaminants	Amino acid supplement (0.3%)	Formaldehyde (<0.8 mcg/mL)
	Phosphate-buffered saline	Nonviral protein (<0.1 mcg/mL)
	Polysorbate 20 (0.05 mg/mL)	DNA ($<4 \times 10^{-6}$ mcg/mL)
	Residual MRC-5 cellular proteins (≤5 mcg/mL)	Bovine albumin ($<10^{-4}$ mcg/mL)
	Formalin (≤0.1 mg/mL)	Sodium borate (70 mcg/mL)
	Neomycin (≤40 ng/mL)	Sodium chloride (0.9%)
		Neomycin (<10 parts per billion)

Continued

TABLE 17.1 — *Continued*

Trade name	Havrix[a]	Vaqta
Latex	Tip cap of prefilled syringe contains latex	Vial stopper and tip cap and plunger of prefilled syringe contain latex
Labeled indications	Prevention of hepatitis A	Prevention of hepatitis A
Labeled ages	≥12 mo	≥12 mo
Dose[c]		
Pediatric (1-18 y)	0.5 mL	0.5 mL
Adult (≥19 y)	1.0 mL	1.0 mL
Route of administration	Intramuscular	Intramuscular
Labeled schedule	Doses at 0 and 6-12 mo	Doses at 0 and 6-18 mo
Recommended schedule (age)	12-18 and 19-23 mo	12-18 and 19-23 mo
	Catch-up, high-risk	Catch-up, high-risk
How supplied (number in package)		
Pediatric/ adolescent formulation	Prefilled syringe (10)	1-dose vial (10)
		Prefilled syringe (10)
Adult formulation	Prefilled syringe (10)	1-dose vial (1, 10)
		Prefilled syringe (10)
Cost per dose (USD, 2023)		
Public	23.00 (pediatric) 38.57 (adult)	23.30 (pediatric) 38.17 (adult)
Private	36.92 (pediatric) 79.71 (adult)	36.66 (pediatric) 76.69 (adult)
Reference package insert	September 2022	April 2023

[a] Havrix is also available in combination with HepB (Twinrix; GSK).
[b] The units used to measure antigen content for these vaccines are different and cannot be directly compared.
[c] The patient's age at the time of the dose determines which formulation is used.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Nearly 100% of persons who receive 2 doses of HepA achieve protective levels of antibody. Seroconversion rates within 1 month of the first dose exceed 95%. Long-term follow-up and mathematical modeling predict that ≥90% of adult vaccinees will still be seropositive 40 years after vaccination.[11]

The efficacy of Havrix was evaluated in a study of 40,119 school children in Thailand aged 1 to 16 years. Two doses of vaccine (360 ELISA units each) or placebo were administered 1 month apart, and efficacy was estimated at 94%. In children 2 to 19 years of age, 1 dose (720 ELISA units) resulted in seroconversion rates of 96.8% to 100%, and 2 doses given 6 months apart resulted in seroconversion rates of 100%. In adult studies, 1 dose (1440 ELISA units) resulted in seroconversion rates of >96%, and 100% were seropositive 1 month after a booster dose. In children immunized with 2 doses 6 months apart beginning at 11 to 13 months of age, the vaccine response rate was 99%.

The efficacy of Vaqta was evaluated in a study of 1037 healthy seronegative children 2 to 16 years of age in Monroe County, New York, a small community with a historically high infection rate.[12] A single dose of vaccine (25 units) or placebo was administered. Beyond the immediate postvaccination period, there were no cases of hepatitis A in the vaccine group and 21 confirmed cases in the placebo group, for an efficacy of 100%. After this study, a subset of vaccinees received a booster dose of vaccine. No cases of hepatitis A occurred among these individuals during 9 years of follow-up.[13] In Butte County, California, a mass immunization campaign in children 2 to 12 years of age between 1995 and 2000 resulted in a 93.5% decline in cases in the entire county population.[14] In studies of children 12 to 23 months of age, seroconversion rates were 96% and 100%, respectively, for 1 or 2 doses of Vaqta (25 units). In studies of children 2 to 18 years of age, seroconversion rates were 97% and 100%, respectively, for 1 or 2 doses (25 units), and in adult studies, seroconversion rates were 95% and 99.9%, respectively, for 1 or 2 doses (50 units). A randomized, double-blind trial published in 2007[15] and experience from other countries suggest that postexposure vaccination also is effective.

In the prevaccine era, the annual incidence of reported cases of hepatitis A in the United Sates was as high as 14.5 per 100,000 (the incidence of hepatitis A infection was probably 10-times higher). By 2011, the reported incidence had fallen to 0.4 per 100,000,[16] but by 2019 the incidence was up to 5.7 per 100,000, mostly caused by person-to-person outbreaks among persons who use drugs and those experiencing homelessness.[17] During 2007 to 2016, almost three-quarters of US adults remained susceptible to hepatitis A.[18]

Safety

Reactions are usually mild and subside within 24 hours. Injection-site reactions, including erythema, swelling, pain, or tenderness, occur in 20% to 50% of patients. Systemic reactions, including low-grade fever, malaise, and fatigue, are reported in <10% of vaccinees. No serious adverse events have been reported.

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)

Recommendations

Pre-Exposure Prophylaxis

All children should be vaccinated against hepatitis A during the second year of life. The first dose of HepA is usually given at 12 to 18 months of age and the second at 19 to 23 months of age. Catch-up vaccination is recommended for all children 2 to 18 years of age, and any adult who wants protection from hepatitis A should be vaccinated.

The following persons are at increased risk for hepatitis A and should be routinely vaccinated if not already immune (see *Chapter 6: Vaccination in Special Circumstances*):

- Persons traveling to or working in countries with high or intermediate endemicity
- Persons (eg, household members) who will be in close contact with an adoptee from an endemic country during the first 60 days after arrival (Dose 1 should be given at least 2 weeks before the adoptee arrives)
- Men who have sex with men (the risk is thought to relate to fecal-oral contact)
- Injecting and noninjecting illegal drug users (transmission probably occurs through percutaneous and fecal-oral routes)
- Persons who work with HAV-infected primates or with HAV in a research laboratory
- Persons who have chronic liver disease, including those who are waiting for or have received a liver transplant (these persons are particularly susceptible to severe disease)
- Homeless persons (this includes persons who spend the night in a supervised public or private facility that provides temporary

living accommodations; those in transitional housing; and those who live on the street, in abandoned buildings, or in vehicles)
- Persons with HIV infection
- Pregnant women who are at risk for infection or at risk for severe outcome if infected

Vaccination should be considered for juveniles in correctional facilities. Recommendations for travelers are given in **Table 6.6**.

Routine vaccination is *not* considered necessary for the following based on occupation alone: health care personnel (HCP); persons attending or working in childcare centers; caretakers in institutions for the developmentally challenged; persons working in correctional facilities; persons working in waste management; food service workers, unless recommended by state or local authorities. Previously, persons with clotting factor disorders were considered high-risk for hepatitis A because of transmission that had occurred from donors who were presumably viremic at the time of donation. By 2019, changes in factor preparation and donor screening had greatly reduced the risk, such that clotting factor disorders were no longer considered a risk factor.

Postexposure Prophylaxis

Table 17.2 gives recommendations for prevention of hepatitis A in unimmunized persons after exposure. Prophylaxis is warranted for the following persons (includes pregnant women):

- Persons who had close personal contact with a case
- Household and sexual contacts
- Persons who used illicit drugs with a case
- Caretakers of a case who did not use appropriate personal protective equipment
- Staff members and attendees at day care centers and day care homes if there has been one or more case in attendees, or if cases occur in two or more households of attendees. If an employee has hepatitis A, the need for prophylaxis depends on the employee's duties (eg, if they had close contact with others), hygienic practices, and symptoms while at work. If the center does not have children who are in diapers, prophylaxis should be given only to classroom contacts of the index case. If two or more families from the center are affected, prophylaxis should be considered for members of households that have children in diapers.
- Consider for restaurant patrons if an infectious food handler directly handled food without gloves and had diarrhea or poor hygienic practices
- Close contact with cases if an investigation indicates transmission has occurred in the setting (ie, among students in a school; among patients at a facility; or between patients and staff members in a hospital)
- Residents and employees of a facility where a case occurs, there is regular close personal contact, and hygiene standards are difficult to maintain (eg, correctional facility, homeless shelter, psychiatric facility, group home or residential facility for the disabled). In a setting containing multiple enclosed units or sections (eg, prison ward), prophylaxis should be limited to persons in the area where there is exposure risk.

TABLE 17.2 — Postexposure Hepatitis A Prophylaxis

Age	Health Status	HepA[a]	IGIM[b]
<12 mo	Healthy	No	Yes
	Immunocompromised[c] or chronic liver disease[d]	No	Yes
12 mo-40 y	Healthy	Yes	No
	Immunocompromised[c] or chronic liver disease[d]	Yes	Yes
	Vaccine contraindicated	No	Yes
≥41 y	Healthy	Yes	Risk assessment[e]
	Immunocompromised[c] or chronic liver disease[d]	Yes	Yes
	Vaccine contraindicated	No	Yes

IGIM, immune globulin intramuscular

These recommendations apply to unimmunized persons. Prophylaxis should be initiated as soon as possible after exposure, preferably within 2 wk (efficacy beyond 2 wk is questionable).

[a] One dose of HepA is sufficient for postexposure prophylaxis. However, Dose 2 should be given at an interval of 6-18 mo to complete the series and provide long-term protection. HepA-HepB should not be used for postexposure prophylaxis.

[b] The dose of IGIM is 0.1 mL/kg. There is no maximum dose. If both HepA and IGIM are indicated they should be given simultaneously at different sites (eg, separate limbs). MMR and VAR, if indicated, should be deferred for 3 mo after receipt of IGIM.

[c] Congenital or acquired immunodeficiency; HIV infection; chronic renal failure or on dialysis; solid organ or stem cell transplant recipient; immunosuppressive therapy.

[d] Chronic hepatitis B or C; cirrhosis; fatty liver disease; alcoholic liver disease; autoimmune hepatitis; transaminases more than twice the upper limit of normal or persistently elevated for 6 mo.

[e] IGIM may be considered for persons at high risk of infection, at risk for suboptimal response to vaccination, or at increased risk for complications of infection (see *Footnotes c* and *d*).

Adapted from Nelson NP, et al. *MMWR*. 2020;69(RR-5):1-38.

- Consider for severely immunocompromised persons (even if previously immunized) and hematopoietic cell transplant patients who have not been revaccinated
- HCP at a facility where another provider is diagnosed with hepatitis A (this can be limited to personnel in the same closed unit, such as an intensive care unit). Prophylaxis should also be considered for patients if an infectious provider had direct contact, did not use gloves when appropriate, and had diarrhea or poor hygienic practices.

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Hepatitis B

The Pathogen

Hepatitis B virus (HBV) is a nonenveloped, partially double-stranded DNA virus in the Hepadnaviridae family. The virus infects hepatocytes and replicates by forming a unique covalently closed circular DNA, or mini-chromosome, which resembles host cell chromatin; this "camouflage" facilitates persistence.[1] Hepatocellular damage occurs through the action of cytotoxic T-cells directed against virus-infected cells. Immune tolerance leads to persistent infection in some individuals; hallmark features include low-grade chronic hepatitis, hepatitis B surface antigen (HBsAg) in the blood, and an increased lifetime risk of hepatocellular carcinoma. Chronic inflammation, with attendant regeneration, fibrosis, and accumulation of cellular mutations, contributes to oncogenesis. Other factors include integration of viral DNA into the host genome; epigenetic changes in host chromatin; the expression of microRNAs; and viral transcription regulatory factors such as HBx.

Clinical Features

The incubation period ranges from 1 to 6 months, and the clinical course of acute infection is indistinguishable from that of other forms of viral hepatitis.[2] While infants and children are usually asymptomatic, icteric hepatitis occurs in about 30% of adults, and fulminant hepatitis may occur in up to 1%. The prodromal phase usually lasts 3 to 10 days and is characterized by the insidious onset of malaise, anorexia, nausea, vomiting, right upper-quadrant abdominal pain, fever, headache, myalgia, rash, arthralgia, arthritis, and dark urine. The icteric phase, which usually lasts from 1 to 3 weeks, is characterized by jaundice, elevated hepatic transaminases, light or gray-colored stools, liver tenderness, and hepatomegaly. During convalescence, malaise and fatigue may persist for weeks to months, while jaundice, anorexia, and other symptoms disappear.

About 95% of acute HBV infections in adults result in complete recovery, with disappearance of HBsAg from the blood and the production of antibody against HBsAg (HBsAb), which is a marker of immunity. However, 90% of newborns and 20% of young children with acute infection become persistently infected (so-called *chronic carriers*). Death from cirrhosis or

hepatocellular carcinoma occurs in 40% of men and 15% of women with perinatal infection.

Epidemiology and Transmission

Humans are the only natural hosts and transmission occurs by contact with contaminated secretions, including semen, vaginal secretions, blood, and saliva; through percutaneous inoculation (eg, accidental needlesticks or sharing of needles with infected people); or by maternal-neonatal transmission (the risk is about 10% if the mother is a chronic carrier). The virus can survive in the environment for 7 days. In China, southeast Asia, most of Africa, most of the Pacific Islands, parts of the Middle East, and the Amazon basin, 8% to 15% of the population are chronic carriers, with infection commonly having occurred at birth or in early childhood. The lifetime risk of infection in these areas exceeds 60%. An estimated 2 billion people worldwide have been infected with HBV and 350 million are chronic carriers.

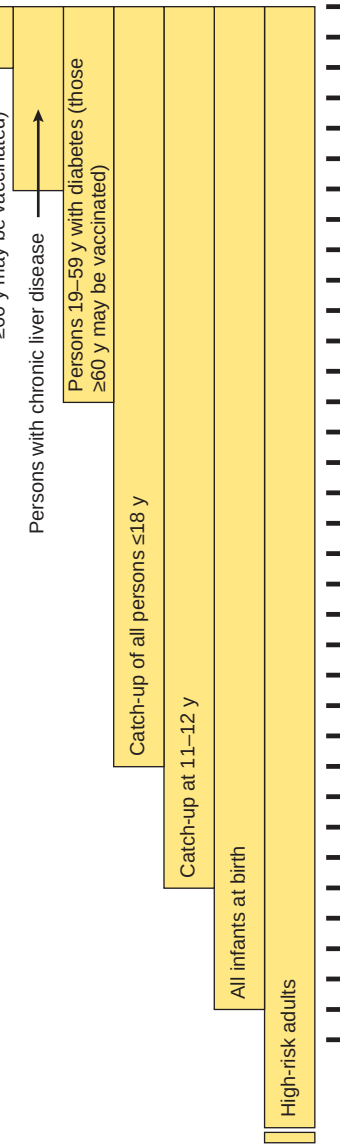
About 60% of patients in the US with acute hepatitis B report no known risk factor. High-risk groups include injection drug users, people with multiple sex partners, men who have sex with men, those who have known contact with a case, and health care personnel (HCP) with needlestick injuries. Serologic screening of all US adults for hepatitis B was recommended in 2023.[3]

Immunization Program

While acute hepatitis B can cause significant morbidity and even death, a major rationale for immunization is to prevent chronic carriage. This is because chronic carriers are often asymptomatic, can infect others over long periods of time, and are at increased risk for developing cirrhosis and primary hepatocellular carcinoma. Universal childhood immunization, including a birth dose, can dramatically decrease the prevalence of chronic carriage and the incidence of hepatocellular carcinoma.[4,5] This makes HepB the first vaccine proven to prevent a human cancer.

Figure 18.1 shows the evolution of hepatitis B immunization recommendations in the US. Notable incremental steps not depicted in the figure include recommendations for immunization of HCP in 2001,[6] 2011,[7] and 2013[8] and for control of hepatitis B in correctional facilities in 2003.[9] Comprehensive recommendations for prevention of hepatitis B were published in 2018[10]; subsequent updates included recommendations for use of HepB-CpG[11] and vaccination of all adults 19 to 59 years of age, permissive vaccination of adults ≥60 years of age without risk factors, and use of HepB3.[12] It was estimated that universal vaccination of persons ≥19 years of age would cost approximately $153,000 (2019 dollars) per quality-adjusted life year gained and would avert nearly one-quarter of cases and associated deaths.[13]

FIGURE 18.1 — HepB Immunization Recommendations Over Time



The figure shows major steps in the evolution of hepatitis B immunization recommendations in the US. Note that selective vaccination of high-risk populations in the 1980s failed to impact disease burden. Universal infant vaccination, first recommended in 1991, aimed to prevent perinatal transmission; arguably, transmission cannot occur if the mother is HBsAg-negative, but some pregnant women are not tested, and those who test negative early in pregnancy may develop infection close to delivery.

Adapted from Hepatitis B ACIP vaccine recommendations. CDC Web site. https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepb.html. Accessed August 12, 2023.

The long incubation period of HBV allows for postexposure prophylaxis through vaccination. However, even an accelerated vaccination series requires a minimum of 4 months to complete, and the series cannot be completed in neonates until 24 weeks of age. Therefore, passive immunization with hepatitis B immune globulin (HBIG) is a necessary adjunct to vaccination for immediate protection after exposure.

Vaccines

Characteristics of the hepatitis B vaccines licensed in the US are given in **Table 18.1**. These are non-live subunit vaccines consisting of HBsAg expressed in vitro using recombinant DNA technology. Heplisav-B contains a novel adjuvant (**Table 1.3**) and PreHevbrio consists of 3 different forms of HBsAg.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Engerix-B was found to be 95% effective in preventing perinatal infection when given without immune globulin on a 0-, 1-, and 2-month schedule to newborns of mothers who were chronic carriers. The seroprotection rate (SPR; proportion achieving a level of HBsAb ≥10 mIU/mL) was 97% among neonates given the vaccine at 0, 1, and 6 months of age; SPRs of 98% were seen in children 6 months to 10 years of age and 97% in adolescents after a 3-dose schedule. Studies in adolescents and adults demonstrate SPRs of >95% after 3 doses, although responses are somewhat lower in those >40 years of age.

Recombivax HB was found to be 95% effective in preventing perinatal transmission among high-risk infants who were given concomitant HBIG. Protective levels of antibody were achieved with 3 doses of vaccine in 100% of infants, 99% of children, and 99% of adolescents. Response rates in adults were 98% in those 20 to 29 years of age, 94% in those 30 to 39 years of age, and 89% in those ≥40 years of age. SPRs in adolescents who received the 2-dose regimen were 99%.

Heplisav-B was licensed in 2017 based on safety and immunogenicity studies using Engerix-B as the comparator. In each study, Heplisav-B recipients were vaccinated at weeks 0 and 4, with saline placebo given at week 24, and Engerix-B recipients were vaccinated at weeks 0, 4, and 24. The first study, which involved 1809 Heplisav-B recipients and 606 Engerix-B recipients 18 to 55 years of age, showed SPRs of 95% and 81%, respectively, a few weeks after the last active vaccine dose.[14] In the second trial,[15] healthy adults 40 to 70 years of age were randomized; in a per-protocol analysis comprising 1123 Heplisav-B recipients and 359 Engerix-B recipients, SPRs 8 weeks after the last active vaccine dose were 90% and 71%, respectively. The SPR (92%) was higher in Heplisav-B recipients 48 weeks after the last dose than in Engerix-B recipients (59%) 24 weeks after the last dose. The largest study[16] included 1144 participants with type 2 diabetes, showing SPRs of 90% and 65% for Heplisav-B and Engerix-B recipients, respectively. In each of these studies, criteria for noninferiority and superiority were met, and local and systemic reactions were similar.

PreHevbrio was licensed in 2021 based on safety and immunogenicity studies in adults using Engerix-B as the comparator, with the vaccines given at 0, 1, and 6 months (in the pivotal studies, which were conducted in North America and Europe from 2017 to 2019, the vaccine was referred to by the trade name Sci-B-Vac). In the first study,[17] which enrolled 1607 subjects ≥18 years of age, the SPR 4 weeks after Dose 3 was 91.4% for PreHevbrio and 76.5% for Engerix-B, meeting criteria for noninferiority; in subjects ≥45 years of age, the respective SPRs were 89.4% and 73.1%, meeting criteria for superiority. In the second study,[18] which enrolled subjects 18 to 45 years of age, the SPR was 99.3% among the 1753 who received PreHevbrio and 94.8% among the 592 who received Engerix-B.

As a result of the incremental immunization program in the US, the prevalence of HBV infection among children 6 to 19 years of age fell from 1.9% in 1988-1994 to 0.6% in 1999-2006, and chronic carriage decreased by 79%; among young adults 20 to 49 years of age, the prevalence fell from 5.9% to 4.6%.[19] Today, there are about 3300 reported acute cases per year. Under the Centers for Disease Control and Prevention's Perinatal Hepatitis B Prevention Program, nearly 95% of the 152,128 infants managed from 1994 to 2008 received HBIG and HepB within 1 day of birth, and the incidence of chronic hepatitis B in tested infants decreased from 2.1% to 0.8%.[20]

Although antibody levels after infant HepB vaccination wane with time, immune memory and protection persist. A study from The Gambia, for example, showed that whereas 50% of persons followed for ≥15 years had antibody levels that fell below 10 mIU/mL, efficacy was 83% against infection and 97% against chronic carriage.[21] In a 2010 meta-analysis that looked at 34 cohorts with a total of 9356 vaccinated subjects of various ages, the cumulative incidence of breakthrough HBV infection 5 to 20 years after vaccination was <1%.[22] There are serologic indicators of protection and cell-mediated immune memory as far as 30 years out from vaccination.[23,24]

Safety

The most common adverse reaction following vaccination is pain at the injection site, reported in 13% to 29% of adults and 3% to 9% of children. Mild systemic complaints, such as fatigue, headache, and irritability, have been reported in 11% to 17% of

TABLE 18.1 — Hepatitis B Vaccines

Trade name	Engerix-B[a]	Recombivax HB[b]	Heplisav-B	PreHevbrio
Abbreviation	HepB	HepB	HepB-CpG	HepB3
Manufacturer/ distributor	GSK	Merck	Dynavax	VBI Vaccines
Type of vaccine	Non-live, subunit, in vitro-expressed	Non-live, subunit, in vitro-expressed	Non-live, subunit, in vitro-expressed	Non-live, subunit, in vitro-expressed
Composition				
Antigen	HBsAg	HBsAg	HbsAg	Small (S), middle (pre-S2) and large (pre-S1) HBsAgs
Expression system	Yeast (*Saccharomyces cerevisiae*)	Yeast (*Saccharomyces cerevisiae*)	Yeast (*Hansenula polymorpha*)	Modified Chinese Hamster Ovary (CHO) cells
Antigen content				
Pediatric/ adolescent formulation	10 mcg/0.5 mL	5 mcg/0.5 mL	—	—
Adult formulation	20 mcg/mL	10 mcg/mL	20 mcg/0.5 mL	10 mcg/mL
Dialysis formulation	—	40 mcg/mL	—	—
Adjuvant	Aluminum hydroxide (0.25 mg/0.5 mL aluminum)	Aluminum hydroxyphosphate sulfate (0.25 mg/0.5 mL aluminum)	CpG 1018, a 22-mer phosphorothioate linked oligodeoxynucleotide (3 mg)	Aluminum hydroxide (0.5 mg/mL aluminum)
Preservative	None	None	None	None
Excipients and contaminants	Yeast protein (≤5%)	Yeast protein (<1%)	Yeast protein (≤5%)	Sodium chloride (8.45 mg/mL)
	Sodium chloride (8 mg/mL)	Formaldehyde (<15 mcg/mL)	Yeast DNA (<20 pg)	Potassium chloride (0.02 mg/mL)
	Disodium phosphate dihydrate (0.9 mg/mL)		Deoxycholate (<0.9 ppm)	Disodium hydrogen phosphate dodecahydrate (0.38 mg/mL)
	Sodium dihydrogen phosphate dihydrate (0.7 mg/mL)		Sodium chloride (9 mg/mL)	Potassium dihydrogen phosphate anhydrous (0.02 mg/mL)
			Sodium phosphate, dibasic dodecahydrate (1.75 mg/mL)	Residual CHO cell proteins (≤2.5 ng/mL)

Continued

TABLE 18.1 — *Continued*

Trade name	Engerix-B[a]	Recombivax HB[b]	Heplisav-B	PreHevbrio
Excipients and contaminants (*continued*)			Sodium phosphate, monobasic dihydrate (0.48 mg/mL)	Residual CHO cell DNA (≤10 pg/mL)
			Polysorbate 80 (0.1 mg/mL)	Bovine serum albumin (≤2.5 ng/mL)
				Formaldehyde (≤500 ng/mL)
Latex	Tip cap of prefilled syringe contains latex	Vial stopper and tip cap and plunger of prefilled syringe contain latex	None	None
Labeled indications	Prevention of hepatitis B	Prevention of hepatitis B	Prevention of hepatitis B	Prevention of hepatitis B
Labeled ages	All ages[c]	All ages[c]	≥18 y	≥18 y
Dose				
Pediatric/adolescent formulation	0.5 mL[d] (≤19 y)	0.5 mL (≤19 y)	—	—
Adult formulation	1 mL[d] (≥20 y)	1 mL[e] (≥20 y)	0.5 mL (≥18 y)	1 mL (≥18 y)
Hemodialysis formulation[f]	2 mL of the adult formulation or 2 simultaneous adult doses of 1 mL each[g]	1 mL	—	—
Route of administration	Intramuscular[h]	Intramuscular[h]	Intramuscular	Intramuscular
Labeled schedule				
Routine	Doses at 0, 1, and 6 mo[i]	Doses at 0, 1, and 6 mo[i]	Doses at 0 and 1 mo	Doses at 0, 1 and 6 mo
Hemodialysis patients	Doses at 0, 1, 2, and 6 mo	Doses at 0, 1, and 6 mo	—	—
	Periodic boosters[j]	Periodic boosters[j]		
Alternate dosing for 11-15 y	—	Doses of adult formulation at 0 and 4-6 mo[e,k]	—	—
Recommended schedule (age)	Birth, 1-2, and 6-18 mo	Birth, 1-2, and 6-18 mo	Doses at 0 and 1 mo	Doses at 0, 1, and 6 mo
	Catch-up, high-risk	Catch-up, high-risk	Catch-up, high-risk	Catch-up, high-risk

Continued

TABLE 18.1 — *Continued*

Trade name	Engerix-B[a]	Recombivax HB[b]	Heplisav-B	PreHevbrio
How supplied (number in package)				
Pediatric/adolescent formulation	Prefilled syringe (10)	1-dose vial (10)	—	—
		Prefilled syringe (10)		
Adult formulation	1-dose vial (10)	1-dose vial (1, 10)	—	1-dose vial (10)
	Prefilled syringe (10)	Prefilled syringe (10)	Prefilled syringe (1, 5)	—
Hemodialysis formulation	—	1-dose vial (1)	—	—
Cost per dose (USD, 2023)				
Public	16.89 (pediatric) 33.50 (adult)	13.93 (pediatric) 32.43 (adult)	74.94	—
Private	27.36 (pediatric) 66.85 (adult)	26.35 (pediatric) 64.90 (adult)	134.15	—
Reference package insert	June 2021	April 2023	May 2023	November 2021

HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen

[a] Engerix-B is available in combination with DTaP and IPV (Pediarix; GSK) and HepA (Twinrix; GSK). See *Chapter 35: Combination Vaccines.*

[b] Recombivax HB is available in combination with DTaP, IPV, and Hib-OMP (Vaxelis; Merck and Sanofi). See *Chapter 35: Combination Vaccines*. Recombivax HB in combination with Hib (Comvax; Merck) was discontinued in 2014.

[c] The hemodialysis formulation and/or dosing schedule is only labeled for adults.

[d] Adolescents 11-19 y may receive the adult formulation.

[e] An adult dose (10 mcg/mL) may be constituted by 2 separate injections of the pediatric (5 mcg/0.5 mL) formulation at the same site or by drawing up 2 pediatric doses in the same syringe.

[f] In general, hemodialysis patients require higher doses to respond, although data in children are lacking. It is acceptable to use the dialysis formulation in patients with renal failure even if they are not on dialysis. Such patients may be immunocompromised and may be starting dialysis soon; moreover, the higher dose is not harmful. The Advisory Committee on Immunization Practices recommends use of standard doses in persons <20 y and dialysis formulations and regimens for persons ≥20 y.

[g] There is no specific hemodialysis formulation. The 40 mcg/2 mL dose can be constituted by 2 separate injections of the adult (20 mcg/mL) formulation at the same site or by drawing up 2 adult doses in the same syringe.

[h] May be administered subcutaneously in patients who are at risk of hemorrhage with intramuscular injections (eg, hemophiliacs). However, reactogenicity may be increased and immunogenicity decreased.

[i] Other dosing regimens are contained in the package insert.

[j] Booster doses are given when annual testing shows that HBsAb levels have fallen below 10 mIU/mL. Annual testing with periodic booster doses may be indicated for other immunocompromised persons, such as those with HIV infection, hematopoietic stem-cell transplant recipients, and those receiving chemotherapy.

[k] If a person turns 16 y before Dose 2 is given, they should be switched to the 3-dose regimen, and Doses 2 and 3 should be given as the pediatric formulation at the appropriate intervals.

adults and up to 20% of children. Low-grade fever is seen in 1% of adults and in up to 6% of children. A review of 20,231 Vaccine Adverse Event Reporting System reports collected from 2005 to 2015 failed to reveal any new or unexpected safety concerns.[25] Well over 1 billion doses of alum-adjuvanted HepB have been given worldwide since the 1980s, and serious systemic adverse events and allergic reactions have rarely been reported.

An integrated safety analysis of Phase 3 clinical trials of Heplisav-B, which included over 9000 exposed adults, showed that reactogenicity and adverse event rates were similar to alum-adjuvanted HepB. Furthermore, the vaccine was not associated with incident immune-mediated disease, and there were no clinically significant increases in a variety of autoantibodies that were assessed.[26] Mild or moderate injection site pain, tenderness, and myalgia appear to be more common among PreHevbrio recipients than standard alum-adjuvanted HepB. In one pivotal clinical trial, the rate of local reactions was 85.0% versus 65.9% for Engerix-B, and systemic reactions occurred in 68.0% versus 60.1% for Engerix-B.

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction; for Engerix-B, Recombivax HB, and Heplisav-B, this includes reactions to baker's yeast)

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- Infant weight <2000 g, unless the mother is HBsAg-positive (risk of poor response to vaccination)

Recommendations

Universal Immunization

All infants should be vaccinated against hepatitis B. The dosing regimen depends on birth weight and maternal HBsAg status (**Table 18.2**). All children and adolescents ≤18 years of age who were not vaccinated as infants should receive a HepB series. Routine postvaccination testing for HBsAb is not recommended. Engerix-B and Recombivax HB are considered interchangeable except for the 2-dose schedule in adolescents, for which only Recombivax HB is approved.

All adults 19 to 59 years of age also should be vaccinated. Engerix-B and Recombivax HB are preferred for pregnant women. If a HepB series is initiated with a dose of Heplisav-B but subsequent doses are another product, a total of 3 doses should be given, and the usual minimum intervals should apply. However, if Dose 1 was another product, Doses 2 and 3 could be given as Heplisav-B 1 month apart (as if the first dose of another product had not been given).

Adults ≥60 Years of Age

Adults ≥60 years of age without risk factors *may* be vaccinated and those with the risk factors listed below *should* be vaccinated:

- Sex partners of persons who are HBsAg-positive
- Persons with more than one sex partner in the past 6 months
- Persons seeking evaluation or treatment for a sexually transmitted disease
- Men who have sex with men
- Injection drug users
- Household contacts of HBsAg-positive persons
- Residents and staff of facilities for developmentally disabled persons
- Health care and public safety personnel at risk for exposure to blood or blood-contaminated body fluids
- Patients with end-stage renal disease, including those on hemodialysis and peritoneal dialysis (vaccination of patients with renal failure is encouraged before they require hemodialysis)
- Persons with diabetes type 1 or 2 (at the discretion of the treating clinician)
- Patients with chronic liver disease, including hepatitis C virus infection, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and transaminase levels greater than twice the upper limit of normal
- Persons with HIV infection
- Travelers to regions where the prevalence of chronic infection is ≥2%
- Incarcerated persons

Standing orders for HepB administration should be implemented in settings where high-risk individuals are seen. Prevaccination testing in high prevalence populations might reduce costs by avoiding vaccination of persons who are already immune; in these situations, the first dose of HepB should be given after the blood is drawn for testing. Recommended serological tests include hepatitis B core antibody (identifies previous or ongoing infection), HBsAb (identifies immunity from vaccination or natural infection), and HBsAg (identifies current infection).

Testing for HBsAb 1 to 2 months after vaccination is recommended for the following groups: potentially exposed infants (*see below*); HCP and public safety personnel at high risk for exposure to blood or body fluids; chronic hemodialysis patients; sex partners of

TABLE 18.2 — HepB Recommendations for Infants

Maternal Hepatitis B Status During Pregnancy	HepB Dosing[a]	
	Birth Weight <2000 g[b]	Birth Weight ≥2000 g
Not infected (HBsAg-negative)	Dose 1 at 1 mo if still hospitalized or at discharge if that occurs before 1 mo Dose 2 at 2 mo Dose 3 at 6[c]-18 mo[d]	Dose 1 within 24 h of birth Dose 2 at 1-2 mo Dose 3 at 6[c]-18 mo[d]
Infected (HBsAg-positive) or not tested but suspected of being infected[e]	Dose 1[f] and HBIG[g] within 12 h of birth Dose 2 (first valid dose) at 1 mo Dose 3 (second valid dose) at 2-3 mo Dose 4 (third valid dose) at 6 mo[c] Test for HBsAg and HBsAb at 9-12 mo[h] Infant may breast feed if appropriate prophylaxis has been given	Dose 1 and HBIG[g] within 12 h of birth Dose 2 at 1-2 mo Dose 3 at 6 mo[c] Test for HBsAg and HBsAb at 9-12 mo[h] Infant may breast feed if appropriate prophylaxis has been given
Unknown or not documented	Dose 1[f] and HBIG[g] within 12 h of birth Test mother at delivery for HBsAg *If positive, result not available, or not tested*: Dose 2 (first valid dose) at 1 mo Dose 3 (second valid dose) at 2-3 mo Dose 4 (third valid dose) at 6 mo[c] Test for HBsAg and HBsAb at 9-12 mo[h] *If negative*: Dose 2 (first valid dose) at 1 mo	Dose 1 within 12 h of birth Test mother at delivery for HBsAg *If positive, results not available, or not tested*: HBIG[g] as soon as possible but no later than 7 d Dose 2 at 1 mo Dose 3 at 6 mo[c] Test for HBsAg and HBsAb at 9-12 mo[h] *If negative*: Dose 2 at 1-2 mo
	Dose 3 (second valid dose) at 2 mo Dose 4 (third valid dose) at 6[c]-18 mo[d] Infant may breast feed immediately after birth	Dose 3 at 6[c]-18 mo[d] Infant may breast feed immediately after birth

HBIG, hepatitis B immune globulin; HBsAb, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen

[a] Only monovalent HepB should be used for the birth dose and any doses given <6 wk. An effective way to implement the birth dose is through *standing orders*. At ≥6 wk, doses may be given as a HepB-containing combination vaccine such as Pediarix (DTaP-HepB-IPV) or Vaxelis (DTaP-IPV-Hib-HepB). If one of these combinations is used for doses beyond the birth dose, they are given at 2, 4, and 6 mo in all of the listed scenarios.

[b] Doses at ≥1 mo should be given even if the baby weighs <2000 g at the time the dose is indicated.

[c] The final dose should not be administered before 24 wk (164 d) of age.

[d] For populations with high rates of hepatitis B in children (eg, Alaska Natives, Pacific Islanders and families from Asia or Africa), the final dose should be administered at 6-12 mo.

[e] This includes mothers who are known to have chronic hepatitis B or have positive tests for HBV DNA or HBeAg.

[f] This dose does not count towards completion of the 3-dose series.

[g] HBIG is used in conjunction with vaccination for postexposure prophylaxis. Available products in the US include Nabi-HB (ADMA Biologics), HepaGam B (Saol), and HyperHEP B (Grifols). They consist of IgG derived from pooled plasma of human donors who have high levels of HBsAb; they are therefore polyclonal (contain a variety of antibodies, including antibodies to other organisms). Various procedures are used to purify the immune globulin and reduce the potential for transmission of blood-borne pathogens, and the products are formulated for intramuscular administration. Patients with selective IgA deficiency may be at increased risk for anaphylactic reactions to HBIG because it may contain minute amounts of IgA. The dose is 0.5 mL intramuscularly at a different site from where the vaccine is administered. HBIG is unlikely to be effective after 7 d.

[h] If HBsAg is negative and HBsAb is ≥10 mIU/mL, the patient is uninfected and immune, and no further testing is needed. If HBsAg is negative and HBsAb is <10 mIU/mL, the patient is uninfected but not immune, and there are 2 options: 1) give an additional dose of HepB and repeat HBsAb 1-2 mo later; if HBsAb remains <10 mIU/mL, complete the second HepB series with 2 more doses and test for HBsAb 1-2 mo after the final dose, or 2) give a second 3-dose series and repeat HBsAb 1-2 mo after the final dose. If HBsAb remains <10 mIU/mL after a second 3-dose series of HepB (and HBsAg is negative), the patient is a non-responder and should be considered not immune (no further doses of HepB are indicated). If HBsAg is positive at any time, the patient should be referred for follow-up.

Adapted from Schillie S, et al. *MMWR*. 2018;67(RR-1):1-31.

HBsAg-positive persons; and HIV-infected and other immunocompromised persons. Levels ≥10 mIU/mL are considered protective. Patients with antibody levels <10 mIU/mL should receive a second HepB series, followed by repeat testing. If the result is still <10 mIU/mL, the person should be tested for HBsAg, since chronic carriage is a reason for nonresponse to vaccination. If they are negative for HBsAg, they are considered primary non-responders and are considered susceptible to infection. Periodic (eg, annual) testing for HBsAb after vaccination is only recommended for dialysis patients and other immunocompromised persons, including those with HIV infection, hematopoietic cell transplant recipients, and persons receiving chemotherapy.

Postexposure Prophylaxis

All pregnant women should be tested for HBsAg early in each pregnancy (this includes women who are already known to be chronically infected—a positive HBsAg test on the chart will help ensure that the infant will receive timely prophylaxis). Women who do test positive for HBsAg should have a quantitative HBV DNA test; guidelines suggest antiviral treatment if the viral load is >200,000 IU/mL.[27] Women who were not screened prenatally, those who are at high risk for infection, and those with clinical hepatitis should be tested at the time of delivery. A copy of the test results should be provided to the birthing hospital and the newborn's health care provider. The management of infants potentially exposed to HBV from their mothers is given in **Table 18.2**.

Recommendations for the management of potential occupational and nonoccupational exposures to HBV are given in **Tables 18.3** and **18.4**, respectively.

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TABLE 18.3 — Management of Potential Occupational Exposures to Hepatitis B[a]

Exposed Person		Source Person	
Vaccination Status	**HBsAb Status[b]**	**HBsAg-Positive or -Unknown[c]**	**HBsAg-Negative**
Vaccinated (3-6 doses)[d]	≥10 mIU/mL	No action required	No action required
Vaccinated (3 doses)[d]	<10 mIU/mL	Give 1 dose of HBIG[e], complete second HepB series[f], test for infection[g], test for response to vaccination[h]	Give 1 dose of HepB or give a second HepB series[f], test for response to vaccination[h]
Vaccinated (6 doses)[d]	<10 mIU/mL	Give 2 doses of HBIG[e] separated by 1 mo, test for infection[g]	No action required
Unvaccinated, incompletely vaccinated, or vaccination not documented	Testing not recommended[i]	Give 1 dose of HBIG[e], initiate or complete HepB series[f], test for infection[g], test for response to vaccination[h]	Initiate or complete HepB series[f], test for response to vaccination[h]

HBIG, hepatitis B immune globulin; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCP, health care personnel.

[a] Percutaneous exposures include needle sticks, lacerations, and bites. Permucosal exposures include splashes of blood, any fluid containing visible blood, other potentially infectious fluid (including semen; vaginal secretions; cerebrospinal fluid; synovial, pleural, peritoneal, pericardial, or amniotic fluids; tracheal secretions; and saliva), or tissue onto any mucosal surface, including the eye and mouth.

[b] Testing for HBsAb 1-2 mo after vaccination is recommended for HCP and public safety workers at high risk for exposure to blood or body fluids. An HBsAb level ≥10 mIU/mL is considered protective; if the level is <10 mIU/mL, a second HepB series should be given, with repeat HBsAb testing 1-2 mo after completion. If the level remains <10 mIU/mL, no further vaccination is indicated, and the person is considered susceptible. HCP who received a complete HepB series in the past can be tested for HBsAb at the time of hire. If the level is ≥10 mIU/mL, they are considered protected. If it is <10 mIU/mL, they should receive 1 dose of HepB and HBsAb should be measured 1-2 mo later—a robust response (≥10 mIU/mL) to one dose indicates prior immune memory and the person is considered protected; a poor response (<10 mIU/mL) indicates the need for completing another full HepB series, with repeat testing after the series is completed. HCP who previously received a complete HepB series but were never tested for HBsAb can be tested at the time of exposure and managed accordingly. For example, let's say a nurse has documentation of having received 3 doses of HepB as a child, but has never been tested for HBsAb. If she has a needle stick injury from a patient who is HBsAg-positive or -unknown, she should be tested for HBsAb. If her level of antibody is ≥10 mIU/mL, no action is required. If the level is <10 mIU/mL, she should receive one dose of HBIG and complete a second HepB series, after which she should be tested for infection and for response to vaccination.

[c] Efforts should be made to test the source individual for HBsAg, unless the exposed person is fully protected.

[d] Vaccinated status may be achieved with fewer doses, depending on the product used.

[e] HBIG is used in conjunction with vaccination for postexposure prophylaxis. Available products in the US include Nabi-HB (ADMA Biologics), HepaGam B (Saol), and HyperHEP B (Grifols). They consist of IgG derived from pooled plasma of human donors who have high levels of HBsAb; they are therefore polyclonal (contain a variety of antibodies, including antibodies to other organisms). Various procedures are used to purify the immune globulin and reduce the potential for transmission of blood-borne pathogens, and the products are formulated for intramuscular administration. Patients with selective IgA deficiency may be at increased risk for anaphylactic reactions to HBIG because it may contain minute amounts of IgA. The dose is 0.06 mL/kg given intramuscularly. HBIG should be given as soon as possible after exposure, preferably within 24 h. The effectiveness of HBIG administered >7 d after percutaneous, mucosal, or nonintact skin exposure is unknown.

[f] In cases where the source is HBsAg-positive or -unknown, the first dose should be given as soon as possible, preferably within 24 h. In cases where the source is HBsAg-negative, the HepB series should be initiated or completed, with appropriate postvaccination testing, because of occupational risk of exposure in the future.

[g] Test for HBcAb at baseline; repeat HBcAb and test for HBsAg 6 mo later.

[h] Test for HBsAb 1-2 mo after the last dose of HepB (if the person received HBIG, wait 4-6 mo—HBIG contains HBsAb, so testing should occur after the passively acquired antibody degrades).

[i] The serological correlate of protection is only valid for persons who have completed an appropriately administered HepB series, so testing in this setting is unnecessary and potentially misleading.

Adapted from Schillie S, et al. *MMWR*. 2018;67(RR-1):1-31.

TABLE 18.4 — Management of Potential Nonoccupational Exposures to Hepatitis B[a]

Status of Exposed Individual	Source HBsAg Status[b]	Management
Not vaccinated or incompletely vaccinated	Negative	Catch-up vaccination
	Positive	Give HBIG[c] and initiate or complete HepB series[d]
	Unknown	Initiate or complete HepB series[d]
Vaccinated[e]	Negative	No action required
	Positive	Give a booster dose of HepB[d]
	Unknown	No action required

HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen.

[a] Percutaneous exposures include needle sticks (needle sharing), lacerations, and bites. Permucosal exposures include splashes of blood, any fluid containing visible blood, other potentially infectious fluid (including semen; vaginal secretions; cerebrospinal fluid; synovial, pleural, peritoneal, pericardial, or amniotic fluids; tracheal secretions; and saliva), or tissue onto any mucosal surface, including the eye and mouth.

[b] Efforts should be made to test the source individual for HBsAg. Needles and syringes discarded in public places, presumably by injection drug users, pose a risk of transmission because HPV can survive on environmental surfaces for up to 7 d. However, the risk depends on the prevalence of hepatitis B in the drug-abusing population and the amount of blood in the needle. There is no consensus opinion regarding the use of HBIG in these situations.

[c] HBIG is used in conjunction with vaccination for postexposure prophylaxis. Available products in the US include Nabi-HB (ADMA Biologics), HepaGam B (Saol), and HyperHEP B (Grifols). They consist of IgG derived from pooled plasma of human donors who have high levels of HBsAb; they are therefore polyclonal (contain a variety of antibodies, including antibodies to other organisms). Various procedures are used to purify the immune globulin and reduce the potential for transmission of blood-borne pathogens, and the products are formulated for intramuscular administration. Patients with selective IgA deficiency may be at increased risk for anaphylactic reactions to HBIG because it may contain minute amounts of IgA. The dose is 0.06 mL/kg given intramuscularly. HBIG should be given as soon as possible after exposure, preferably within 24 h. Intervals exceeding 7 d after percutaneous exposure and 14 d after sexual exposure are unlikely to be of benefit.

[d] A dose should be given as soon as possible, preferably within 24 h.

[e] Documentation of a complete HepB series (2 or 3 doses, depending on the product used) should be provided.

Adapted from Schillie S, et al. *MMWR*. 2018;67(RR-1):1-31.

Human Papillomavirus

The Pathogen

Human papillomavirus is a small, nonenveloped, double-stranded DNA virus in the Papillomaviridae family that is tropic for epithelial surfaces.[1] The virion capsid is composed of major and minor late proteins, L1 and L2. Oncogenic human papillomaviruses are a *necessary* but not *sufficient* cause of cervical cancer. Approximately 90% of new infections clear within 2 years, but the remaining 10% of infections that persist can lead to cancer. Certain biologic factors put young women at particularly high risk for infection, persistence, and neoplasia. The most important of these involves the *cervical transformation zone*, an area of metaplasia where the columnar epithelium of the endocervix meets the squamous epithelium of the exocervix. In young girls, the squamocolumnar junction is located outside the cervical opening; during puberty, it regresses into the cervical opening. The area traversed during this regression is thin, friable, and vulnerable to damage; the basal cell layer, which is the site of viral replication and persistence, is easily exposed. The *anal transformation zone*, where the columnar epithelium of the rectum meets the squamous epithelium of the anus, is analogous. The pathogenesis of oral cancers caused by the virus is less well understood.[2]

In basal cells, expression of the viral proteins E6 and E7 prevents cell differentiation, causes delayed cell-cycle arrest, and interferes with the function of tumor suppressor proteins. This, along with the virus' mechanisms for evading host immune surveillance, results in vertical expansion of the dividing cell population. Integration of viral DNA into the host genome causes overexpression of E6 and E7, leading to further unchecked cell proliferation and the accumulation of germ-line mutations, which ultimately lead to invasive cancer.

Human papillomavirus types 6 and 11 cause anogenital warts, although they may cause low-grade cervical dysplasia that eventually regresses.

Clinical Features

Most infections are asymptomatic and self-limited. In a minority of women, however, persistent cervical infection leads

to *cervical intraepithelial neoplasia* grades 1 (CIN 1) through 3 (CIN 3). Approximately 60% of CIN 1 cases spontaneously regress and <1% lead to cancer. On the other hand, only 30% to 40% of CIN 2 or 3 lesions regress, and >12% develop into cancer—*squamous cell carcinoma* (75% of cervical cancers in the US) or *adenocarcinoma*. In the US, human papillomavirus types 16 and 18 cause two thirds of cervical cancers; an additional 15% are caused by types 31, 33, 45, 52, and 58. The duration of time from the first intraepithelial lesion to invasive cancer is 15 to 20 years. Human papillomavirus also causes *vaginal* and *vulvar intraepithelial neoplasia* (VaIN and VIN) that can progress to cancer; about 40% of vulvar and 70% of vaginal cancers are caused by human papillomavirus.

Human papillomavirus also causes *anal intraepithelial neoplasia* (AIN), which can progress to *anal cancer*—in fact, up to 90% of anal cancers are caused by the virus.[3] Human papillomavirus also causes 50% of *penile cancers,* 25% of *oropharyngeal cancers* (including the tonsils and base of the tongue) and may be involved in other squamous cell carcinomas of the head and neck,[4] as well as bladder cancer.[5] For most of these tumors, types 16 and 18 predominate.

Approximately 90% of *anogenital warts* are caused by types 6 and 11. These are typically small, soft, raised flesh-colored growths; some develop into large, cauliflower-like clusters called *condyloma acuminata*. In women, warts can be seen anywhere from the cervix to the vagina, urethra, inguinal region, or upper thighs. In males, the most common site is the shaft of the penis, and lesions may occur on the anus in both sexes. Most cases are asymptomatic, but itching, burning, pain, bleeding, and tenderness can occur. *Recurrent respiratory papillomatosis* (RRP), defined by wart-like lesions on the larynx, nasopharynx, oropharynx, trachea and/or esophagus, is also caused by types 6 and 11; it is seen classically in infants and young children who acquired infection from their mothers during vaginal delivery. Infants may present with hoarseness, weak cry, stridor, feeding difficulties, and failure to thrive. Airway obstruction can result from enlarged lesions, and multiple surgical laser procedures are often necessary. Rarely, malignancy can develop.

Epidemiology and Transmission

Infection occurs only in humans. Direct contact is required; generally, this means sexual activity where there is direct contact between the genitalia, anus, and/or mouth. However, there is some evidence that non-penetrative sexual, and even non-sexual, contact can transmit the virus.[6] Anal infection is common among women with genital neoplasia, even in the absence of a history of anal sex, and there is evidence of sequential infection from cervix to anus and vice versa.[7,8] Anal infection is found in men who have never had anal sex with men.[9] These data suggest transmission through anodigital sexual behavior, vaginal secretions, and autoinoculation.

Approximately 7% of US adults have oral infection with human papillomavirus, and the data suggest that transmission can occur without oral-genital contact (through, for example, deep kissing).[10] The prevalence of oral infection is 5-fold higher among women with cervical infection than among those without cervical infection, suggesting that infection at these sites is not independent.[11]

The overall risk of infection correlates directly with sexual activity. In the prevaccine era, studies showed that over half of female college students acquired human papillomavirus infection within 4 years of their first sexual intercourse,[12] and the prevalence of infection among women 20 to 24 years of age in the US approached 50%.[13] Estimates of the prevalence of infection in men vary widely, but some are as high as 70%,[14] and the dominant risk factors for acquisition are the lifetime number of female sexual partners, as well as male anal sex partners.[15,16]

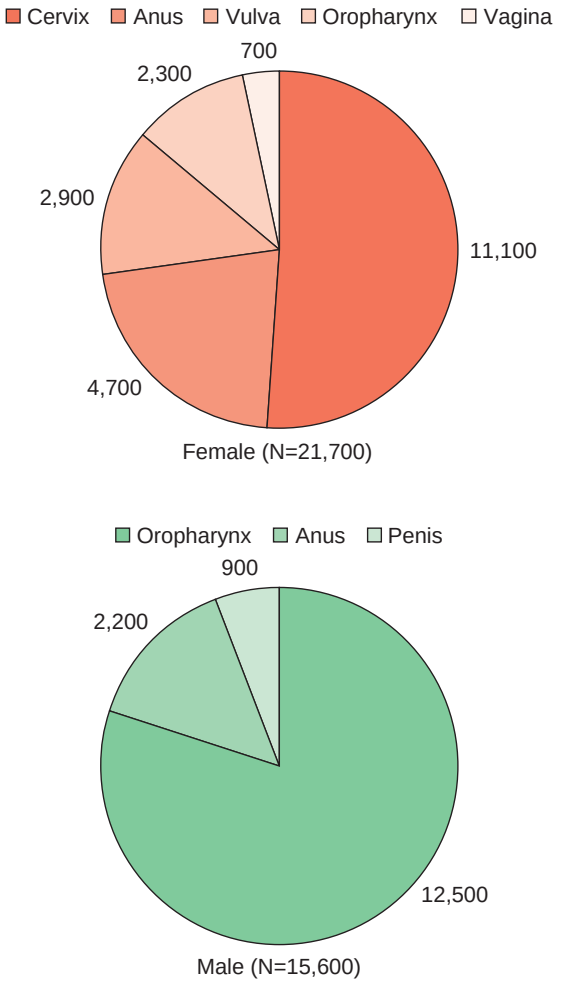
Worldwide, human papillomavirus causes 690,000 cancers each year.[17] In the prevaccine era in the US, an estimated 14 million new human papillomavirus infections occurred every year among persons 15 to 59 years of age.[18] The annual burden from cervical disease alone included over 11,000 new invasive cancers and >400,000 cases of carcinoma in situ,[19] and 1% of the sexually active population had genital warts.[20] The rate of anal cancer doubled between the 1970s and the 1990s,[21] and the incidence of anal squamous cell carcinoma increased 2.7% per year from 2001 to 2015.[22] In 2015-2019, human papillomavirus was estimated to cause over 37,000 cancers per year in the US (**Figure 19.1**).

Immunization Program

Figure 19.2 shows the evolution of human papillomavirus immunization recommendations in the US. Comprehensive recommendations were published in 2014,[23] with updates in 2015[24], 2016[25], and 2019[26]. Several things are worth highlighting. First, the virus types represented in HPV9 account for over 90% of human papillomavirus-attributable cancers in the US.[27] Second, the benefits of vaccination are best realized before sexual debut; even those who plan to abstain from sex and ultimately enter a monogamous relationship can benefit, since the sexual history of the eventual sex partner may not be known. Whereas vaccination does not lead to clearance of persistent infection or prevent neoplasia in those who are already infected, sexually active persons and those known to be infected can still benefit from vaccination by becoming immune to virus types they have not yet encountered.

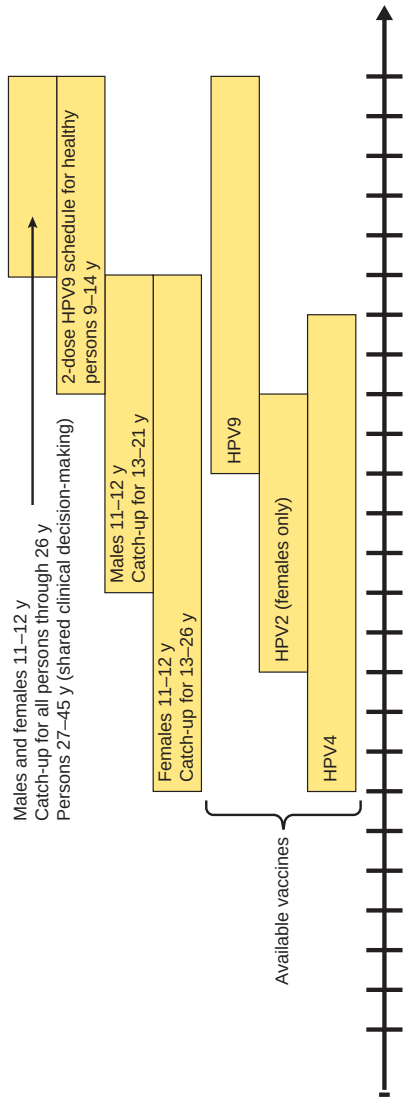
Third, vaccination against human papillomavirus is highly cost-effective. At the beginning of the HPV4 program, models placed the cost per quality-adjusted life year (QALY) gained of universally immunizing young females at $3000 (2005 dollars),[28] and studies suggested that male vaccination would also be cost effective.[29] Substitution of

FIGURE 19.1 — Cancers Attributable to Human Papillomavirus—United States, 2015-2019



Adapted from Number of HPV-attributable cancer cases per year. CDC Web site. https://www.cdc.gov/cancer/hpv/statistics/cases.htm. Accessed August 13, 2023.

FIGURE 19.2 — Human Papillomavirus Immunization Recommendations Over Time



The figure shows major steps in the evolution of human papillomavirus immunization recommendations in the US. Note that the indications for HPV expanded over time from prevention of genital cancers and warts in females only to prevention of genital warts in males and prevention of anal, oropharyngeal, and other head and neck cancers in both males and females.

Adapted from Human papillomavirus (HPV) ACIP vaccine recommendations. CDC Web site. https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html. Accessed August 13, 2023.

HPV9 for HPV4 for both females and males was estimated to be cost-saving (irrespective of cross-protection assumptions for HPV4), as long as the incremental cost of HPV9 was <$13.[30] Extending routine immunization to all adults through 45 years of age increases costs to as high as $1.5 million (2018 dollars) per QALY gained.[31]

Vaccines

Characteristics of the HPV available in the US are given in **Table 19.1**. The vaccine is produced by recombinant DNA techniques, much the same way as HepB. It is composed exclusively of the L1 major capsid protein of the virus, which self-assembles into virus-like particles that do not contain genetic material and are incapable of replicating, causing infection, or inducing disease.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Pivotal prelicensure studies of HPV4 in females demonstrated 100% per-protocol efficacy over 3 years in preventing a range of outcomes, including VaIN, VIN, CIN and cancers.[32,33] Protection appears to last as long as it has been measured—in one study persistent antibody responses were demonstrated 14 years out from vaccination, and there were no breakthrough cases of high-grade HPV 16- or HPV 18-related cervical dysplasia.[34] Per-protocol efficacy against similar outcomes caused by the 5 incremental virus types contained in HPV9 was 97%, and immune responses to the common types was noninferior.[35] Analogous studies in males demonstrated 90% efficacy against external genital lesions caused by vaccine types in per-protocol populations followed for 3 years.[36] After almost 10 years of follow-up, there were no breakthrough cases of vaccine-type external genital warts, external genital lesions, high-grade AIN, or anal cancer.[37]

Infection with one HPV type does not preclude vaccine-derived protection against other types. HPV9 provides homotypic protection against oncogenic types 16, 18, 31, 33, 45, 52, and 58 and also protects against types 6 and 11, which cause most genital warts. The vaccine is not therapeutic for established infection.

The vaccination program in the US has been highly successful (**Figure 19.3**), even though coverage rates for the human papillomavirus vaccine series are only slightly above 60% (see **Figure 2.6**). About 10 years into the program, there was a 78% decrease in the prevalence of cervical infection with vaccine types among women 20 to 24 years of age undergoing cervical cancer screening; declines among both vaccinated and unvaccinated women suggested herd immunity.[38] Data from the National Health and Nutrition Examination Survey showed that as of 2015 to 2018, the prevalence of infection with HPV4 types among girls and young women had decreased >80% compared to the prevaccine era.[39] A meta-analysis that included data from 60 million individuals in 14 high-income countries showed a 51% reduction CIN 2-plus lesions among screened girls 15 to 19 years of age within 5 to 9 years of implementation of a females-only vaccination program.[40] The same study suggested strong herd effects, in that young males (who were not being immunized) had marked reductions in anogenital warts. In a population-based study of approximately 1.7 million girls in Sweden who were 10 to 30 years of age between 2006 and 2017, the incidence of cervical cancer among vaccinated girls almost two-thirds less than that of unvaccinated girls; among those vaccinated before 17 years of age, the incidence was one-tenth.[41] Data from the US also show decreases in cervical cancer incidence and mortality after vaccine introduction.[42] Real-world experience suggests that vaccination programs can reduce the prevalence of high-grade cervical lesions by as much as 85%.[43] There is also emerging evidence at the population level that vaccination prevents human papillomavirus infection of the oral cavity, RPP, and anal cancer.[44-46]

In 2007, Australia became one of the first countries to implement a national HPV program. A modeling study has suggested that—assuming immunization rates remain high—Australia is on track to *eliminate* cervical cancer by 2028.[47]

Safety

Prelicensure studies of HPV4 demonstrated injection site pain in 84% of vaccinees (in a blinded comparison, HPV4 was found to be more painful than other vaccines[48]). Swelling and erythema were reported in about 25% of vaccinees. Approximately 5% of female vaccinees reported a temperature of ≥100°F (≥37.8°C) after any dose, but high fevers were rare. The rates of systemic adverse events, serious adverse events, and new medical conditions arising within 4 years were similar in vaccinees and placebees. The safety profile of HPV9, as assessed in over 15,000 subjects who participated in the prelicensure clinical trials, was similar to HPV4, although injection site reactions were more common.[49]

In a postlicensure review of safety data from clinical trials, there were 11 deaths among vaccinees and 7 among placebees, none of which were related to immunization; new autoimmune phenomena were reported in 2.4% of both groups.[50] From 2009 to 2015, >60 million doses of HPV4 were distributed and 19,760 reports were received by the Vaccine Adverse Event Reporting System (VAERS), 94% of which were considered non-serious.[51] There were 29 verified reports of death, with no pattern in diagnosis, comorbidity, age, or time since vaccination. Reporting rates for a variety of conditions, including autoimmune disorders, postural orthostatic tachycardia syndrome, Guillain-Barré syndrome (GBS), venous thromboembolism (VTE), complex regional pain syndrome, and primary ovarian

TABLE 19.1 — Human Papillomavirus Vaccine[a]

Trade name	Gardasil 9
Abbreviation	HPV9
Manufacturer/distributor	Merck
Type of vaccine	Non-live, subunit, in vitro-expressed
Composition	Virus-like particles composed of self-assembled L1 major capsid protein molecules
Expression system	Yeast (*Saccharomyces cerevisiae*)
Antigen content	L1 protein from types 6 (30 mcg), 11 (40 mcg), 16 (60 mcg), 18 (40 mcg), 31 (20 mcg), 33 (20 mcg), 45 (20 mcg), 52 (20 mcg), 58 (20 mcg)
Adjuvant	Aluminum hydrophosphate sulfate (0.5 mg aluminum)
Preservative	None
Excipients and contaminants	Sodium chloride (9.56 mg)
	L-histidine (0.78 mg)
	Polysorbate 80 (50 mcg)
	Sodium borate (35 mcg)
	Yeast protein (<7 mcg)
Latex	None
Labeled indications[b]	
Females	Prevention of cervical, vulvar, vaginal, anal, oropharyngeal, and other head and neck cancers caused by types 16, 18, 31, 33, 45, 52, and 58
	Prevention of genital warts caused by types 6 and 11
Males	Prevention of anal, oropharyngeal, and other head and neck cancers caused by types 16, 18, 31, 33, 45, 52, and 58
	Prevention of genital warts caused by types 6 and 11
Labeled ages	9-45 y
Dose	0.5 mL
Route of administration	Intramuscular
Labeled schedule	Doses at 0 and 6-12 mo (9-14 y only[c])
	Doses at 0, 2 and 6 mo (15-45 y)
Recommended schedule (age)	11-12 y[d]
	27-45 y (shared clinical decision-making)
	Catch-up, high-risk
	9-14 y: doses at 0 and 6-12 mo[c]
	15-45 y: doses at 0, 1-2, and 6 mo
How supplied (number in package)	1-dose vial (10)
	Prefilled syringe (10)
Cost per dose (USD, 2023)	
Public	224.63 (pediatric) 164.56 (adult)
Private	268.77
Reference package insert	April 2023

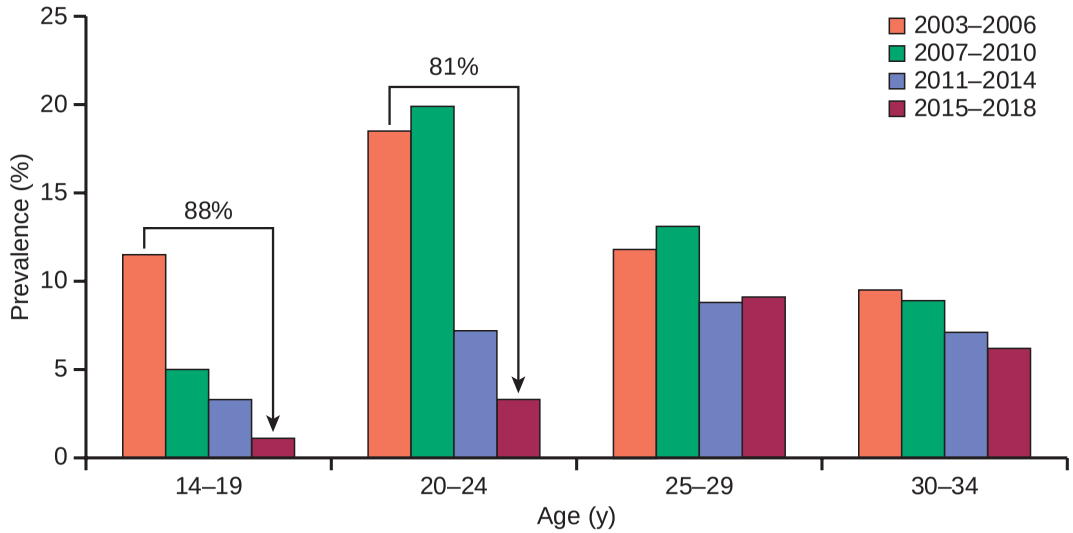
[a] HPV2 (Cervarix, GSK), which contains HPV types 16 and 18, was not distributed in the US after 2017. Manufacture of HPV4 (Gardasil, Merck), which contained HPV types 6, 11, 16 and 18, was discontinued in 2017. Persons who received either of these vaccines before 15 y on a 0 and 6-12 mo or 0, 1-2, and 6 mo schedule are considered adequately vaccinated (in this sense, the 2-dose schedule is "retroactive"). Persons who received either of these vaccines at ≥15 y on a 0, 1-2, and 6 mo schedule are considered adequately vaccinated. HPV9 may be used to complete a schedule initiated with either HPV2 or HPV4.

[b] Labeled indications also include prevention of certain precancerous lesions.

[c] If Dose 2 is administered earlier than 5 mo after Dose 1, administer a third dose at least 4 mo after Dose 2. Immunocompromised persons in this age group, including those with humoral or cellular immune deficiencies, HIV infection, cancer, organ transplantation, autoimmune disease, and immunosuppressive therapy, should receive the 3-dose schedule. Those with asplenia, asthma, chronic granulomatous disease, chronic liver, lung, or renal disease, cochlear implants, cerebrospinal fluid leaks, complement deficiencies, diabetes, heart disease, and sickle cell disease may receive the 2-dose schedule.

[d] See text regarding age of initiation.

FIGURE 19.3 — Effectiveness of Human Papillomavirus Immunization in the United States



The figure shows the prevalence of infection with HPV4 types among females by age group and across sequential survey periods, from the prevaccine era (2003 to 2006) to the most recent postvaccine era (2015 to 2018). Note the dramatic decrease (arrows) in prevalence among younger women after routine vaccination of girls and young women was recommended in 2006. During roughly the same period there was a 77% decrease in the detection of HPV16- and HPV18-attributable precancers among young women who had been screened (Gargano JW, et al. *Int J Cancer*. 2023;152:137-150). Moreover, studies have found that the prevalence of infection with HPV4 types decreased among unvaccinated women, suggesting herd effects (Rosenblum HG, et al. *Ann Intern Med*. 2022;175:918-926; Shahmoradi Z, et al. *JAMA Health Forum*. 2022;3:e222706).

Adapted from Markowitz LE, et al. *N Engl J Med*. 2023;388:1790-1798.

insufficiency, were extremely low. The crude reporting rate for syncope was 47 per million. Similar results were seen in a study of VAERS reports for HPV9 analyzed from 2014 to 2017.[52] A Vaccine Safety Datalink (VSD) study of over 600,000 doses of HPV4 found no statistically significant increased risk of GBS, stroke, VTE, or other serious events, and a subsequent study determined that the incidence of GBS following HPV4 was 0.36 per million, much less than the background rate.[53,54] Likewise, a VSD study of over 800,000 doses of HPV9 conducted from 2015 to 2017 yielded no new safety concerns.[55] Large studies from Scandinavia reveal no associations between HPV4 and multiple sclerosis, other neurologic or demyelinating diseases, autoimmune diseases, or VTEs,[56,57] and a study performed by the US Food and Drug Administration and involving 1.4 million doses of HPV4 showed no association between the vaccine and VTE.[58] Reassurance with respect to VTE was provided by a study from Denmark, wherein researchers identified 4375 incident cases of VTE occurring among 1,613,798 women; in the 889 cases occurring in women vaccinated with HPV4 during the study period, the risk of VTE was no higher in the 42 days following vaccination than at any other time period.[59]

In a comprehensive review of postlicensure safety data from 2006 to 2015, encompassing more than 15 studies and involving over 1 million people, only syncope and possibly skin infections were associated with vaccination; there was no evidence of an increase in autoimmune diseases, VTE or stroke above background rates.[60]

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component, including baker's yeast (risk of recurrent allergic reaction)
- HPV should not be administered during pregnancy (theoretical risk to the fetus or attribution of birth defects to vaccination). No deleterious effects have been demonstrated from HPV administration during pregnancy, and the risk of adverse fetal effects from a non-live vaccine is extremely low.

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)

Recommendations

All adolescents should be vaccinated against human papillomavirus. The Advisory Committee on Immunization Practices recommends initiation of HPV9 at 11 to 12 years of age, noting that the series may be started as early as 9 years of age, and that it *should* be started that early in children with a history of sexual abuse or assault. The American Academy of Pediatrics recommends initiating the HPV9 series at 9 to 12 years of age,[61] and the American Cancer Society (ACS) encourages providers to start offering the vaccine at 9 or 10 years of age.[62] Justifications for earlier initiation include more flexibility, the potential for higher completion rates, greater acceptance by parents, evidence of excellent immunogenicity, no evidence of waning immunity, fewer shots at the 11- to 12-year visit, and dissociation of the "vaccine question" from the "sex talk" that might take place with older pre-teens.[63,64]

All previously unvaccinated persons (males and females) 13 to 26 years of age should be vaccinated, whether or not they are sexually active. Unvaccinated or inadequately vaccinated persons 27 to 45 years of age may be vaccinated based on shared clinical decision-making (SCDM; see *Chapter 2: Vaccine Infrastructure in the United States—Policy and Recommendations*). Note that the ACS does not endorse vaccination of persons 27 to 45 years of age due in part to the low effectiveness and cancer prevention potential in this age group.

Persons 9 to 14 years of age at the time the series is initiated need only 2 doses (0 and 6 to 12 months); those who are 15 to 45 years of age at the time of initiation, and certain high-risk persons (see *Footnote c* in **Table 19.1**), need 3 doses (0, 1 to 2, and 6 months). Screening for human papillomavirus infection before vaccination is not recommended, and vaccine should be given regardless of personal history of human papillomavirus infection, cervical, vaginal, or vulvar dysplasia, genital warts, and Pap test results. Persons who were appropriately vaccinated with HPV2 or HPV4 do not need to receive HPV9.

Cervical cancer screening guidelines have evolved with changes in the epidemiology of human papillomavirus infection and the advent of new technologies. Current versions can be found at the following Web sites (accessed August 13, 2023):

- US Preventive Services Task Force: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/cervical-cancer-screening (note that updates to these guidelines were in progress as of August 2023)
- ACS: https://www.cancer.org/health-care-professionals/american-cancer-society-prevention-early-detection-guidelines/cervical-cancer-screening-guidelines.html
- American College of Obstetricians and Gynecologists: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/04/updated-cervical-cancer-screening-guidelines.

There are no national guidelines for cytological screening for anal cancer.

In the US, a decade and a half into the human papillomavirus vaccination program, after >100 million doses of vaccine had been distributed, only half of teenagers were up-to-date,[65] and a quarter of parents were hesitant to have their adolescents immunized.[66] Ironically, concerns about HPV safety *increased* from 2010 to

2018,[67] a time when adverse event reports actually *decreased*.[68] In the end, studies, suggest that parents trust providers and want them to give strong recommendations, as opposed to offering the "option" of vaccination.[69] Providers need to normalize vaccination against human papillomavirus by framing it as a routine part of the adolescent immunization platform.

There is no evidence that vaccination leads to increases in sexual activity.[70,71] In fact, a Canadian study showed decreases in the proportion of adolescent girls ever having had sexual intercourse after implementation of a school-based vaccination program,[72] and in the US, legislation designed to increase HPV uptake appears to have no effect on adolescent sexual behavior.[73]

Table 19.2 gives some tips for communicating about routine childhood vaccination against human papillomavirus, and **Table 19.3** gives some discussion points for SCDM. Increasing HPV uptake in practice is not easy. In one study, implementation of a 5-component communication toolkit for providers—a fact sheet library, a customized parent education web site, a binder containing disease images, a vaccination decision aid, and training in presumptive communication style and motivational interviewing—nudged initiation rates up by only 10% and completion rates by only 4% (still, these are wins).[74] Tablet-based educational interventions that directly target patient families while they wait in the exam room show promise.[75]

TABLE 19.2 — Making Strong HPV Recommendations

Parental Hesitancy	Strong Provider Position
My child does not need a vaccine against a sexually transmitted disease.	This vaccine will protect your child from getting cancer.
The vaccine is only important for girls.	Over 40% of human papillomavirus-associated cancers in the US occur in males.
My child is too young to get this vaccine.	The vaccine is more immunogenic at younger ages, and I want your child to be protected before there is any chance of exposure.
Being vaccinated will open the door to sexual activity.	There is no evidence that vaccination changes adolescent sexual behavior.
My child won't be exposed.	With 14 million new infections per year in the US, future partners could be carrying the virus and transmit to your child.
I've heard the vaccine is not safe.	Tens of millions of doses have been given in the US since 2006, with no serious safety concerns being raised.
Would you give the vaccine to your own children?	I did (or will, or would).

Adapted from Tips and time-savers for talking with parents about HPV vaccine. CDC Web site. https://www.cdc.gov/hpv/hcp/for-hcp-tipsheet-hpv.pdf. Accessed August 13, 2023.

TABLE 19.3 — Discussion Points for Shared Clinical Decision Making About HPV Vaccination for Persons 27 to 45 Years of Age

- Human papillomavirus is a common sexually transmitted infection
- Most infections are transient and asymptomatic
- Persistent infection can lead to precancers and cancers, usually after several decades
- The virus is commonly acquired in adolescence and early adulthood
- Having a new sex partner is a risk factor
- Persons in long-term monogamous relationships are not likely to acquire new infection
- Most sexually active adults have been exposed to some, but not all, of the virus types in the vaccine
- Antibody tests to determine who is immune or susceptible to a given virus type are not available
- Vaccination is not routinely recommended in this age group
- Vaccine efficacy is high in uninfected persons
- Vaccine effectiveness may be low in high-risk persons and those with immunocompromising conditions
- Vaccination is prophylactic, not therapeutic

Adapted from Meites E, et al. *MMWR*. 2019;68:698-702; HPV vaccination for adults aged 27-45 years. CDC Web site. https://www.cdc.gov/vaccines/hcp/admin/downloads/isd-job-aid-scdm-hpv-shared-clinical-decision-making-hpv.pdf. Accessed June 11, 2023.

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Influenza

The Pathogen

Influenza virus, which belongs to the Orthomyxoviridae family, is enveloped and has a segmented, single-stranded RNA genome. Two major surface proteins are involved in infectivity and generation of protective immune responses.[1] Hemagglutinin (H) mediates attachment, and antibodies directed against it block attachment and fusion, neutralize infectivity, and are protective against infection. Neuraminidase (N) mediates release from cells, and antibodies against it limit the spread of infection and reduce disease severity. Proteolytic cleavage of the H molecule is required for infectivity. H and N types for influenza A viruses are designated by numbers—since 1977, the predominant circulating strains have been A(H1N1) and A(H3N2). The H and N molecules undergo minor changes from year to year that result in slight variation in antigenicity, termed *antigenic drift* (this is why infection or immunization one year may not prevent infection the next year). Occasionally, a major change occurs, resulting in strains that express novel H or N molecules to which few people have immunity—this is termed *antigenic shift*.

Antigenic shift can occur when an animal (usually a pig) is simultaneously infected with an animal strain of influenza A (usually an avian strain) and a human strain (pigs are in a position to be exposed to both). Through *reassortment*, the human strain packages the RNA segment encoding the avian H or N molecule, creating a human virus with the avian H or N type. A global reservoir of influenza viruses (and gene segments) exists in aquatic birds.[2] These viruses are adapted to the avian enteric tract and do not cause disease. However, when they enter the pig along with human influenza strains, new strains can emerge that spread from person to person; this is what leads to pandemics. Pigs are good "mixing vessels" because their respiratory epithelial cells express both alpha 2,3-linked sialic acid residues, to which avian influenza viruses bind (via the H molecule), as well as alpha 2,6-linked sialic acid residues, to which human influenza viruses bind.

Pandemic strains can also emerge when an animal influenza virus adapts directly to humans. This is what happened in 1918, when the "Spanish flu" strain of A(H1N1) killed 50

million people worldwide in what has been called the "mother of all influenza pandemics".[3,4] All interpandemic influenza A epidemics since then have been caused by descendants of the 1918 strain that underwent antigenic drift; the 1957 H2N2 "Asian flu" and the 1968 H3N2 "Hong Kong flu" pandemics were caused by descendants of the 1918 virus that underwent antigenic shift. The 2009 A(H1N1) pandemic was caused by a reassortant that derived from several exchange events between circulating viruses.[5] In particular, the H gene came from classic swine influenza and the N gene from Eurasian swine influenza (both of which were descendants of the 1918 virus); other genes came from a human H3N2 strain and an avian strain. Fewer than 10% of adults <65 years of age had antibodies to the 2009 A(H1N1) pandemic strain, suggesting that the virus had not circulated among humans for several generations.[6] The virus emerged in April 2009, and by March 2010 in the US alone there had been an estimated 60 million cases, 270,000 hospitalizations, and 12,270 deaths.[7] Most cases (35 million), hospitalizations (158,000), and deaths (9420) had occurred among persons 18 to 64 years of age. The same strain of A(H1N1) has persisted seasonally since then.

Influenza B viruses do not change as much from year to year because they have a limited host range (humans and seals), and they mutate at a slower rate. There are two main lineages of B strains—Victoria and Yamagata.[8] From year to year, B strains account for varying proportions of disease but seldom predominate, and from year to year, Victoria and Yamagata account for varying proportions of the prevalent B strains. Until 2012, influenza vaccines only contained the B Victoria lineage; now all of them contain both B lineages. There is some evidence that the B/Yamagata lineage might have become extinct during the COVID-19 pandemic.[9]

Influenza virus infects columnar epithelial cells of the respiratory tract, causing necrosis, edema, and inflammation. Systemic symptoms are probably caused by circulating interleukin-6 and interferon-alpha induced by the infection. Influenza A virus infects all age groups and causes the most severe disease. Influenza B is milder and occurs more often in children.

Clinical Features

The incubation period is 1 to 4 days. Symptoms include abrupt onset of fever, myalgia, headache, sore throat, photophobia, tearing, rhinitis, and nonproductive cough. Older children may experience nausea and vomiting, and infants may present with a sepsis-like syndrome. Fever is usually high and may be accompanied by prostration. Uncomplicated illness lasts from 3 to 7 days, and while recovery is usually rapid, some patients may have lingering cough and fatigue for several weeks.

Secondary bacterial infection (eg, pneumonia, sinusitis, and otitis media) is the most common complication of influenza. The risk of complications and hospitalization with influenza is highest among persons ≥65 years of age, the very young, and those with certain underlying medical conditions. The virus itself may cause pneumonia, encephalitis, myocarditis, and myositis. Young children and persons with morbid obesity were at particular risk for complications during the 2009 pandemic, as were pregnant women.[10]

Epidemiology and Transmission

Influenza virus is transmitted from person to person through large-particle respiratory droplets that are expelled during coughing or sneezing. Maximum communicability occurs from 1 day before the onset of illness to 5 days after. Disease activity typically peaks between December and March in temperate regions of the Northern Hemisphere and between April and September in temperate regions of the Southern Hemisphere. In tropical areas, activity occurs throughout the year; because of this, traveling with tourist groups that include persons from these areas increases the risk of infection during the summer. Annual infection rates are approximately 1 in 5 for children and 1 in 10 for adults.[11] School-aged children are at low risk for complications, but they play a key role in spreading the virus in the community. In fact, during the 2009 pandemic a tight correlation was seen between the date of school opening and the beginning of influenza activity in communities.[12] Routine vaccination of school children in Japan between the 1960s and early 1980s resulted in dramatic reductions in influenza-related mortality among the elderly and other high-risk groups.[13]

Annual hospitalization rates for laboratory-confirmed influenza are around 20 per 100,000 for children 2 to 5 years of age, but as high as 240 to 720 per 100,000 for infants <6 months of age.[14] The rate of hospitalization for infants is similar to the rate for children with high-risk conditions and is comparable to that for adults ≥65 years of age. The annual outpatient burden of influenza may be as high as 100 clinic visits and 30 emergency department visits per 1000 children.

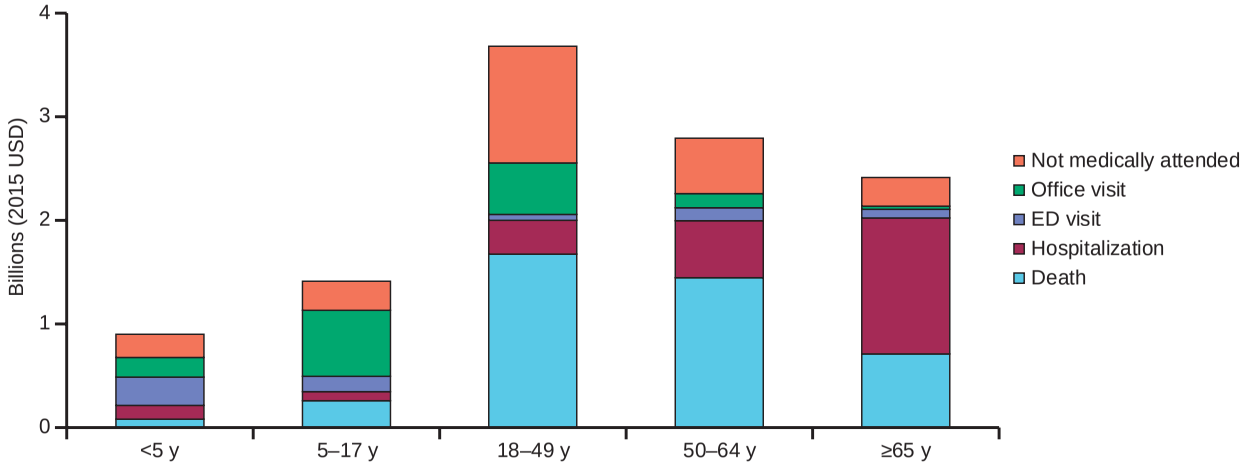
Table 20.1 shows the annual influenza disease burden in the US and **Figure 20.1** shows the estimated annual economic impact. The seasonal influenza epidemic that was expected to overlay a surge in COVID-19 cases in the fall and winter of 2020 never materialized, likely due to the physical measures implemented to control COVID-19. Influenza did return in the 2021-2022 season; however, the overall cumulative influenza hospitalization rate was only 16 per 100,000, lower that during the 4 seasons preceding the COVID-19 pandemic, when hospitalization rates ranged from 62 to 103 per 100,000.[15]

TABLE 20.1 — Annual Estimated Influenza Disease Burden in the United States

Season	Symptomatic Illnesses			Hospitalizations			Deaths		
	Age								
	≤17 y	18-64 y	≥65 y	≤17 y	18-64 y	≥65 y	≤17 y	18-64 y	≥65 y
2017-2018	10,568,005	25,341,114	5,134,430	43,386	200,420	466,766	526	8,118	43,002
2018-2019	9,641,666	17,019,469	2,247,586	39,205	131,595	204,326	372	5,986	21,261
2019-2020	11,631,555	21,437,176	1,881,249	48,298	160,888	171,023	486	7,911	11,945
2021-2022[b]	3,636,441	5,092,898	568,547	13,730	35,846	51,686	0[c]	783	3,818
Annual average	8,869,417	17,222,664	2,457,953	36,155	132,187	223,450	346	5,700	20,007
Annual average total (all ages)			28,550,034			391,792			26,052

[a] The table shows data for the most recent 4 seasons as posted on the CDC Web site at https://www.cdc.gov/flu/about/burden/past-seasons.html (accessed September 26, 2023).
[b] Influenza activity was minimal during the 2020-2021 season and estimates are not available. Estimates for 2021-2022 are preliminary.
[c] Deaths (N=39) in this age group were reported in another surveillance system (Influenza-Associated Pediatric Mortality. FluView Interactive Web site. https://gis.cdc.gov/GRASP/Fluview/PedFluDeath.html. Accessed September 26, 2023).

FIGURE 20.1 — Economic Burden of Influenza



Annual US economic burden by age group and influenza-attributable outcome. Estimates include direct and indirect costs.

Adapted from Putri WCWS, et al. *Vaccine*. 2018;36:3960-3966.

Immunization Program

Figure 20.2 shows the evolution of influenza immunization recommendations in the US. Recommendations for seasonal influenza vaccination are updated each summer. Recommendations for influenza vaccination of health care personnel (HCP) were last updated in 2011.[16]

Studies conducted before universal immunization was recommended suggested that influenza immunization of working adults could reduce health care provider visits and lost workdays by nearly half, at a net cost savings,[17] but the potential benefits would be highly dependent on the strain match in a given season.[18] The cost of immunization per quality-adjusted life year (QALY) gained was estimated to be $28,000 (2000 dollars) for persons 50 to 64 years of age, compared to $980 for persons ≥65 years of age.[19] The cost per QALY gained in healthy children 6 to 23 months of age was estimated to be around $12,000 (2003 dollars), and for adolescents around $119,000.[20] The additional benefits that would accrue from the herd immunity effects of immunizing all school-aged children were difficult to assess.

Between 2000 and 2009, incremental recommendations included more segments of the population, such that by 2010 routine immunization of all persons ≥6 months of age was recommended. Vaccines containing two A strains (H1N1 and H3N2) and two B strains (Victoria and Yamagata lineages) were first licensed in 2012, and by 2020 had replaced 3-valent vaccines. Several models predicted public health benefits and cost savings with the switch to 4-valent vaccines.[21,22] One that included herd effects suggested that the switch would reduce annual influenza cases by about 2 million, with the accrual of 18,500 QALYs and total savings of $7.1 billion.[23]

Since 2022, the Advisory Committee on Immunization Practices (ACIP) has preferentially recommend *higher dose or adjuvanted influenza vaccines* (see below) for persons ≥65 years of age. One model predicted that substitution of high-dose IIV (hdIIV) for IIV4 in US seniors would avert nearly 170,000 cases of influenza, 21,000 hospitalizations, and 5200 deaths, at a net societal cost savings[24]; another study suggested that the impact of hdIIV among adults ≥65 years of age from its introduction in 2010 through 2019 was the aversion of 1.3 million influenza cases, 0.5 million cardiorespiratory hospitalizations, and 74,000 deaths, with an absolute savings of $4.6 billion.[25] Studies predict that similar benefits would accrue from using adjuvanted IIV (aIIV) in persons ≥65 years of age. A dynamic modeling study showed, for example, that from the societal perspective a routine strategy of aIIV3 for persons ≥65 years of age and standard (non-adjuvanted) IIV (sIIV) for persons <65 years of age dominated over an all-IIV4 strategy regardless of the intensity of the influenza season and the degree of match between vaccine and circulating strains.[26] Real-world assessments suggest that use of aIIV and hdIIV in persons ≥65 years of age are associated with comparable annualized all-cause and influenza-related costs.[27] Finally, in a model of routine use of higher dose or adjuvanted vaccines among persons ≥65 years of age, accounting for variability in vaccine effectiveness and disease severity from season to season, 20% of scenarios were cost-saving and 90% showed incremental cost-effectiveness of <$195,000 per QALY gained.[28]

Vaccines

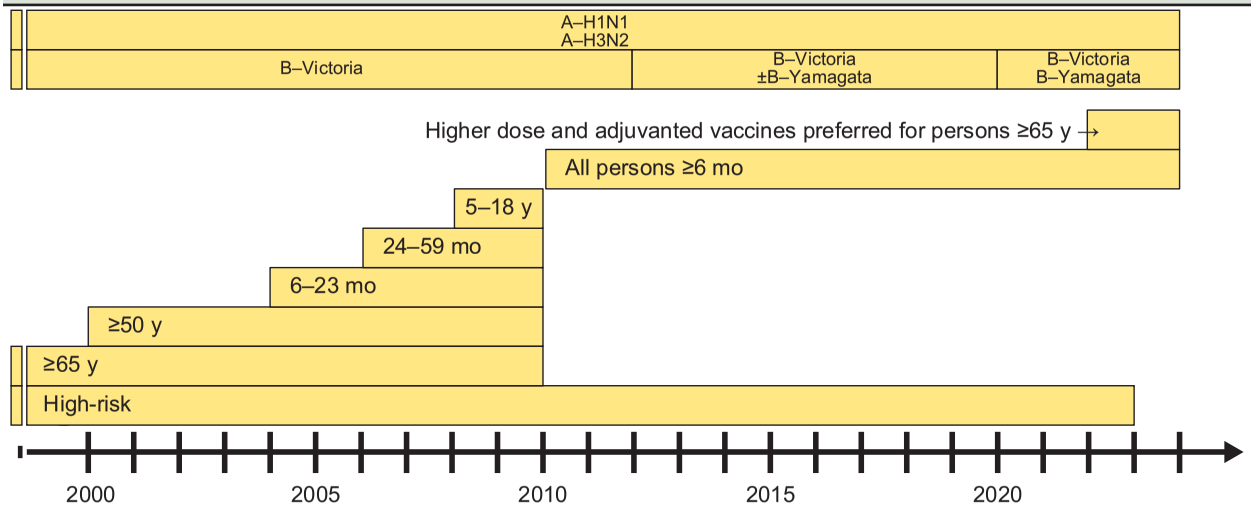
Characteristics of the influenza vaccines licensed in the US are given in **Table 20.2**.

Influenza virus surveillance is conducted by the World Health Organization's (WHO's) Global Influenza Surveillance and Response System.[29] Each year, Collaborating Centers isolate and test thousands of circulating viruses, determining which strains predominate and which are likely to emerge (so called *fitness forecasting)*; the phenotypic, genetic, antigenic, and serologic properties of these viruses are characterized, and the data and isolates are shared with the WHO.[30] Twice a year—in February for the Northern Hemisphere and in September for the Southern Hemisphere—the directors of the Collaborating Centers, Essential Regulatory Laboratories and representatives of key national laboratories and academies convene to select the strains that will be recommended for inclusion in the respective seasonal vaccines. The final decision about strains to be included in vaccines used in the US is made by the U.S. Food and Drug Administration.[31]

The WHO provides candidate vaccine viruses (CVVs) to manufacturers. For egg-based manufacturing, the CVVs are originally isolated and propagated in eggs. If a given virus grows well, it may be provided to manufacturers as low-passage seed virus. If it does not grow well, it may be reassorted in the laboratory with a *donor strain* that does grow well in eggs (since the 1970s, a strain called PR8 that is well adapted to growth in eggs has been used as a donor virus for influenza A reassortants). The reassortant CVV will have the backbone of the donor virus but the H and N of the clinical isolate; further selection for high growth characteristics is necessary after reassortment because the "new" H and N may affect replication. The CVVs provided for egg-based vaccine manufacturing have only been passaged in eggs.

The CVVs for cell-based manufacturing are isolated and passaged in mammalian cells, and they are selected for their ability to grow in cells or reassorted with donor viruses that grow well in cells.[32] For rIIV, the earliest available sequence encoding the H of cell culture-isolated CVVs is used to express the protein in-vitro.[33] Because the source CVVs for ccIIV and rIIV have never "seen" eggs, the H in these vaccines does not contain egg adaptation mutations (see below for the implications of this). Note that for

FIGURE 20.2 — Influenza Immunization Recommendations Over Time



The figure shows major steps in the evolution of influenza immunization recommendations in the US (bottom boxes), as well as the influenza virus strains represented in the vaccines (top boxes). Beginning around 2008, there was a shift in objective from direct protection of high-risk persons (eg, those with underlying medical conditions, older adults, and young children) to protection of the community, best accomplished by the immunization of older children (one model estimated that immunizing 20% of school children would reduce overall mortality in adults >65 y more effectively than immunizing 90% of those adults [Longini IM. *Pediatrics*. 2012;129:S63-S67]). By 2010, influenza vaccine was recommended for approximately 85% of the US population, paving the way for annual immunization of all persons ≥6 mo.

Adapted from Influenza ACIP vaccine recommendations. CDC Web site. http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html. Accessed September 26, 2003

TABLE 20.2 — Influenza Vaccines, 2023-2024 Season[a]

Trade Name[b]	Manufacturer/ Distributor	Egg-Based?	Abbreviation	Presentation	Preservative	Labeled Ages	Dose/ Administration
Afluria	CSL Seqirus	Yes	IIV	Prefilled syringe (10)	None	≥36 mo	≥36 mo: 0.5 mL IM
				5 mL vial (1)[c]	Thimerosal (24.5 mcg mercury)	≥6 mo	6-35 mo: 0.25 mL IM ≥3 mo: 0.5 mL IM
Fluad[d]	CSL Seqirus	Yes	aIIV	Prefilled syringe (10)	None	≥65 y	0.5 mL IM
Fluarix	GSK	Yes	IIV	Prefilled syringe (10)	None	≥6 mo	0.5 mL IM
Flublok	Sanofi	No[e]	rIIV	Prefilled syringe (10)	None	≥18 y	0.5 mL IM
Flucelvax	CSL Seqirus	No[f]	ccIIV	Prefilled syringe (10)	None	≥6 mo	0.5 mL IM
				10-dose vial (1)	Thimerosal (25 mcg mercury)		
Flulaval	GSK	Yes	IIV	Prefilled syringe (10)	None	≥6 mo	0.5 mL IM
Flumist	AstraZeneca	Yes	LAIV	Prefilled sprayer (10)	None	2-49 y	0.1 mL per nostril[g]
Fluzone	Sanofi	Yes	IIV	Prefilled syringe (10)	None	≥6 mo	0.5 mL IM
				1-dose vial (10)	None	≥6 mo	0.5 mL IM[h]
				10-dose vial (1)	Thimerosal (25 mcg mercury/ 0.5 mL)	≥6 mo	6-35 mo: 0.25 mL or 0.5 mL IM[i] ≥36 mo: 0.5 mL IM
Fluzone High-Dose	Sanofi	Yes	hdIIV	Prefilled syringe (10)	None	≥65 y	0.7 mL IM[j]

[a] All influenza vaccines in the US are 4-valent, containing A(H1N1), A(H3N2), B (Victoria lineage), and B (Yamagata lineage) strains. For IIV, the standard hemagglutinin content is 15 mcg/0.5 mL from each of the strains; Flublok contains 45 mcg/0.5 mL from each strain and Fluzone High-Dose contains 60 mcg/0.5 mL from each strain. LAIV contains 106.5-7.5 fluorescent focus units of each live attenuated, cold-adapted, temperature-sensitive reassortant strain per 0.2 mL. None of the listed products contain latex. The dose of Flulaval and Fluarix is 0.5 mL for all ages; the dose of Fluzone is either 0.25 mL or 0.5 mL from 6 mo-2 y and 0.5 mL at ≥3 years of age. See the respective package inserts, which are usually updated each summer, for details on dosing, excipients, and contaminants. Influenza vaccines are interchangeable in the sense that one product (any inactivated influenza vaccine or live influenza vaccine) can be used one year and a different product the next year. Although no data are available regarding 2 consecutive doses of different products in the same year, it is assumed that this is acceptable. Costs are generally as follows (2023 USD): pediatric public sector, 15-21; pediatric private sector, 18-30; adult public sector, 14-19; adult private sector, 18-30. Note that idIIV (Fluzone Intradermal; Sanofi) was discontinued after the 2017-2018 influenza season.

[c] The 5 mL vial is approved for up to 20 punctures (for example, one could withdraw 20 x 0.25 mL doses or 10 x 0.5 mL doses). Afluria is approved for administration to persons 18-64 y using the PharmaJet Stratis Needle-Free Injection System.

[d] Fluad contains the adjuvant MF59, a squalene-based oil-in-water emulsion (see **Table 1.3**).

[e] Prepared by recombinant DNA technology.

[f] Prepared in cell culture.

[g] If the patient sneezes after administration, the dose should not be repeated. However, if only one-half of a dose is given (ie, administration in only one nostril), the dose is considered invalid; options include completing the vaccination on the same day with a half-dose in the other nostril, giving a dose of IIV at any time, or giving a (full) dose of LAIV in 4 weeks. Individuals who are too old to receive LAIV themselves or who have medical contraindications other than severe immunosuppression may administer the vaccine. Administration of LAIV is not considered an aerosol-generating procedure.

[h] If a 1-dose vial is used for a 0.25 mL dose, the remainder of the vaccine should be discarded.

[i] The multidose vial cannot be used to deliver >10 doses, regardless of the volume of each dose.

[j] The dose for 4-valent Fluzone High-Dose is higher (0.7 mL) than it was for the 3-valent version (0.5 mL).

Adapted from Grohskopf LA, et al. *MMWR*. 2023;72(RR-2):1-25. Also see the respective package inserts.

the same season, the strains used in non–egg-based vaccines may be different than those in the egg-based vaccines; while antigenically similar, the strains are selected for their ability to grow well in their respective substrates. In the 2023-2024 season, the egg-based vaccines contained the H from an A/Victoria/4897/2022 (H1N1)pdm09-like virus and an A/Darwin/9/2021 (H3N2)-like virus; the non–egg-based vaccines contained the H from an A/Wisconsin/67/2022 (H1N1)pdm09-like virus and an A/Darwin/6/2021 (H3N2)-like virus. The B-Victoria and B-Yamagata strains (B/Austria/1359417/2021-like and B/Phuket/3073/2013-like, respectively) were the same for each type of vaccine.

Manufacturing proceeds as follows:

- Egg-based vaccines—To produce IIV, the seed viruses are inoculated into hen's eggs; progeny virions are concentrated from allantoic fluid, chemically inactivated, disrupted or *split* using solvents and detergents, and the H and N are then purified and formulated for inclusion in the final product. To produce LAIV, the seed viruses are reassorted with a donor virus that is *attenuated, cold-adapted* (replication is efficient at 25°C), and temperature-sensitive (replication is restricted at 37°C to 39°C). The reassortants are grown in hen's eggs; progeny viruses are concentrated from allantoic fluid, suspended in stabilizing buffer, and packaged for intranasal administration. LAIV replicates in the (relatively cold) nasopharynx but not in the (relatively warmer) lower respiratory tract, and therefore does not produce disease.
- Cell-based IIV—The seed viruses are inoculated into bulk mammalian cell culture bioreactors; progeny virions are concentrated from the supernatants, chemically inactivated, disrupted or *split* using solvents and detergents, and the H and N are then purified and formulated into the final product.
- Recombinant IIV—The genes encoding H from the seed viruses are introduced into a baculovirus vector, which is used to express the protein in bioreactors containing suitable substrate cells; the H is then purified and formulated into the final product.

Table 20.3 gives a comparison of the various influenza vaccine manufacturing technologies. Note that H is viewed as the dominant antigen for protection against influenza, although N may have an independent role.[34,35] Inactivated vaccines are only standardized by their H content, and whereas split virus vaccines contain N as well as small amounts of other viral proteins, recombinant vaccines only contain H. sIIVs have been used for decades; they contain 15 mcg of H from each strain. Higher dose or adjuvanted vaccines build upon the standard platform[36] to improve immunogenicity, as follows: *hdIIV* (licensed in 2009) contains 60 mcg of H from each strain; *rIIV* (licensed in 2012) contains 45 mcg of recombinant-derived H from each strain; and *aIIV* (licensed in 2015) contains 15 mcg of H from each strain plus an adjuvant (MF59C.1) (see *Chapter 1: Introduction to Vaccinology—The Germinal Center Reaction*).

TABLE 20.3 — Comparison of Influenza Vaccine Technologies

Characteristic	Egg-Based	Cell-Based	Recombinant
Dependence on hens	Yes	No	No
Time from candidate selection to production	6-8 mo	<6 mo	<6 mo
Production capacity	Excellent	Good	Good
Production cost	Low	High	High
Contains hemagglutinin	Yes	Yes	Yes
Contains neuraminidase	Yes	Yes	No
Yield dependent on influenza virus replication	Yes	Yes	No
Pandemic preparedness	Good	Better	Better
Type of vaccine	Live or non-live	Non-live	Non-live
Antigenic fidelity with wild-type	At risk	Good	Good

An A(H5N1) IIV (Sanofi) directed against the avian strain that emerged in Southeast Asia in 2005[37] was approved in 2007. An A(H5N1) IIV containing the adjuvant AS03 (manufactured by ID Biomedical Corporation and distributed by GSK) was licensed in 2013, and a cell-based A(H5N1) IIV containing the adjuvant MF59 (Audenz; CSL Seqirus) was licensed in 2019. These vaccines are not commercially available but are included in the National Stockpile for emergency use.

Domestic influenza vaccine production is inefficient and insufficient, vaccine effectiveness is suboptimal, and coverage rates are low. The National Influenza Vaccine Modernization Strategy 2020-2030[38] aims to strengthen and diversify influenza vaccine development, manufacturing, and supply chain (including the use of non–egg-based vaccines and the capability to deliver a pandemic vaccine within 12 weeks); promote innovative approaches and use of new technologies to detect, prevent, and respond to influenza (including the development of a universal vaccine that can provide protection against multiple subtypes of the virus); and increase vaccine access and coverage across all populations.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Each years' influenza vaccines are licensed based on potency (antigen content) as opposed to efficacy. The assumption is made that, given the same potency as last year's vaccine, this year's should be just as immunogenic. The accepted correlate of protection is a hemagglutination inhibition titer of ≥1:40; 50% of individuals who achieve this level of antibody are presumed to be protected.[39] Vaccine-induced immunity to influenza is good for only 1 year because antibody wanes and the vaccine strains chosen for a given year may not be a good match with the prevailing strains. Vaccination during previous seasons does not appear to negatively affect vaccine effectiveness in the current season.[40] However, there is evidence that protection from IIV wanes during the influenza season itself. Potential explanations include evolution of antigenic mismatch between circulating strains and the vaccine, immune senescence in the elderly, and lack of priming in the young,[41,42] and vaccine effectiveness may wane as much as 8% to 9% per month after vaccination.[43] Any potential benefits of delaying vaccination in order to provide better protection during peak season need to be balanced with the unpredictability of influenza activity and the likelihood of missing opportunities to vaccinate.[44]

Efficacy (eg, reduction in laboratory-confirmed cases in studies) and effectiveness (eg, reduction in symptomatic cases when the vaccine is used in the real world) may differ markedly. For example, a systematic review in 2005 found that the efficacy of IIV in children >2 years of age was 65% but effectiveness was only 28%.[45] The messaging around influenza vaccine effectiveness must be nuanced—whereas vaccinees may still get the flu, they are less likely to have *severe flu* and are likely better off with vaccine induced immunity than without. Moreover, modeling predicts that even vaccines with low efficacy can have profound effects on hospitalizations and deaths—if uptake is sufficient in the right segments of the population.[46]

Standard IIV

Estimates of effectiveness against influenza illness in children range widely, from about 20% to over 90%.[47-49] Meta-analyses place the effectiveness against pediatric hospitalization due to A(H1N1) above 70%[50]; effectiveness is lowest (36%) for A(H3N2) and may be higher for IIV (69%) than for LAIV (44%).[51] For young, previously unvaccinated children, effectiveness is nearly doubled if they receive 2 doses in the same season.[52]

Among healthy adults <65 years of age, randomized controlled trials demonstrate efficacy of 70% to 90% against laboratory-confirmed influenza illness. Whereas estimates of efficacy drop to 50% to 77% when the vaccine and circulating strains are not well matched, protection against hospitalization appears to be preserved, and protection against death among persons hospitalized with respiratory symptoms has been demonstrated.[53] Efficacy against illness is lower among adults ≥65 years of age, but protection against influenza-related death may be as high as 80%.

The H receptors on avian cells are different from those in humans; in order to grow well in eggs, human influenza virus isolates must acquire mutations in H that improve avian cell receptor binding.[54] These mutations—commonly referred to as *egg adaptation*—can affect immunogenicity and reduce vaccine effectiveness.[55] A(H3N2) strains appear to be particularly susceptible to egg adaptation,[56] and this may in part explain the lower effectiveness of A(H3N2) vaccines (**Table 20.4**).[57,58] ccIIV may have greater antigenic relatedness to circulating strains, and this can translate into better effectiveness. In a controlled study of ccIIV4 in children and adolescents across 3 influenza seasons and 8 countries, overall efficacy against laboratory confirmed influenza was 55%; efficacy was highest (81%) for A(H1N1) and lowest (42%) for A(H3N2).[59] A retrospective cohort study of >13 million Medicare beneficiaries during the 2017-2018 season showed that the effectiveness of 4-valent ccIIV was about 10% higher than 4-valent egg-based IIV,[60] and similar results were seen among commercially insured adults 50 to 64 years of age during the same season.[61] In another study conducted during the same season, adjusted relative vaccine effectiveness was as high as 36%.[62] However, the relative benefits of ccIIV may depend on age. For example, a large electronic health records study showed that the relative effectiveness of ccIIV against influenza-related medical encounters among children 4 to 17 years of age (2019-2020 season) was 12.2%[63]; another study done during the same season showed no relative benefit for those ≥65 years of age.[64] Any advantages of cell-based over egg-based IIV are also dependent on the dominant circulating strains in a given season.[65]

TABLE 20.4 — Effectiveness of IIV Against Laboratory-Confirmed, Medically-Attended Influenza

Influenza Strain	Children and Adolescents (<20 y)	Working Age Adults (20-64 y)	Older Adults (>60 y)
A(H1N1)	69% (49-81)	73% (52-84)	62% (36-78)
A(H3N2)	43% (28-55)	35% (14-51)	24% (–6-45)
B	56% (38-69)	54% (16-75)	63% (33-79)

Adapted from Belongia EA, et al. *Lancet Infect Dis*. 2016;16:942-951. Data are from a systematic review and meta-analysis of test-negative design studies published from 2004 to 2015. Pooled effectiveness estimates are shown (95% confidence intervals are in parentheses). For A(H1N1), the data shown are only for multivalent seasonal vaccines containing the 2009 pandemic strain.

Efficacy of maternal immunization with IIV in preventing hospitalization of infants due to influenza exceeds 90%.[66]

Higher Dose or Adjuvanted IIV

Currently available higher dose or adjuvanted vaccines (see above) produce stronger humoral and cellular immune responses than sIIV,[67] and their special status with respect to protecting older individuals is supported by clinical trials and real-world evidence.

A Phase 3 study involving almost 32,000 adults ≥65 years of age demonstrated 24% relative efficacy of hdIIV against laboratory-confirmed influenza-like illness compared to sIIV,[68] and a study of approximately 75,000 veterans showed 25% better protection against influenza- or pneumonia-associated hospitalizations.[69] A retrospective cohort study involving over 900,000 recipients of hdIIV and 1.6 million recipients of sIIV found hdIIV to be 22% more effective in preventing hospitalizations,[70] and a recent meta-analysis supports higher efficacy of hdIIV over sIIV.[71] hdIIV was 36% more effective in preventing influenza-related death during the 2012-2013 season,[72] although a study conducted from 2016 to 2019 among patients with cardiovascular disease showed no incremental benefit of 3-valent hdIIV in preventing all-cause mortality or cardiopulmonary hospitalization when compared to 4-valent sIIV.[73] A meta-analysis that included data from 10 consecutive influenza seasons (2009 to 2019) and over 22 million people showed the relative effectiveness of hdIIV3 was 16% against influenza-like illness and 12% against influenza hospitalization as compared to sIIV; relative effectiveness against pneumonia/influenza mortality was 40%.[74]

In a study involving nearly 7000 adults ≥65 years of age who were randomized to receive aIIV4 or Tdap as control during the 2016-2017 season in both Northern and Southern Hemispheres, vaccine efficacy against all influenza was only 19.8%.[75] Importantly, the majority of cases were caused by influenza A(H3N2); 85% of characterized isolates were mismatched to the vaccine strain and, in fact, efficacy was much higher (49.9%) against influenza caused by matched strains. The mismatch during this season negatively affected the performance of all vaccines among older adults, including hdIIV.[76] hdIIV and aIIV have comparable incremental effectiveness against hospital encounters among adults ≥65 years of age when compared to sIIV, of the order of 10%.[77,78] In a systematic review and meta-analysis of 21 studies conducted in North America or Europe between 2006 and 2020,[79] pooled estimates of absolute effectiveness of aIIV against hospitalization was around 50% to 60% compared to sIIV, and relative effectiveness against influenza-related medical encounters was around 14%.

A head-to-head comparison of 4-valent rIIV to 4-valent (non-recombinant) IIV among nearly 9000 adults ≥50 years of age showed 30% better efficacy against influenza-like illness.[80] In a study comparing the effectiveness of multiple types of IIV in persons ≥65 years of age, rIIV4, aIIV3, and hdIIV3 showed relative efficacies of 13.3%, 8.2%, and 6.8%, respectively, against hospital encounters compared to sIIV4.[81]

LAIV

In a multinational trial conducted during the 2004-2005 influenza season in children <5 years of age, culture-confirmed influenza illness caused by any strain was reduced by 55% in recipients of LAIV compared with recipients of IIV; for matched strains, the reduction was 45% and for mismatched strains it was 58%, suggesting that LAIV provided broader cross-protection.[82] A meta-analysis published in 2009 suggested that LAIV was 46% more effective than IIV in preventing influenza illness due to matched strains among young children receiving 2 doses in one season[83]; the relative efficacy among older children receiving one dose was 35%. A pooled analysis of clinical trials suggested that LAIV was 85% efficacious at preventing acute otitis media related to influenza compared with placebo and 54% compared with IIV.[84] LAIV has also been shown to be efficacious in adults,[85] albeit more comparable to IIV.[86,87]

Consistent data emerged after the 2013-2014 season suggesting that the LAIV in use at the time was ineffective against influenza A(H1N1).[88-91] Whereas in the 2014-2015 season the ACIP had expressed a preference for LAIV for healthy children 2 to 8 years of age,[92] the preference was retracted in the 2015-2016 season, and for the 2016-2017 and 2017-2018 seasons it was recommended that LAIV not be used.[93] A new A(H1N1) strain was incorporated into LAIV for the 2017-2018 season, restoring immunogenicity to that of pre-pandemic LAIV[94] and leading ACIP to reinstate LAIV as an option for the 2018-2019 season.[95] Since then, CVVs for inclusion in LAIV have been tested for replicative fitness in human nasal epithelial cells.

Safety

IIV cannot cause influenza. Less than one third of vaccinees develop local redness or induration for 1 to 2 days at the site of injection. Fever, chills, headache, and malaise, although infrequent, most often affect children who have had no previous exposure to the antigens contained in the vaccine. These reactions generally begin 6 to 12 hours after vaccination and persist for only 1 to 2 days. Immediate reactions, which are rare and presumably allergic in nature, may consist of hives, angioedema, allergic asthma, or systemic anaphylaxis. hdIIV and aIIV are more reactogenic than sIIV.

In a retrospective study of 45,000 children 6 to 23 months of age, receipt of IIV was not associated with any adverse medically attended outcome,[96] and no serious medically attended events were seen in a Vaccine Safety Datalink study of IIV involving approxi-

mately 66,000 children 24 to 59 months of age.[97] Some studies in adults show similar rates of systemic symptoms, such as fever, malaise, myalgia, and headache, between vaccinees and placebees. There is no evidence that IIV has any deleterious impact on HIV infection.

After receipt of LAIV, children report rhinorrhea or congestion (20% to 75%), headache (2% to 46%), fever (up to 26%), vomiting (3% to 13%), abdominal pain (2%), and myalgias (up to 21%). Symptoms are more often associated with the first dose and are self-limited. Adult vaccinees report rhinorrhea (44%), headache (40%), sore throat (28%), tiredness (26%), muscle aches (17%), cough (14%), and chills (9%). Among 2619 Vaccine Adverse Event Reporting System reports received between 2005 and 2012, there was no pattern suggesting new or unexpected adverse events related to LAIV; serious events were rare and largely unrelated to vaccine.[98] Likewise, prospective surveillance of 62,040 recipients of 4-valent LAIV during the 2013-2014 season yielded no safety signal.[99] Up to 80% of children shed at least one vaccine virus strain from 1 to 21 days postvaccination, but the risk of horizontal transmission is very low. Up to 50% of adults may have viral antigen in nasal secretions for the first 7 days after vaccination. Person-to-person transmission among adults has not been assessed.

In August 2023, the ACIP removed all precautions regarding egg allergy and influenza vaccine.[100] A person with egg allergy of any severity may receive any age- and health status-appropriate influenza vaccine without safety measures beyond those employed for routine vaccination. A severe allergic reaction to a prior dose of influenza vaccine remains a contraindication to future doses of that vaccine, and in some cases, other influenza vaccines (**Table 20.5**).

Contraindications (IIV)

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction).
- See **Table 20.5**.

Contraindications (LAIV)

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction).
- See **Table 20.5**.
- Immunodeficiency or immunosuppression, including HIV infection (risk of disease caused by live virus)
- Functional or anatomic asplenia (paucity of safety data)
- Cerebrospinal fluid leak or cochlear implant (paucity of safety data)

TABLE 20.5 — Contraindications and Precautions for Persons With a History of Severe Allergic Reaction to a Previous Dose of Influenza Vaccine

	Available Vaccine		
Vaccine Associated With Previous Reaction	**Egg-based IIV and LAIV**	**ccIIV**	**rIIV**
Egg-based IIV and LAIV	Contraindication	Precaution[a]	Precaution[a]
ccIIV	Contraindication	Contraindication	Precaution[a]
rIIV	Contraindication	Precaution[a]	Contraindication
Unknown	Consultation with allergist recommended		

[a] Vaccination should generally be deferred but might be indicated if the benefit outweighs the risk for individual patients. Providers can consider vaccination in a medical setting where health care providers can recognize and manage severe allergic reactions, as follows: 1) if there is a history of severe allergic reaction to any egg-based IIV or LAIV, consider administering ccIIV or rIIV; 2) if there is a history of severe allergic reaction to ccIIV, consider administering rIIV; and 3) if there is a history of severe allergic reaction to rIIV, consider administering ccIIV.

Adapted from Grohskopf LA, et al. *MMWR*. 2023;72(RR-2):1-25.

- Children 2 to 4 years of age who have asthma or who have had a wheezing episode in the past 12 months (risk of asthma exacerbation)
- Aspirin and other salicylate-containing therapy in children and adolescents (theoretical risk of Reye syndrome). Given the association between natural influenza infection, aspirin use and Reye syndrome, there is a theoretical risk of Reye syndrome in children who are taking aspirin (or other salicylates) and who receive LAIV. The manufacturer recommends withholding aspirin-containing medications for ≥4 weeks after vaccine administration, unless clearly needed.
- Pregnancy (theoretical risk to the fetus of live-virus vaccine or attribution of birth defects to vaccination)
- Household or health care contacts of severely immunosuppressed patients, eg, hematopoietic cell transplant recipients who are confined to protective environments with regulated airflow, filtration, etc (risk of transmission of live virus to immunosuppressed person). Persons who receive LAIV should avoid contact with severely immunosuppressed patients for 7 days; contact with patients who have lesser degrees of immunosuppression is acceptable. HCP who work in the neonatal intensive care unit may receive LAIV.
- Receipt of oseltamivir or zanamivir within the previous 48 hours, peramivir within the previous 5 days, or baloxavir within the previous 17 days (risk of decreased viral replication and poor immune response)

Precautions (IIV)

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- Personal history of Guillain-Barré syndrome (GBS) within 6 weeks of a prior dose of influenza vaccine (risk of recurrent GBS; family history not relevant)
- See **Table 20.5**.

Precautions (LAIV)

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- Personal history of GBS within 6 weeks of a prior dose of influenza vaccine (risk of recurrent GBS; family history not relevant)
- Asthma in persons ≥5 years of age (risk of asthma exacerbation)
- Underlying medical conditions that place patients at high risk for complications of influenza and serve as an indication for influenza vaccination, including chronic cardiopulmonary disease (except hypertension), diabetes (type 1 or 2), renal dysfunction, hemoglobinopathy, immunodeficiency, or immunosuppression (risk of exacerbating underlying condition or causing influenza-like disease)
- Severe nasal congestion (interference with delivery of vaccine). Use of nasal steroids is not a contraindication or precaution.
- See **Table 20.5**.

Recommendations

Every person ≥6 months of age should be immunized every year. **Table 20.6** summarizes recommendations for the timing of vaccination (see *Footnote d* for the special situation of children 6 months to 8 years of age). hdIIV, aIIV, and rIIV are preferred for persons ≥65 years of age, but there is no preference among these options. Either LAIV or IIV may be used in healthy persons 2 to 49 years of age, and there is no preference for the various versions of IIV in persons 6 months to 64 years of age. The most common reasons for not being vaccinated are people's perception that they are at low risk for influenza, lack of concern regarding serious disease, worry about side effects, and the notion that they can get influenza from the vaccine.[101] Providers should take an affirmative stance—everyone is at risk, the disease can be deadly, and the vaccines are safe.

Within the context of universal immunization, the following groups that are at high risk of complications or high risk of spreading influenza should be given priority when vaccine supply is limited:

- Adults ≥50 years of age, regardless of underlying conditions
- Children 6 months to 4 years of age
- Women who are or will be pregnant during influenza season, regardless of trimester. There is no preference for thimerosal-free products (see *Chapter 6: Vaccination in Special Circumstances—Pregnancy, Postpartum, and Breast-Feeding* and *Chapter 7: Addressing Concerns About Vaccines—Autism*).
- Patients with chronic conditions involving the following systems:
  - Pulmonary (eg, emphysema, chronic bronchitis, asthma)
  - Cardiovascular, except for hypertension (eg, congestive heart failure)
  - Metabolic diseases (eg, type 1 or type 2 diabetes)
  - Renal (eg, nephrotic syndrome, hemodialysis)
  - Hepatic (eg, cirrhosis)
  - Hematologic (eg, sickle cell disease, other hemoglobinopathies)
  - Immunologic (eg, immunosuppressive medications, congenital immunodeficiency, HIV infection)

TABLE 20.6 — Timing of Influenza Vaccination[a]

Population	July or August[b]	September or October	November to End of Season[c]
Children 6 mo-8 y who require 2 doses[d]	Dose 1 Dose 2 ≥4 wk after Dose 1	Should be vaccinated before the end of October	Catch-up
Children of any age who need only 1 dose	Consider vaccination[e]		
Pregnant women in the third trimester	Consider vaccination[f]		
Nonpregnant adults	Defer[g]		

[a] In general, influenza activity can occur as early as October and peaks in January or February.
[b] Vaccine usually becomes available in the summer preceding the influenza season.
[c] It is never too late in the season to vaccinate, and efforts should continue if influenza is circulating, and unexpired vaccine is available.
[d] Children in this age group who have never received an influenza vaccine need 2 doses ≥4 wk apart during their first influenza season. Those who have received only 1 dose in the past, and those with unknown vaccination history, also need 2 doses ≥4 wk apart before the next season. Children who have received a total of 2 previous doses (not necessarily in the same season) of any influenza vaccine (including LAIV) need only 1 dose. Two doses in the same season are not recommended for any other age group or any high-risk condition.
[e] Waning immunity late in the season is less of an issue for children than adults, so early vaccination is acceptable.
[f] Vaccination protects the baby, who will be born during influenza season but cannot be vaccinated until 6 mo.
[g] Early vaccination might be associated with decreased vaccine effectiveness toward the end of the season, especially for older adults.

Adapted from Grohskopf LA, et al. *MMWR*. 2021;70(RR-5):1-28.

  - Neurologic (eg, cognitive dysfunction, spinal cord injury, seizure disorder, neuromuscular disorder that compromises respiratory function or handling of secretions)
- Persons 6 months to 18 years of age on long-term aspirin or salicylate therapy (note the contraindication for LAIV)
- Persons who are extremely obese (adults with body mass index ≥40)
- American Indians and Alaska Natives

- Household contacts of, and persons who provide care for, children <5 years of age (especially <6 months), adults ≥50 years of age, and persons with any high-risk condition
- HCP (mandatory influenza immunization for HCP is discussed in *Chapter 3: Standards, Principles, and Regulations—Mandates and Exemptions*)
- Residents and employees of assisted-living residences, chronic or long-term care facilities, correctional facilities, nursing homes, and similar residential institutions.

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Japanese Encephalitis

The Pathogen

Japanese encephalitis (JE) virus is a mosquito-borne flavivirus with a single-stranded RNA genome surrounded by a protein nucleocapsid and lipid envelope. It is antigenically related to West Nile virus and St. Louis encephalitis virus.

Clinical Features

Only 1 in 250 to 1 in 1000 infections with JE virus results in symptomatic illness.[1] The incubation period is 5 to 15 days. The most common clinical syndrome is *acute encephalitis*, followed by *aseptic meningitis* and *undifferentiated febrile illness*. Symptoms begin abruptly with fever, lethargy, headache, abdominal pain, nausea, and vomiting. Mental status changes, including disorientation, personality change, agitation, delirium, and abnormal movements are seen, classically resembling parkinsonism, with tremor, ataxia, choreoathetosis, cogwheel rigidity, mask-like facies, and extrapyramidal signs; progression to confusion, delirium, and coma are common.[2] Mutism is a presenting sign in some cases. Up to 75% of patients present with or develop seizures. One third of patients develop cranial nerve palsies and some develop generalized or asymmetric muscular weakness, flaccid or spastic paralysis, and clonus, and some cases resemble polio.

The cerebrospinal fluid shows moderate lymphocytic pleocytosis and moderately elevated protein. Imaging studies may show diffuse white matter edema, abnormal signal in the thalamus, and hemorrhage. Hyponatremia due to inappropriate secretion of antidiuretic hormone is a frequent complication. The case fatality rate is 20% to 30%; recovery may take months to years, and 30% to 50% of survivors have neurologic or psychiatric sequelae, including memory loss, motor and cranial nerve paresis, movement disorders, chronic seizures, cortical blindness, and behavioral disorders. JE virus may cause intrauterine infection and miscarriage when it is acquired in the first or second trimester of pregnancy.

Epidemiology and Transmission

JE is endemic throughout China, Southeast Asia, the Indian subcontinent, Indonesia, the Philippines, and Australia; approximately half of the world's population is potentially at risk.[3] In temperate areas, transmission generally occurs from May through September with periodic seasonal epidemics. In subtropical Asia, transmission is hyperendemic and the season is longer, from March through October. In tropical Asia, transmission occurs year-round without noticeable seasonable epidemics. In areas where the virus is endemic, almost all individuals will have been infected by early adulthood.

The virus is spread by *Culex* mosquitoes, which breed in ground pools (eg, rice paddies and ditches) in rural areas. These mosquitoes feed on aquatic birds and other animals that remain asymptomatic despite infection. Domestic pigs in particular have sustained viremia and serve as host to many feeding mosquitoes. Humans, horses, and domestic animals are incidental hosts. The risk of transmission is highest in rural areas, and the incidence of disease correlates with abundance of mosquitoes, proximity of pigs and birds, rainy season, and irrigation of agricultural fields. Most cases occur in children 2 to 10 years of age. Persons who travel extensively in or move to endemic areas acquire symptomatic infection at a rate of 1 per 50,000 persons per month.[4] The risk of disease in short-term travelers to developed or urban areas is <1 per million; the risk for travelers to rural areas during the season of risk is between 1 in 5000 and 1 in 20,000 travelers per week. The risk of infection increases with travel during transmission season, exposure to rural areas, extended period of travel or residence, and outdoor activities, especially in the evenings when mosquitoes are active. Despite the known risks, only around 10% of at-risk travelers are vaccinated.[5]

Immunization Program

Residing in air-conditioned or screened-in areas, avoiding outdoor activities, and using permethrin-treated mosquito nets, insect repellents, and protective clothing can reduce the risk of infection. Societal changes, such as urbanization, less agriculture, use of pesticides, centralized pig rearing, and improved standards of living, may also contribute to lower disease rates. Since 1996, childhood immunization programs in China, Taiwan, Japan, and Korea have resulted in marked decreases in the number of reported cases. However, there are still 30,000 to 50,000 annual cases worldwide, mostly among children.

Historically, the only vaccine available in the US was a non-live, whole-virus vaccine derived from mouse brain (JEV-MB). The vaccine was highly immunogenic but was also reactogenic, and there were reports of a possible association with acute disseminated encephalomyelitis, an autoimmune disease of the central nervous system. A new Vero cell culture-derived vaccine (JE-VC) was approved for use in adults in 2009, and the label was extended to include children in 2013. JE-VC is now the only available vaccine. Comprehensive recommendations for use of JEV were published in 1993,[6] 2010,[7] and 2019.[8]

Assessments of the cost-benefit ratio of JE vaccination for travelers are widely divergent. One study concluded that the productivity benefits of vaccinating business travelers outweigh the costs for those staying in endemic areas ≥1 month (or ≥2 weeks if there are outdoor activities) during transmission season.[9] Another study concluded that 700,000 travelers staying ≥1 month would need to be vaccinated for every case averted, at a cost (from the societal perspective) of $600 million (2017 dollars).[10]

Vaccines

Characteristics of the JEV licensed in the US are given in **Table 21.1**. This is a non-live, whole-virus vaccine, made much the same way as the Salk polio vaccine.[11]

Immunogenicity, Efficacy, Effectiveness, and/or Impact

JEV-MB was tested in a placebo-controlled trial involving over 21,000 children in Thailand, where the efficacy of a 2-dose regimen was found to be 91%. Studies in the US demonstrated that 3 doses were necessary, and the standard regimen became doses at 0, 7, and 30 days, with a booster dose in 2 years if exposure was anticipated. Immunogenicity of JEV-VC (2 doses) was compared with JEV-MB (3 doses) in a blinded, randomized controlled trial involving 867 adults.[12] The proportion of subjects who achieved a plaque reduction neutralization titer of ≥1:10 (a recognized correlate of protection) after 2 doses was 96.4%, compared with 93.8% in the control group, and the respective geometric mean titers were comparable. Licensure of JEV-VC was based on immunogenicity that was noninferior to JEV-MB.

Protective levels of antibody were found in 58% of adults in one study 12 months after a 2-dose primary series of JEV-VC; by 24 months, fewer than half had protective levels, but all responded to a booster dose.[13] In another study, high titers of antibody persisted for at least a year after a booster dose.[14] While JEV-VC represents only one genotype (GIII), it elicits protective antibody to other circulating genotypes,[15] and it effectively boosts immunity in persons primed with JEV-MB (which was made from a different strain of the virus).[16,17]

TABLE 21.1 — Japanese Encephalitis Vaccine[a]

Trade name	Ixiaro
Abbreviation	JEV-VC (Vero cell-derived)
Manufacturer/distributor	Valneva
Type of vaccine	Non-live, whole agent
Composition	
Virus strain	SA_{14}-14-2
Propagation	Vero cells
Inactivation	Formaldehyde
Adjuvant	Aluminum hydroxide (0.25 mg)
Preservative	None
Excipients and contaminants	Formaldehyde (≤200 ppm)
	Bovine serum albumin (≤100 ng/mL)
	Host cell DNA (≤200 pg/mL)
	Sodium metabisulphite (≤200 ppm)
	Host cell proteins (≤100 ng/mL)
	Protamine sulfate (≤1 mcg/mL)
Latex	None
Labeled indications	Prevention of JE
Labeled ages	≥2 mo
Dose	2 mo-2 y: 0.25 mL[b]
	≥3 y: 0.5 mL
Route of administration	Intramuscular
Labeled schedule	Doses at 0 and 28 d[c]
	A booster dose may be given ≥11 mo after completion of the primary series (0.25 mL for children 14 mo-2 y, 0.5 mL for persons ≥3 y)
Recommended schedule	Same
How supplied (number in package)	Prefilled syringe (1)
Cost per dose (USD, 2023)	
Public	—
Private	358.99
Reference package insert	October 2018

[a] Mouse brain-derived vaccine (JEV-MB; JE-Vax, Sanofi) was not manufactured after 2006 and stockpiled vaccine was not available after 2011.

[b] The 0.25 mL dose is delivered using the 0.5 mL prefilled syringe by first expelling and discarding half of the volume (the plunger stopper should be pushed to the red line on the syringe barrel).

[c] Adults 18-65 y may receive 2 doses 7 d apart.

Safety

In a pooled analysis of over 4000 subjects from 10 Phase 3 trials, local reactions occurred in about half of vaccinees, including pain (33%), tenderness (33%), redness (9%), hardening (8%), swelling (5%), and itching (4%).[18] Three percent of subjects reported at least one severe local reaction. Systemic adverse events felt to be vaccine-related included headache (19%), myalgia (13%), fatigue (10%), flu-like illness (9%), and nausea (5%). There were no vaccine-related serious adverse events. Post-marketing reports suggest that hypersensitivity reactions such as urticaria and swelling of the upper airway are less common after JEV-VC than was reported after JEV-MB. From 2012 to 2016, 119 adverse events were reported to the Vaccine Adverse Event Reporting System, for a reporting rate of 14.8 per 100,000 doses distributed; only 9 were classified as serious.[19] The most common event was hypersensitivity reaction, and there was one report of anaphylaxis.

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)

Precautions

- Moderate or severe acute illness
- Pregnancy (theoretical risk to the fetus or attribution of birth defects to vaccination). No deleterious effects have been demonstrated from JEV administration during pregnancy, and the risk of adverse fetal effects from a non-live vaccine is extremely low.

Recommendations

Vaccination is not recommended for short-term travelers who will be restricted to urban areas or who are traveling outside of transmission season. Factors that should be considered in the decision to vaccinate include the incidence of JE in the location of intended stay, the condition of housing, nature of activities, duration of stay, and the possibility of unexpected travel to high-risk areas. In general, persons spending a month or longer (this includes those taking up residence) in epidemic or endemic areas during the transmission season, especially if travel will include rural areas, should be vaccinated, as should persons who frequently travel to endemic areas (see *Chapter 6: Vaccination in Special Circumstances—Travel*). Depending on the epidemic circumstances, vaccination should be considered for persons spending <30 days who are at particularly high risk, such as those engaging in extensive outdoor activities (eg, camping, hiking, fishing) in rural areas and those whose accommodations lack air conditioning, screens, or bed nets. Vaccination

also should be considered for travel to areas with ongoing outbreaks and those who have uncertain or nonspecific itineraries. The vaccine series should be completed at least 1 week before potential exposure, and travelers should take personal precautions to reduce mosquito bites. Current Centers for Disease Control and Prevention advisories (https://wwwnc.cdc.gov/travel/notices; accessed August 14, 2023) should be consulted with regard to disease activity in specific locales.

Laboratory workers with potential exposure to infectious JE virus should be vaccinated. Periodic monitoring for neutralizing antibodies and/or administration of booster doses may be indicated.

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Measles, Mumps, and Rubella

The Pathogens

Measles

Measles (rubeola) virus is an enveloped, single-stranded RNA virus in the Paramyxoviridae family.[1] There is only one serotype. Two proteins—the hemagglutinin, which mediates attachment, and the fusion protein, which facilitates cell-to-cell spread—are important in generating neutralizing antibodies. The virus infects the nasopharyngeal epithelium and then spreads to regional lymph nodes, where replication leads to widespread dissemination, including the reticuloendothelial system, viscera, respiratory tract, and skin. Pathologic changes include lymphoid hyperplasia, mononuclear cell infiltration of infected tissues, and multinucleated giant cells. Virus-induced immune suppression leads to secondary infections, and immunosuppressive effects can last 2 to 3 years.[2] In fact, one study showed that severe measles results in the loss of 40% of a person's pre-existing pathogen-specific antibody repertoire (measles vaccination does not have this effect).[3]

Mumps

Mumps virus is an enveloped, single-stranded RNA virus in the Paramyxoviridae family.[4] While the virus is not classified into serotypes, there are 12 known genotypes (A through L) that vary in geographic distribution. A surface hemagglutinin-neuraminidase and fusion protein mediate, respectively, adsorption to cells and fusion with the cell membrane. Initial infection occurs in the nasopharyngeal epithelium and then spreads to regional lymph nodes, where replication leads to plasma viremia and dissemination via mononuclear cells. The virus is tropic for glandular epithelia, including the salivary glands (especially the parotids), pancreas, ovaries, and testes, where infection can lead to atrophy of the germinal epithelium. Pathologic changes include interstitial edema and lymphocytic infiltration. The virus also may spread to the central nervous system (CNS), where it infects the choroidal epithelium and ependymal lining of the ventricles, resulting in aseptic meningitis, and, in some cases, encephalitis.

Rubella

Rubella virus is an enveloped, single-stranded RNA virus in the Togavirus family.[5] Neutralizing antibodies are directed predominately against E1, a major surface glycoprotein with hemagglutinin and fusion activity. There is only one serotype, although the virus is classified into genotypes I and II based on E1 sequences. Infection occurs in the nasopharyngeal epithelium and then spreads to regional lymph nodes, where replication leads to viremia and dissemination to the respiratory tract, skin, lymph nodes, body fluids, and, in pregnant women, the placenta. While postnatal infection is relatively benign, infection of the fetus leads to progressive, generalized vasculitis, affecting organ development. A characteristic feature of early fetal infection is cell necrosis without an inflammatory response, consistent with the immaturity of the fetal immune system and the virus' ability to induce apoptosis. Another characteristic is persistent viral replication, thought to be related to immune tolerance.

Clinical Features

Measles

Measles is characterized by a several-day prodrome of malaise, fever, anorexia, *cough*, *coryza*, and *conjunctivitis*. Temperature usually increases for 5 or 6 days and can be high. *Koplik's spots*—small white lesions on the buccal mucosa that resemble grains of sand on a moist, red background—appear between the second and fourth days. After this, a characteristic *rash* appears around the ears and hairline and spreads downward and outward to cover the face, trunk, and extremities. Initially erythematous, maculopapular, and splotchy, the rash tends to become confluent as it spreads, especially on the face and neck; it lasts about 5 days and resolves in the order of appearance.

Complications, including diarrhea, middle ear infection, and bronchopneumonia, occur in up to 40% of patients. *Encephalitis* occurs in approximately 1 out of every 1000 cases, and survivors often have permanent brain damage. Death, usually from pneumonia or acute encephalitis, occurs in 1 to 2 out of every 1000 cases; the risk is greater for infants, young children, and adults. *Subacute sclerosing panencephalitis* is a fatal degenerative disease of the CNS that appears years after measles infection; historical data place the incidence at 1 in 10,000 to 100,000 patients, but recent estimates are more like 1 in 600 for those infected with measles under 1 year of age.[6]

In developing countries, measles is often more severe, with case-fatality rates as high as 25%. The disease can be severe in persons with vitamin A deficiency, as well as in immunocompromised persons, particularly those who have leukemia, lymphoma, or HIV infection. Long-lasting immunosuppressive effects are thought to contribute significantly to childhood deaths from heterologous infectious diseases.

Mumps

About two thirds of infections are symptomatic, and 95% of those with symptoms develop *parotitis*, usually characterized by fever, headache, malaise, myalgia, anorexia, and bilateral swelling of the parotid glands. Parotitis occurs more commonly among children and subclinical infection is more common among adults. The disease is usually self-limited, but complications do occur. *Orchitis*, characterized by abrupt onset of testicular swelling, warmth, and tenderness accompanied by high fever, vomiting, headache, and malaise, is the most common complication in adult males, occurring in up to 30% of cases. Half of patients are left with some degree of testicular atrophy, but sterility is unusual. *Oophoritis* develops in 5% of postpubertal women. *Aseptic meningitis* is common, occurring asymptomatically in half of patients and associated with headache and stiff neck in up to 10%. Adults are at greater risk for this complication than children, and boys are more often affected than girls. *Encephalitis* is rare, occurring in 0.1% of infections. Mumps was a leading cause of acquired *sensorineural deafness* in the prevaccine era, with an estimated incidence of one per 20,000 cases.

Rubella

Rubella is characterized by nonspecific signs and symptoms including transient, erythematous, and sometimes pruritic *rash*, postauricular or suboccipital lymphadenopathy, arthralgia, and low-grade fever. Twenty-five percent to 50% of infections are subclinical, and while up to 60% of postpubertal women develop *arthritis*, the disease is generally considered benign and self-limited—unless you are a fetus. Manifestations of *congenital rubella syndrome* (CRS) at birth include deafness, cataracts, micro-ophthalmia, cardiac defects, and CNS abnormalities. Late effects, most notably type 1 diabetes, may occur. Maternal-fetal transmission rates approach 100% in the first trimester, and fetal damage is almost universal; fetopathy is rare after maternal infection in the third trimester.

Epidemiology and Transmission

Measles

Humans are the only natural hosts. In temperate climates, measles usually occurs in late winter and spring. Transmission is primarily person to person via large respiratory droplets. Airborne transmission has been documented in closed areas (such as office examination rooms) after the presence of an infected person. Measles is one of the most contagious diseases known to man, with an R_0 of 10 to 15 (see *Chapter 1: Introduction to Vaccinology—Epidemiological Concepts*) and a secondary household attack rate that exceeds 90%.

Mumps

Humans are the only natural hosts. Incidence peaks in winter and spring, but disease has been reported throughout the year. Transmission occurs through airborne droplet nuclei or direct contact with saliva. Contagiousness is similar to that of influenza and rubella but less than that for measles and chickenpox. The infectious period is from 3 days before to 4 days after the onset of disease.

Rubella

Humans are the only natural hosts. In temperate climates, rubella occurs in late winter and early spring. There is no carrier state per se, but infants with CRS may shed large quantities of virus for up to a year. Rubella is only moderately contagious and spreads from person to person via airborne droplet nuclei shed from the respiratory tract. Transmission by subclinical cases, which constitute 20% to 50% of all infections, can occur. The disease is most contagious when the rash is erupting, but virus may be shed from 7 days before to 7 days after rash onset.

Immunization Program

The rationale for measles and mumps immunization is to prevent complications and death in the general population; the rationale for rubella immunization is to prevent CRS by preventing infection of pregnant women. The first live attenuated measles vaccine was licensed in 1963; mumps vaccine was licensed in 1967, and rubella vaccine in 1969. MMR (Merck) was licensed in 1971. In 1979, a rubella vaccine grown in human diploid fibroblasts (RA 27/3) replaced the duck embryo-passaged strain that was in MMR (the trade name was changed to M-M-R_{II}). The combination of measles, mumps and rubella vaccines has been the preferred vaccine against these diseases since 1980. A single dose was recommended for all children at 15 months of age until 1989, when a resurgence of measles (*see below*) prompted recommendations for a routine second dose at 4 to 6 years of age.[7]

In 1998, the age for the first dose was changed to 12 to 15 months. Priorix (MMR [GSK]) was licensed in June 2022, and the Advisory Committee on Immunization Practices recommended the vaccine as an option in all situations where MMR is recommended.[8] MMRV was licensed in 2005 and was initially preferred over separate MMR plus VAR[9]; the preference was retracted in 2008 because of concerns over febrile seizures[10,11] (see *Chapter 7: Addressing Concerns About Vaccines—Febrile Seizures*). The American Academy of Pediatrics has maintained that either MMR plus VAR or MMRV is acceptable, as long as the caregivers are fully informed about the risks and benefits (ie, febrile seizures with MMRV, extra injection with MMR plus VAR).[12] MMRV is preferred for the second dose, in the context of the general preference for combination vaccines.[13]

In 2006, in response to a resurgence of mumps (*see below*), the 2-dose requirement for measles vaccine was extended to mumps (practically speaking, this had already occurred because the vast majority of doses were given as MMR).[14] Recommendations for health care personnel (HCP) were updated in 2011,[15] and updated recommendations for prevention of measles, mumps, and rubella were published in 2013.[16] In 2018, a third dose of mumps-containing vaccine was recommended for persons identified by public health authorities as at increased risk during outbreaks.[17]

Vaccines

Characteristics of the MMR vaccines licensed in the US are given in **Table 22.1**. Both products are a mixture of live attenuated strains of measles, mumps, and rubella viruses, each attenuated by serial passage in tissue culture, much the same way as the Sabin polio vaccine.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

The impact and safety data presented in this chapter derive from studies of M-M-R_{II}, which was the only vaccine available in the US from 1979 to 2022. Priorix had been in use elsewhere for 25 years before it was licensed in the US in 2022, with more than 800 million doses distributed and studies demonstrating effectiveness.[18] Licensure in the US was based on noninferior immunogenicity compared to M-M-R_{II} and a safety profile that is similar to M-M-R_{II}.[19]

Measles

Studies show that >99% of persons who receive 2 doses of vaccine (separated by at least 1 month) at ≥1 year of age develop serologic evidence of measles immunity. Although vaccine-induced antibody titers are lower than those following natural disease, immunity is probably life-long in most people. Individuals who lose antibody over time have demonstrable anamnestic responses to revaccination, indicating that they are most likely still protected. A small percentage of vaccinated individuals may lose protection after several years.

Before the introduction of the first vaccine in 1963, there were 3 to 4 million cases of measles each year in the US; by 1983, that number had fallen to about 1500.[20] However, between 1989 and 1991, there were almost 56,000 reported cases and 123 deaths.[21] This resurgence was primarily due to pockets of low vaccine coverage in the population. Another contributing factor was the fact that infants <1 year of age were more susceptible than in previous eras—their mothers had vaccine-induced immunity rather than natural immunity, and they had received less transplacental antibody.

TABLE 22.1 — Measles, Mumps, and Rubella Vaccines[a]

Trade name	M-M-R_{II}	Priorix
Abbreviation	MMR (Merck)	MMR (GSK)
Manufacturer/ distributor	Merck	GSK
Type of vaccine	Live, attenuated, classical	Live, attenuated, classical
Composition	Measles virus, Moraten strain, propagated in chick embryo cells, at least 1000 $TCID_{50}$	Measles virus, Schwarz strain, propagated in chick embryo cells, at least 2500 $CCID_{50}$
	Mumps virus, Jeryl Lynn strain (actually consists of two distinct strains), propagated in chick embryo cells, at least 12,500 $TCID_{50}$	Mumps virus, RIT 4385 strain, propagated in chick embryo cells, at least 15,800 $CCID_{50}$
	Rubella virus, RA 27/3 strain, propagated in human diploid lung fibroblast (WI-38) cells, at least 1000 $TCID_{50}$	Rubella virus, RA 27/3 strain, propagated in human diploid (MRC-5) cells, at least 2000 $CCID_{50}$
Adjuvant	None	None
Preservative	None	None
Excipients and contaminants	Sorbitol (14.5 mg)	Anhydrous lactose (32 mg)
	Sucrose (1.9 mg)	Sorbitol (9 mg)
	Hydrolyzed gelatin (14.5 mg)	Amino acids (9 mg)
	Recombinant human albumin (≤0.3 mg)	Mannitol (8 mg)
	Fetal bovine serum (<1 ppm)	Neomycin sulphate (≤25 mcg)
	Neomycin (25 mcg)	Ovalbumin (≤60 ng)
	Buffer and media ingredients	Bovine serum albumin (≤50 ng)
Latex	None	Tip cap of prefilled syringe of diluent contains latex
Labeled indications	Prevention of measles, mumps, and rubella	Prevention of measles, mumps, and rubella
Labeled ages	≥12 mo	≥12 mo
Dose	0.5 mL	0.5 mL
Route of administration	Subcutaneous or intramuscular	Subcutaneous
Labeled schedule (age)	12-15 mo and 4-6 y	12-15 mo and 4-6 y
Recommended schedule	Same	Same
How supplied (number in package)	1-dose vial (10), lyophilized, with diluent	1-dose vial (10), lyophilized, with diluent in prefilled syringe (10)
Cost per dose (USD, 2023)		
Public	24.96 (pediatric) 55.89 (adult)	24.97 (pediatric) 55.89 (adult)
Private	89.87	89.87
Reference package insert	March 2023	June 2022

$CCID_{50}$, median cell culture infective dose; $TCID_{50}$, median tissue culture infective dose

[a] The components of MMR (Attenuvax [measles], Mumpsvax [mumps], Meruvax II [rubella], and M-M-Vax [measles and mumps]) are licensed by Merck as separate vaccines but have not been available in the US since 2008. MMR is also available in combination with VAR (MMRV; ProQuad, Merck).

Primary vaccine failure after one dose, which occurs in 2% to 5% of children, also may have contributed.

Renewed efforts to vaccinate young children and the institution of a second dose at school entry reversed the resurgence, such that by 2000, measles was considered to be no longer endemic in the US.[22] In 2016, the Region of the Americas was declared measles-free,[23] but cases continue to occur despite elimination status. In fact, in 2019 there were 1282 cases in the US—the highest number since 1992[24]—most of which occurred in unvaccinated people. Responding to measles outbreaks is expensive—a review of 11 outbreaks in the US between 2004 and 2017 found that the median cost was $152,000 per outbreak, or $33,000 per case (2018 dollars).[25] Importation of measles continues to be a problem in the post-elimination era: from 2001 to 2016, there were almost 30 imported cases every year, the majority being US residents who had traveled to areas with ongoing transmission.[26] Outbreaks like the one associated with Disneyland in 2015[27] underscore the importance of maintaining population immunity. Eradication of measles is considered feasible, but there are many obstacles.[28]

Mumps

In studies conducted between 1973 and 1989, efficacy of a single dose was estimated at 75% to 91%, and efficacy of 2 doses during the 2006 US outbreak (*see below*) was estimated at 76% to 88%.[29] A study published in 2008 showed that 94% of university students and staff had antibody to mumps virus after having received 2 doses of vaccine.[30] The level of antibody was lower among those vaccinated ≥15 years earlier compared with those vaccinated in the preceding 5 years, but seronegative subjects mounted anamnestic responses after repeat vaccination. Whereas antibody titers have been shown to wane with time,[31] cellular responses have been shown to persist beyond 15 years.[32]

In 1968, just after licensure of the first vaccine, there were nearly 200,000 cases of mumps in the US. By 2006, despite a resurgence among teenagers in the late 1980s, the number of cases had fallen to below 500.[33] However, 2006 saw a multistate outbreak with nearly 7000 cases, mostly among college students and other young adults, many of whom had received 2 doses of the vaccine.[34] Another large outbreak occurred in the New York area in 2009.[35] The index case was an 11-year-old boy who had acquired mumps in the United Kingdom and attended a tradition-observant Jewish summer camp after returning to the US; most cases occurred among members of the Orthodox Jewish community, the majority of whom were fully immunized.

The continued occurrence of mumps outbreaks has raised concerns about vaccine efficacy and persistence of immunity.[36,37] It is possible that 2 doses of the current vaccine may not be enough

to overcome contagion in high-density communal living situations. Moreover, as 2-dose coverage rates exceed 90%, the herd immunity threshold (see *Chapter 1: Introduction to Vaccinology—Epidemiological Concepts*) may be higher than once thought and not achievable with current recommendations.[38]

Rubella

At least 95% of vaccinees ≥12 months of age develop protective antibody titers, and antibodies have persisted in >90% of vaccinees at least 15 years. Lifelong protection against clinical reinfection, asymptomatic viremia, or both usually results from a single dose of vaccine early in childhood. In some cases, vaccinees exposed to natural rubella develop an asymptomatic increase in antibody titer (reinfection with wild-type rubella virus has been observed in persons with previous natural rubella). However, infection of vaccinees is rarely associated with viremia or pharyngeal shedding, and, among vaccinated women, the risk of CRS from rubella infection during pregnancy is extremely low.

Between 1964 and 1965, there were >12 million cases of rubella in the US and 20,000 babies were born with CRS.[39] After vaccination was initiated in 1969, the number of cases declined dramatically, such that by 2004, rubella was considered to be no longer endemic in the US.[40] Rubella was declared eliminated from the Region of the Americas in 2015.[41]

Safety

In an integrated safety review of postlicensure trials of MMR (Merck) conducted between 1988 and 2009 involving over 13,000 children, temperature of ≥102°F was reported in 25% after Dose 1 and 13% after Dose 2; the respective rates of measles/rubella-like rash, usually occurring on days 5 to 12, were 3% and 0.5%.[42] Injection site reactions (mostly pain and tenderness) occurred in 17% after Dose 1 and 43% after Dose 2. Transient lymphadenopathy can occur and parotitis has been reported rarely. Arthralgia, reported in up to 25% of susceptible adult women given MMR, is attributed to the rubella component; persistent or recurrent joint symptoms are rare.

One case of immune thrombocytopenia, defined as a platelet count ≤50,000/mcL with clinical bleeding, occurs for every 40,000 doses; this is much less than the incidence after natural measles or rubella.[43] Severe bleeding is rare and the vast majority of patients recover completely.[44] The risk of febrile seizures is increased 2- to 3-fold in the second week after the first dose, but there is no association with subsequent seizures or neurodevelopmental disabilities.[45] Most allergic reactions are minor and consist of a wheal and flare or urticaria at the injection site, and anaphylactic reactions are extremely rare. The vaccine does not contain significant amounts

of egg protein and can safely be given to patients with allergies to eggs, chickens, and feathers without prior skin testing and without incremental dosing.

Not a single case of measles vaccine virus transmission from a vaccine recipient has been found, despite hundreds of millions of doses having been used worldwide[46]; therefore, the vaccine can be given to contacts of immunosuppressed and pregnant persons.

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction; this includes reactions to gelatin and neomycin)
- Severe immunodeficiency or immunosuppression (risk of disease caused by live virus); providers should pay special attention to this possibility in children who have a first-degree relative with a primary immune deficiency
- Pregnancy (theoretical risk to the fetus of live virus vaccine or attribution of birth defects to vaccination). Vaccinees should avoid pregnancy for 1 month.

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction). The package insert for MMR (Merck) specifically includes active, untreated tuberculosis (risk of exacerbation of tuberculosis).
- History of thrombocytopenia or thrombocytopenic purpura (risk of recurrent thrombocytopenia)
- Recent receipt of antibody-containing blood product (risk of impaired response to vaccine)
- Measles vaccine virus replication can suppress the response to a tuberculin skin test (TST) and may cause false negative results in an interferon-gamma release assay (IGRA). If testing for tuberculosis is warranted, the preferred option is to place the TST or perform the IGRA before or on the same day as measles vaccination (any immunosuppression would occur later, at the peak of viral replication). Otherwise, the tuberculosis test should be delayed ≥4 weeks.

Recommendations

All persons who do not have evidence of immunity to measles, mumps, and rubella (**Table 22.2**) should be vaccinated with MMR. Either of the available products may be used. For children, the first dose is usually given at 12 to 15 months of age and the second dose at 4 to 6 years of age. The second dose may be given any time ≥28 days following the first dose. High-risk adults who lack evidence of immunity should receive 2 doses of MMR separated by ≥28 days

(those who have a history of 1 dose in the past should have a second dose). Low-risk adults who lack evidence of immunity should receive at least 1 dose. Women who might become pregnant and who lack evidence of immunity should receive 1 dose of MMR (2 doses if they are at high risk for exposure to measles or mumps).

During measles outbreaks, when the likelihood of exposure is high, measles vaccine can be given to infants as young as 6 months of age. Doses given before the first birthday, however, *do not count* in the series, and these children should receive 2 subsequent doses according to the usual schedule. A third lifetime dose of MMR may be recommended by public health authorities for persons at increased risk during mumps outbreaks. Recommendations for persons traveling outside the US are given in *Chapter 6: Special Circumstances—Travel*.

Postexposure prophylaxis against measles is recommended for susceptible persons and certain high-risk persons regardless of measles susceptibility status. Note that 1) prophylaxis is not indicated if it has been ≥7 days since exposure, and 2) postexposure prophylaxis using MMR is on-label for M-M-R_{II} and off-label for Priorix.

- Healthy infants <6 months of age—Give immune globulin intramuscular (IGIM), 0.5 mL/kg (maximum dose 15 mL).
- Healthy infants 6 to 11 months of age—If it has been 1, 2, or 3 days since exposure, give MMR. This prophylactic dose does not "count" towards the routine vaccine series, so these infants should be given Dose 1 of the routine series at 12 to 15 months of age and Dose 2 at 4 to 6 years of age. If it has been 4, 5, or 6 days since exposure, give IGIM, 0.5 mL/kg (maximum dose 15 mL).
- Susceptible healthy persons ≥12 months of age (see special situations below)—If it has been 1, 2, or 3 days since exposure, give MMR. This prophylactic dose should be followed by a second dose in ≥4 weeks (this completes the MMR series). If it has been 4, 5, or 6 days since exposure, giving IGIM, 0.5 mL/kg (maximum dose 15 mL), is an option. Priority candidates include persons exposed in close quarters, such as households, childcare settings, or classrooms.
- Susceptible pregnant women—Give immune globulin intravenous (IGIV), 400 mg/kg.
- Severely immunocompromised persons of any age, regardless of vaccination or immunity status—Give immune globulin intravenous (IGIV), 400 mg/kg. Candidates include patients with severe primary immunodeficiency; hematopoietic cell transplant recipients (especially those with graft versus host disease); patients being treated for leukemia; and HIV-infected persons with evidence of severe immunosuppression.

Postexposure prophylaxis is not indicated for mumps and rubella.

TABLE 22.2 — Immunity to Measles, Mumps, and Rubella

Criteria[a]	Persons to Whom the Criteria Apply		
	Measles	**Mumps**	**Rubella**
Birth before 1957	Everyone except HCP[b]	Everyone except HCP[b]	Everyone except HCP[b,c]
Personal history of laboratory-confirmed disease	Everyone	Everyone	Everyone
Documentation of at least 1 properly administered vaccine dose[d,e]	Children 1 y to school age	Children 1 y to school age	Anyone ≥1 y
	Low-risk adults	Low-risk adults	
Documentation of at least 2 properly administered vaccine doses[d]	School-aged children (grades K-12)	School-aged children (grades K-12)	Not required
	High-risk adults (HCP[b], international travelers, students at postsecondary educational institutions)	High-risk adults (HCP[b], international travelers, students at postsecondary educational institutions)	
Positive virus-specific IgG antibody test[f]	Everyone	Everyone	Everyone

HCP, health care personnel

[a] Any single criterion is considered sufficient. Clinical, virologic, and vaccination criteria trump the results of serologic tests. For example, HCP with documentation of 2 properly administered doses of MMR are considered immune even if their antibody tests are negative. A personal history of clinical disease (whether or not diagnosed by a physician) is not a criterion for any of these diseases.

[b] Vaccination (2 doses of MMR separated by ≥28 days) should be considered for unvaccinated HCP born before 1957 without laboratory evidence of immunity or a history of laboratory-confirmed disease (only 1 dose of MMR is necessary if all that is lacking is immunity to rubella). If there is an outbreak, vaccination should be *recommended* (not just *considered*).

[c] Birth before 1957 does not provide evidence of immunity for women who might become pregnant, but as of 2023 such women would be ≥65 years of age and therefore very unlikely to become pregnant.

[d] From 1963-1967, both the live attenuated and an ineffective, inactivated measles vaccine were available. Doses given during that period are considered invalid unless there is evidence that the live attenuated vaccine was used.

[e] Young children being considered for solid organ transplantation should have had 2 doses to be considered immune.

[f] Once a person has demonstrable antibody, he or she is considered immune for life ("once immune, always immune"). Equivocal results are considered negative.

Adapted from McLean HQ, et al. *MMWR*. 2013;62:(RR-4):1-34.

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Neisseria meningitidis

The Pathogen

N meningitidis is a gram-negative bacterium that typically appears as intracellular diplococci on Gram stain.[1] The polysaccharide capsule is the basis for classification into serogroups, the most important of which are A, B, C, W (formerly W-135), and Y. The capsule contributes to virulence by inhibiting complement-mediated lysis, phagocytosis by neutrophils, and the action of antimicrobial peptides; pathogenicity is enhanced by the release of endotoxin. Antibodies to the capsule are protective.[2] *N meningitidis* often colonizes the nasopharynx, and disease results from bacteremia and spread to distant sites such as the meninges. Colonization occurs through the interaction between host cell receptors and bacterial adhesins, which undergo antigenic and phase variation that facilitate evasion of host immunity.[3] Certain genetic polymorphisms, particularly those involving the complement and coagulation systems, contribute to disease outcome.[4]

Clinical Features

Meningococcemia (bloodstream infection) is characterized by the sudden onset of fever, lethargy, myalgia, rash, and vomiting, followed by altered mental status, high fever or hypothermia, tachypnea, and hypotension.[5] Initially, the rash may be macular or maculopapular, but there is rapid transition to petechiae and/or purpura. *Purpura fulminans* is characterized by rapid progression to disseminated intravascular coagulation, hypotension, and shock within hours, despite antimicrobial therapy and supportive measures. Death is common, and survivors may lose extensive areas of skin or extremities due to ischemia. Some individuals experience transient bacteremia that resolves spontaneously without treatment.

Meningococcal *meningitis* presents with fever, vomiting, headache, and photophobia. It is distinguished from other forms of pyogenic meningitis by the association with petechial or purpuric rash in two thirds of patients. Neurologic sequelae include deafness, cranial nerve palsies, hydrocephalus, and developmental delay. Meningococcus also causes pneumonia, myocarditis, pericarditis, arthritis, conjunctivitis, endophthalmitis, urethritis, and pharyngitis. Immune-mediated arthritis,

cutaneous vasculitis, and pericarditis can occur late in the course of infection, after antibiotic therapy is instituted.

The case-fatality rate for invasive meningococcal disease (IMD) is <10% for infants and 15% to 20% in adolescents and adults.[6] Survivors are at increased risk for early mortality, hearing and cognitive impairment, behavioral and emotional problems, motor deficits, seizures, and decreased quality of life.[7]

Epidemiology and Transmission

Humans are the only natural hosts and transmission occurs by direct person-to-person contact or via respiratory droplets. Asymptomatic carriage of *N meningitidis* is around 5% in infants and 25% in young adults.[8] Colonization with invasive strains approaches 50% in closed settings where a case has occurred. The secondary attack rate in households is 3% to 4%, and the risk to household members is 500 to 800 times the risk in the general population—this is why chemoprophylaxis is used for close contacts.

The incidence of IMD in the US has decreased dramatically since the late 1990s in all age groups and for all serogroups. The decrease predated the universal adolescent MenACWY program, raising speculation that it was related to natural cycles, less smoking, less crowding, and increased antibiotic use. From 2006 to 2015, the average annual incidence was 0.26 per 100,000.[9] In 2021, the incidence was 0.06 per 100,000; serogroup B predominated in persons <24 years of age and serogroup C in persons ≥24 years of age.[10] Disease occurs predominantly in late winter and early spring and may parallel increases in influenza activity. Outbreaks account for about 5% of cases; serogroup B predominates in organization-based outbreaks and serogroup C in community-based outbreaks.[11] The serotype distribution can change over time; for example, serogroup Y, rare in the US in the 1980s, accounted for about a third of cases in the 1990s[12] but now accounts for <15% of cases.

Individual risk factors include active and passive smoking, respiratory illness, steroid use, new residence, new school, lower socioeconomic status, and household crowding. College attendance is a risk factor for serogroup B disease.[13] Persons with primary or acquired immunodeficiencies are at increased risk, including those with persistent complement component deficiencies (10,000-fold increased risk) and complement inhibitor use (2000-fold increased risk). Persons with asplenia are at increased risk and have a mortality rate of 40% to 70%. Increased risk of IMD has been seen in men who have sex with men, largely driven by outbreaks of serogroup C.[14] HIV infection is also a risk factor; in New York City, for example, the relative risk of IMD among HIV-infected men was 12.2 between 2000 and 2011,[15] and an increase in cases among HIV-infected persons was noted in 2022.[16] During outbreaks, alcohol use and patronizing bars and nightclubs are risk factors.

Epidemics caused by serogroup A most commonly occur in the *meningitis belt* of sub-Saharan Africa, central Asia, the Indian subcontinent, and Saudi Arabia (serogroup A is rare in the US).

Immunization Program

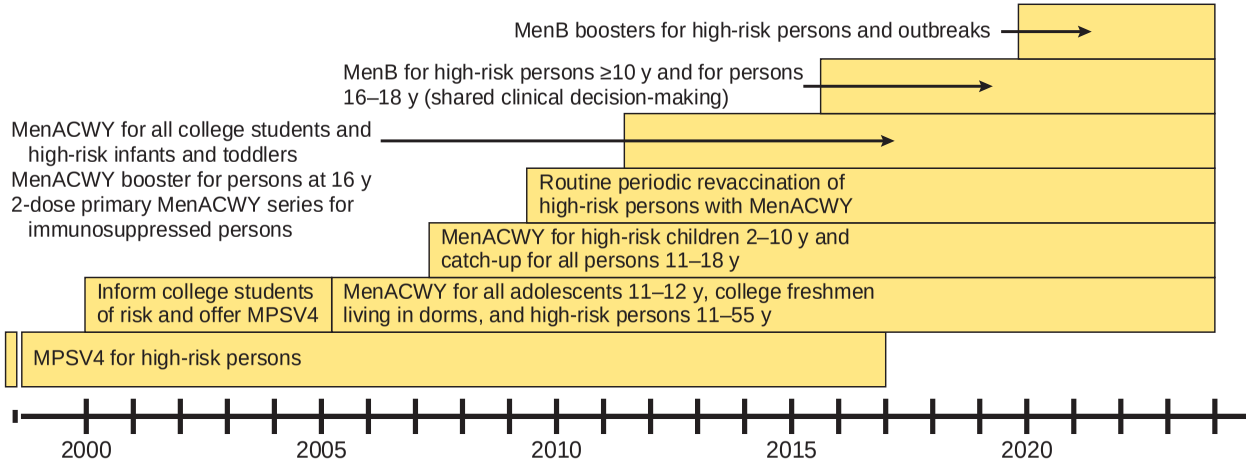
Figure 23.1 shows the evolution of meningococcal vaccine recommendations in the US (comprehensive recommendations were published in 2020[17]). Several things are worth highlighting. First, at the beginning of the program for young adolescents, it was estimated that universal vaccination would prevent >5000 cases of IMD over a 10-year period, at a cost of $532,000 per case prevented and $5.9 million per death prevented. These estimates made routine meningococcal vaccination costlier per health outcome than other vaccine programs at the time. Second, while MenACWY vaccines have been labeled down to 2 years of age since 2007 and down to 2 months of age since 2013, routine administration to healthy children <11 years of age has not been recommended. Third, *revaccination* with MenACWY, first recommended in 2009 for persons who remain at high risk, was recommended for all adolescents in 2011 because of studies demonstrating waning immunity.

Fourth, outbreaks of serogroup B on college campuses in the early 2010s called attention to IMD that is not prevented by MenACWY, and by the late 2010s, serogroup B had become the most common serogroup causing IMD in adolescents and young adults.[18] This lead to recommendations for routine use of MenB in high-risk persons and for vaccination based on shared clinical decision-making (SCDM, then called Category B; see *Chapter 2: Vaccine Infrastructure in the United States—Policy and Recommendations*) in healthy persons.[19-21] The following considerations led to the recommendation for SCDM rather than routine use: 1) the burden of disease was low among adolescents and young adults—about 50 to 60 cases and 5 to 10 deaths per year; 2) the cost per quality-adjusted life year (QALY) gained of a universal adolescent immunization program was estimated at $3.7 to $8.7 million; 3) the breadth of strain coverage was unclear; 4) effectiveness data were not available; and 5) the impact on carriage and microbial epidemiology was not known (data germane to some of these issues have begun to emerge—*see below).*[22] Surveys show wide variation in how providers interpret the SCDM recommendation for MenB,[23,24] and many parents are unaware of the disease and vaccine.[25] It has been estimated that routine immunization of college students with MenB would cost approximately $14 million per QALY gained (2015 dollars).[26]

Vaccines

Characteristics of meningococcal vaccines licensed in the US are given in **Tables 23.1** and **23.2**. Menactra, Menveo and

FIGURE 23.1 — Meningococcal Immunization Recommendations Over Time



The figure shows major steps in the evolution of meningococcal immunization recommendations in the US. MPSV4 was licensed in 1981 and was recommended for high-risk patients (the vaccine was discontinued in 2017). By the early 2000s it was evident that college freshmen living in dormitories were at increased risk, leading to the recommendation to inform them about the disease and offer vaccination. Licensure of MenACWY-D in 2005 allowed reassessment of the high-risk only strategy, given the ability of protein-polysaccharide conjugate vaccines to induce more robust antibody responses, reduce nasopharyngeal colonization, and lead to herd immunity (MenACWY-CRM was subsequently licensed in 2010 and MenACWY-T in 2020). Extension of the age indication for MenACWY-CRM and MenACWY-D in 2013 allowed for protection of high-risk infants, although universal infant immunization was not recommended. Licensure of MenB-FHbp and MenB-4C by early 2015 made prevention of serogroup B disease possible.

Adapted from Meningococcal ACIP vaccine recommendations. CDC Web site. http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html. Accessed August 17, 2023.

TABLE 23.1 — *N meningitidis* Serogroups A, C, W, and Y Vaccines[a]

Trade name	Menactra	Menveo	MenQuadfi
Abbreviation	MenACWY-D	MenACWY-CRM	MenACWY-T
Manufacturer/ distributor	Sanofi	GSK[b]	Sanofi
Type of vaccine	Non-live, subunit, engineered	Non-live, subunit, engineered	Non-live, subunit, engineered
Composition	Group-specific polysaccharides (4 mcg each) from *N meningitidis* serogroups A, C, W, and Y, conjugated to diphtheria toxoid (48 mcg)	Group-specific polysaccharides (serogroup A, 10 mcg; serogroups C, W, Y, 5 mcg each) from *N meningitidis*, conjugated to CRM_{197}, a nontoxic mutant diphtheria toxin (25.4-65.5 mcg)	Group-specific polysaccharides (10 mcg each) from *N meningitidis* serogroups A, C, W, and Y, conjugated to tetanus toxoid (55 mcg)
Adjuvant	None	None	None
Preservative	None	None	None
Excipients and contaminants	Formaldehyde (<2.66 mcg)	Formaldehyde (≤0.3 mcg)	Formaldehyde (<1.5 mcg)
	Sodium phosphate buffered isotonic sodium chloride	Yeast[c]	Sodium chloride (3.35 mg)
			Sodium acetate (1.23 mg)
Latex	None	None	None
Labeled indications	Prevention of IMD due to serogroups A, C, W, and Y	Prevention of IMD due to serogroups A, C, W, and Y	Prevention of IMD due to serogroups A, C, W, and Y
Labeled ages	9 mo-55 y	2-vial presentation: 2 mo-55 y 1-vial presentation: 10-55 y	≥2 y
Dose	0.5 mL	0.5 mL	0.5 mL
Route of administration	Intramuscular	Intramuscular	Intramuscular
Labeled schedule (age)	9-23 mo: 2 doses separated by 3 mo	Infants: 2, 4, 6, and 12 mo	≥2 y: 1 dose
	2-55 y: 1 dose	7-23 mo: 2 doses separated by 3 mo[d]	≥15 y: booster dose
	15-55 y: booster dose	2-55 y: 1 dose[e]	
		15-55 y: booster dose	
Recommended schedule (age)[f]	11-12 and 16 y	11-12 and 16 y	11-12 and 16 y
	Catch-up, high-risk (≥9 mo)[g]	Catch-up, high-risk (≥2 mo)	Catch-up, high-risk (≥2 y)
	Periodic boosters (**Figure 6.2**)	Periodic boosters (**Figure 6.2**)	Periodic boosters (**Figure 6.2**)

Continued

TABLE 23.1 — *Continued*

Trade name	Menactra	Menveo	MenQuadfi
How supplied (number in package)	1-dose vial (5)	2-vial presentation: 1-dose vial (5), lyophilized serogroup A, with diluent containing serogroups C, W, and Y 1-vial presentation: 1-dose vial (10)	1-dose vial (1, 5, 10)
Cost per dose (USD, 2023)			
Public	—	105.60 (pediatric) 76.23 (adult)	107.84 (pediatric) 80.24 (adult)
Private	180.00	148.49	156.11
Reference package insert	July 2019	October 2022	June 2022

IMD, invasive meningococcal disease

[a] *N meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine in combination with Hib-T (HibMenCY-T [MenHibrix]; GSK) was discontinued in 2016. The 4-valent meningococcal polysaccharide vaccine (MPSV4 [Menomune—A/C/Y/W-135]; Sanofi) was discontinued in 2017 and MenACWY-D (Menactra; Sanofi) was no longer being distributed as of October 2023. A 5-valent vaccine (MenABCWY; Penbraya, Pfizer) was licensed in the fall of 2023 and recommendations for use were pending as of October 2023.

[b] GSK acquired this product from Novartis in 2015.

[c] Yeast extract-based medium is used in the production of CRM_{197}, but the package insert does not list yeast as a contaminant in the final product.

[d] Dose 2 should be given in the second year of life.

[e] Two doses separated by 2 mo may be given to children 2-5 y at continued high risk of meningococcal disease.

[f] Use of MenACWY-D and MenACWY-CRM at >55 y is off-label.

[g] See **Figure 6.2** regarding "spacing rules" between DTaP, PCV13 and MenACWY-D.

MenQuadfi are capsular polysaccharide-based 4-valent vaccines, consisting of protein-polysaccharide conjugates analogous to Hib and PCV. Biologic differences between conjugate and polysaccharide vaccines are discussed in *Chapter 1: Introduction to Vaccinology—The Germinal Center Reaction* and are summarized in **Table 1.4**.

Polysaccharide-based vaccines against serogroup B are not feasible because humans are tolerant to the serogroup B polysaccharide—it is antigenically similar to glycopeptides found on human brain tissue, and the immune system does not recognize it as "foreign" (see *Chapter 1: Introduction to Vaccinology—Basic Vaccine Immunology*). FHbp is a lipoprotein expressed on the surface of *N meningitidis* that binds Factor H, a complement regulator in serum, inhibiting activation of the alternative complement pathway and protecting the organism from complement-mediated lysis.[27] When used as a vaccine antigen, FHbp engenders antibodies that bind to the surface of the organism and kill it through activation of the classical complement pathway; antibodies may also block binding of Factor H, "uncloaking" the organism and amplifying its susceptibility to complement-mediated lysis via the alternative pathway.[28] To make MenB-FHbp, the genes for FHbp from two distinct subfamilies—A, representing 30% of isolates, and B, representing 70%—were cloned and expressed in *E coli*. The protein is lipidated, meaning it has a small lipid tail—similar to the natural protein—that appears to enhance immunogenicity. MenB-4C contains FHbp from a subfamily B isolate in the form of a recombinant-derived fusion protein. It also contains a recombinant-derived Neisserial heparin binding antigen fusion protein, a partial length Neisserial adhesin A, and physically-purified outer membrane vesicles, which contain PorA serosubtype P1.4. These antigens were identified by reverse vaccinology (see *Chapter 1: Introduction to Vaccinology—Non-live Vaccines*).

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Licensure of MenACWY-D was based on demonstration of immunologic noninferiority to MPSV4, for which efficacy data existed. Between 2005 and 2008, the effectiveness of MenACWY-D was estimated to be 80% to 85% within 3 years of vaccination,[29] but studies suggest that effectiveness dropped by nearly half within a few years of a single dose.[30] Licensure of MenACWY-CRM was based on immunologic noninferiority to MenACWY-D. In a randomized, controlled trial in adolescents, the seroresponse rate for each serogroup for MenACWY-CRM was noninferior to that of MenACWY-D; for serogroups A, W, and Y, the seroresponse rates and geometric mean titers were superior.[31] Five years out from primary vaccination, a majority of vaccinees still had protective levels of antibody to serogroups C, W, and Y.[32] The seroresponse

TABLE 23.2 — *N meningitidis* Serogroup B Vaccines[a]

Trade name	Bexsero	Trumenba
Abbreviation	MenB-4C	MenB-FHbp
Manufacturer/ distributor	GSK[b]	Pfizer
Type of vaccine	Non-live, subunit, purified and in vitro-expressed	Non-live, subunit, in vitro-expressed
Composition	Factor H binding protein (variant 1.1, subfamily B) fusion protein with the accessory protein 936 (50 mcg) expressed in *E coli*	Lipidated factor H binding protein from *N meningitidis* serogroup B (strains A05 [subfamily A] and B01 [subfamily B], 60 mcg each) expressed in *E coli*
	Neisserial heparin binding antigen (peptide 2) fusion protein with accessory protein 953 (50 mcg) expressed in *E coli*	
	Neisserial adhesin A fragment (peptide 8 variant 2/3) (50 mcg) expressed in *E coli*	
	Outer membrane vesicles from strain NZ98/254 containing PorA serosubtype P1.4 (25 mcg)	
Adjuvant	Aluminum hydroxide (0.519 mg aluminum)	Aluminum phosphate (0.25 mg aluminum)
Preservative	None	None
Excipients and contaminants	Sodium chloride (3.125 mg)	Polysorbate 80 (18 mcg)
	Histidine (0.776 mg)	
	Sucrose (10 mg)	Histidine buffered saline (10 mM)
	Kanamycin (<0.01 mcg)	
Latex	Tip cap of prefilled syringe contains latex	None

Continued

TABLE 23.2 — *Continued*

Trade name	Bexsero	Trumenba
Labeled indications	Prevention of IMD due to serogroup B	Prevention of IMD due to serogroup B
Labeled ages	10-25 y	10-25 y
Dose	0.5 mL	0.5 mL
Route of administration	Intramuscular	Intramuscular
Labeled schedule	2 doses ≥1 month apart	Doses at 0 and 6 mo or 0, 1-2, and 6 mo
Recommended schedule (age)[c]	16-18 y (shared clinical decision-making): same	16-18 y (shared clinical decision-making): doses at 0 and 6 mo[d]
	High-risk ≥10 y: same	High-risk ≥10 y: doses at 0, 1-2, and 6 mo[e]
	Periodic boosters (**Figure 6.2**)	Periodic boosters (**Figure 6.2**)
How supplied (number in package)	Prefilled syringe (10)	Prefilled syringe (1, 5, 10)
Cost per dose (USD, 2023)		
Public	141.71 (pediatric) 118.37 (adult)	130.77 (pediatric) 102.85 (adult)
Private	211.32	179.70
Reference package insert	January 2022	November 2021

IMD, invasive meningococcal disease

[a] A 5-valent vaccine (MenABCWY; Penbraya, Pfizer) was licensed in the fall of 2023 and recommendations for use were pending as of October 2023.

[b] GSK acquired this product from Novartis in 2015.

[c] See *Chapter 2: Vaccine Infrastructure in the United States—Policy and Recommendations* and **Table 2.7** for discussion of shared clinical decision-making. Use of MenB at >25 y is off-label.

[d] If Dose 2 of MenB-FHbp is given ≤6 mo after Dose 1, another dose should be given ≥4 mo after Dose 2. If Dose 3 is given ≤4 mo after Dose 2, another dose should be given ≥4 mo after Dose 3.

[e] Persons at high risk for IMD, and those needing immediate protection, should receive the 3-dose (not the 2-dose) schedule of MenB-FHbp (if Dose 2 is administered ≥6 mo after Dose 1, a third dose is not necessary). While not considered high-risk for invasive serogroup B disease, persons with HIV infection should receive the 3-dose series because they may not respond optimally to the vaccine.

rate for each serogroup among adults who received MenACWY-CRM also was noninferior to that of MenACWY-D recipients, and in fact the responses were superior for serogroups C, W, and Y. In a study of children 2 to 10 years of age, MenACWY-CRM was noninferior to MenACWY-D for all serogroups and was statistically superior for serogroups C, W, and Y.[33] In addition, after 3 doses of MenACWY-CRM given at 2, 4, and 6 months of age, approximately 95% of infants have protective levels of antibody to serogroups C, W, and Y, and 76% have protective levels against serogroup A. Booster responses are seen after a dose at 12 months of age, and the seroprotection rate against serogroup A approaches 90%. However, antibody appears to wane after infant immunization, particularly for serogroup A.[34]

In a head-to-head trial in children 2 to 9 years of age, seroresponse rates for MenACWY-T were noninferior to MenACWY-CRM; the vast majority of subjects achieved protective antibody titers, and the safety profile was comparable.[35] A Phase 2 study in adolescents demonstrated seroresponse rates that were noninferior to MenACWY-CRM; seroprotection rates for each serogroup were higher for MenACWY-T, and geometric mean antibody titers were higher for serogroups C, W, and Y.[36] Similar results were seen when MenACWY-T was compared with MenACWY-D among adolescents and adults,[37] as well as when the vaccine was compared with MPSV4 among older adults.[38] In a Phase 3 study, booster responses in older adolescents were demonstrated, regardless of which meningococcal conjugate was used for priming.[39]

Meningococcal conjugate vaccines appear to reduce nasopharyngeal carriage of the organism,[40] and there is evidence of real-world effectiveness of the MenACWY program in the US.[41]

For serogroup B, antibody responses are measured against test strains that represent the current distribution of antigenically diverse isolates. Endpoints have included the proportion of vaccinees who achieve a 4-fold or greater rise in titer for each strain tested, as well as the proportion who achieve a titer equal to or above the lower limit of detection for all test strains (this is referred to as the *composite response*). Composite responses among adolescents after the 3-dose schedule of MenB-FHbp are around 83% and after the 2-dose schedule around 54%[42]; titers decline rapidly after vaccination, although 4 years after vaccination over 50% of vaccinees still have protective levels to most strains.[43] Over 85% of adolescents receiving a 2-dose schedule of MenB-4C develop protective antibodies against indicator strains, and responses appear to persist at least 18 to 24 months from vaccination.[44,45] A study done in the context of a college campus outbreak of serogroup B disease showed that about 34% of MenB-4C recipients failed to mount an antibody response to the outbreak strain, even though no cases occurred among vaccinated students.[46]

In the United Kingdom, where a universal infant immunization program with MenB-4C was introduced in 2015, effectiveness against all serogroup B disease following doses at 2, 4, and 12 months of age was 59%, and protection lasted at least 2 years.[47] A matched incidence density case-control study from 2014 to 2019 in Portugal estimated the effectiveness of infant immunization with MenB-4C against serogroup B IMD to be 79%,[48] and a matched case-control study in Spain among children <60 months of age showed that complete vaccination was 76% effective against IMD caused by any serogroup and 71% against IMD caused by serogroup B.[49] Data on real-world effectiveness of MenB vaccines in other age groups are limited. MenB vaccines do not appear to reduce carriage of *N meningitidis*[50]; therefore, disease prevention in specific populations will depend on individual, rather than herd, immunity.

Strains of *N meningitidis* serogroup B differ in their expression of the various antigens contained in MenB vaccines. Various techniques predict that over 90% of strains prevalent in the US should be susceptible to the antibodies produced after vaccination with either of the available MenB vaccines.[51,52]

Safety

Pain is reported in about half of adolescent and adult MenACWY-D recipients and is of moderate severity in <15%. Induration or erythema occur in 10% to 20% but is moderate or severe in <5%. Headache occurs in 36% to 41%, fatigue 30% to 35%, malaise 22% to 24%, and fever 2% to 5%. One percent or less of these reactions is considered severe. The reactogenicity of MenACWY-CRM and MenACWY-T is comparable. The most common solicited adverse reactions for MenB-FHbp in clinical trials were pain at the injection site (≥85%), fatigue (≥40%), headache (≥35%), myalgia (≥30%), and chills (≥15%). For MenB-4C, they were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%). Serious adverse events associated with both vaccines are rare.

Postlicensure studies have failed to detect serious safety signals for any of the meningococcal vaccines.[53,54]

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction). For MenACWY-D and MenACWY-CRM, this includes reactions to any diphtheria toxoid-containing vaccine, since these vaccines contain either diphtheria toxoid or CRM, a mutant diphtheria toxin; for MenACWY-CRM, this may include yeast (see *Footnote c* in **Table 23.1**).

TABLE 23.3 — Shared Clinical Decision-Making Around MenB

Talking Points		
The disease is serious	**Safe and effective vaccines are available**	**There are reasons why a person might want to be vaccinated**
Meningococcal disease is rare but can lead to permanent disability and death The infection spreads through respiratory droplets and secretions The disease moves rapidly and early on is difficult to distinguish from benign viral illness Most cases in US adolescents are caused by serogroup B The routinely-recommended MenACWY does not protect against serogroup B	Two safe and effective vaccines are available The vaccines likely protect against most circulating serogroup B strains Protection wanes within 1-2 y of completing the series MenB provides individual protection against disease, but herd immunity is unlikely The vaccines are covered by insurance and the Vaccines for Children Program Vaccination should be discussed with all adolescents at 16-18 y	College students are at increased risk, especially those who are freshmen, attend 4-year universities, live on campus, or participate in sororities or fraternities A person who has specific concerns or anxiety about meningococcal disease may want to be vaccinated Persons with chronic medical conditions[b] may want to be vaccinated Anyone wanting to prevent the disease may be vaccinated

[a] MenB is recommended routinely for persons 16 to 23 y who are at increased risk and all high-risk persons ≥10 y, such as those with asplenia or complement component deficiency.

[b] Examples include conditions like asthma, diabetes, and immunosuppression that place patients at higher risk for similar infections, but which are not specifically considered high-risk for serogroup B meningococcal disease.

Adapted from Mbaeyi SA, et al. *MMWR*. 2020;69:RR-9:1-41; Middleman AB, et al. *Acad Pediatr*. 2022;22:564-572; Meningococcal B vaccination. CDC Web site. https://www.cdc.gov/vaccines/hcp/admin/downloads/isd-job-aid-scdm-mening-b-shared-clinical-decision-making.pdf. Accessed June 10, 2023.

TABLE 23.4 — Immunization Against *N meningitidis*

Population	MenACWY[a]	MenB[b]
Healthy adolescents	✓	Shared clinical decision-making
Persons with functional or anatomic asplenia	✓	✓
Persons with persistent complement component deficiency[c]	✓	✓
Microbiologists with ongoing exposure to *N meningitidis*	✓	✓
Outbreaks	✓	✓
Travelers to endemic regions	✓	
College freshmen living in dormitories	✓	
Military recruits	✓	
Persons with HIV infection	✓	

[a] MenACWY-CRM is labeled from 2 mo-55 y and MenACWY-D is labeled from 9 mo-55 y; use of either product at >55 y is off-label. MenACWY-TT is labeled for ≥2 y.

[b] MenB-FHbp and MenB-4C are indicated from 10-25 y. Use of either product at >25 y is off-label. MenB is not recommended in the US for high-risk persons <10 y.

[c] Deficiency of C3, C5–C9, properdin, Factor H, or Factor D; complement inhibitor treatment (eg, eculizumab or ravulizumab; vaccinate ≥2 wk before initiation of treatment if possible).

Adapted from Mbaeyi SA, et al. *MMWR*. 2020;69:RR-9:1-41.

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- Personal or family history of Guillain-Barré syndrome is not considered a contraindication or precaution for MenACWY, even though the package inserts list it in the Warnings and Precautions section (see *Chapter 7: Addressing Concerns About Vaccines—Guillain-Barré Syndrome*)
- Preterm birth and <9 months of age (risk of apnea after intramuscular injection; applies to MenACWY-CRM only)

Recommendations

All adolescents should be vaccinated against *N meningitidis* serogroups A, C, W and Y (there is no preference among the available vaccines). The usual schedule is 1 dose at 11 to 12 years of age followed by a one-time booster dose at 16 years of age (doses given before 10 years of age do not count as part of this routine schedule). Adolescents ≤18 years of age who have not been vaccinated should receive a dose at the earliest opportunity. For those who receive Dose 1 at 13 to 15 years of age, Dose 2 is recommended at 16 to 18 years of age (Dose 2 can be given any time after the person turns 16 years of age, as long as the minimum interval of 8 weeks has passed). Since adolescents and young adults are at increased risk for IMD, and since immunity from vaccination wanes over the first 5 years, a dose at 16 to 21 years of age is recommended—even if a person has received more than one dose before 16 years of age. Persons who are first immunized at 16 to 21 years of age do not need a booster dose. Routine vaccination of persons >21 years of age is not recommended. Vaccination against serogroup B disease using MenB-FHbp or MenB-4C (the series must be completed with the same product; mixed schedules are considered invalid) is recommended under SCDM (see *Chapter 2: Vaccine Infrastructure in the United States—Policy and Recommendations* and **Table 2.7**); if given, the recommended age is 16 to 18 years. **Table 23.3** provides a guide to the SCDM process for MenB. In general, MenACWY and MenB should be offered to anyone wanting to reduce his or her risk of meningococcal disease.

In addition to age-based routine use, MenACWY is recommended for the persons or situations listed below:

- Unvaccinated incoming college students ≤21 years of age (incoming college students whose last dose of a meningococcal vaccine was >5 years earlier should receive a booster dose; unvaccinated students, and those who are already in college and whose last dose was >5 years earlier, also may be vaccinated)
- Microbiologists routinely exposed to *N meningitidis*
- Military recruits
- Travelers to or residents of countries in which *N meningitidis* is hyperendemic or epidemic
- Outbreak control

MenB is recommended for microbiologists routinely exposed to *N meningitidis* and can be used in outbreak control (it is not routinely recommended for travelers or military recruits, and the recommendation for college students is the same as for other adolescents and young adults [SCDM]). Vaccination and revaccination of high-risk persons, including travelers and persons with HIV infection, is discussed in *Chapter 6: Vaccination in Special Circumstances* and is outlined in **Figure 6.2**; a summary of the routine and special meningococcal vaccination recommendations is given in **Table 23.4**.

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Polio

The Pathogen

Poliovirus is a small, nonenveloped, single-stranded RNA virus in the Picornaviridae family. Initial replication occurs in the pharynx, lower gastrointestinal tract, and associated lymph nodes. This leads to primary viremia that seeds peripheral sites, including the viscera and skeletal muscle. Most infections are contained at this point and are subclinical. In a minority of individuals, replication at peripheral sites leads to secondary viremia and nonspecific symptoms such as fever and malaise; about 1% of the time the central nervous system (CNS) is involved, either through hematogenous spread or axonal transport from muscle. Once in the CNS, poliovirus can cause self-limited aseptic meningitis, but can also replicate in and destroy anterior horn cells of the spinal cord, leading to lower motor-neuron paralysis.

Clinical Features

Approximately 95% of infections are asymptomatic. Minor, nonspecific illness with low-grade fever and sore throat occurs in about 5% of infected people; *aseptic meningitis*, sometimes with paresthesias, occurs in 1% to 2% of patients a few days after these symptoms resolve. The cerebrospinal fluid may show mild pleocytosis with lymphocytic predominance. Less than 1% of patients experience rapid onset of *asymmetric flaccid paralysis* and areflexia; the proximal lower extremity muscles are most often involved, and some patients have cranial nerve involvement. Prior to the availability of modern assisted ventilation, most deaths occurred from respiratory failure; patients who survived the acute illness but failed to recover respiratory muscle function lived out the remainder of their lives in iron lungs. Today, tracheostomy and positive-pressure ventilation are used. Somewhat more than half of patients who develop limb paralysis have permanent functional deficits.

Epidemiology and Transmission

Humans are the only natural hosts and transmission occurs by the fecal-oral route, although pharyngeal secretions may be involved. Communicability is greatest shortly before

and after onset of clinical illness, but patients may be contagious in the absence of symptoms and fecal excretion may persist for weeks. Immunodeficient patients can excrete the virus for >6 months.

Infection is more common in infants and young children and occurs at an earlier age among children living in poor hygienic conditions. The risk of paralytic disease increases with age. In temperate climates, poliovirus infections are most common during the summer and autumn. In the tropics, the seasonal pattern is variable with a less-pronounced peak of activity.

The last reported indigenous case of polio in the US occurred in 1979; since then, all other cases arising in the US (an average of eight per year between 1980 and 1996) were caused by OPV-derived strains. While OPV has not been used in the US since 2000, infections with OPV-derived strains imported from other countries can still occur.[1] Vaccine-derived poliovirus that has reverted to virulence can emerge because of continuous replication in immunodeficient individuals or continuous circulation in unimmunized populations. The latter phenomenon was highlighted during an outbreak of paralytic polio in the Caribbean in 2000 and 2001, which was caused by a strain of OPV that had reverted to virulence in areas of very low vaccine coverage.[2] More recently, vaccine-derived poliovirus type-2 has been detected in wastewater in London, New York, and Jerusalem,[3] and a case of polio caused by this virus occurred in an unvaccinated person in Rockland County, New York in 2022.[4]

Immunization Program

OPV was the vaccine of choice for children in the US since the early 1960s because it induced optimal intestinal immunity, was inexpensive and painless, required little training to administer, and contributed to immunity at the population level through fecal-oral spread. For these same reasons, OPV has been used in the worldwide eradication effort. However, the continued use of OPV, with the attendant risk of vaccine-associated polio, was unjustified in the US in the absence of wild-type disease; accordingly, by 2000 IPV had replaced OPV in the routine childhood schedule.[5,6] Polio vaccination recommendations were updated in 2009[7] and 2023[8]; the latter update included catch-up vaccination for unvaccinated and incompletely vaccinated adults. Updated travel recommendations were published in 2014.[9]

Proof of immunity to all three polio types is recommended in the US; because some countries now use 2-valent (types 1 and 3) OPV, persons vaccinated outside the US may be incompletely immunized (*see below*).

Vaccines

Characteristics of the polio vaccine licensed in the US are given in **Table 24.1**. This is a non-live, whole-virus vaccine, made much the same way as the Salk polio vaccine.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Ninety-percent or more of vaccinees develop protective antibody to all three serotypes after 2 doses, and ≥99% are immune after 3 doses. Protection against paralytic disease correlates with the presence of serum antibody. IPV appears to induce less mucosal immunity than does OPV, so persons who receive IPV are more readily infected in the gastrointestinal tract with wild poliovirus. Thus, a person immunized with IPV could become infected in an endemic area and shed virus upon return to the US. The infected person would be protected from paralytic polio, but the wild virus shed in the stool could be transmitted to a contact. Immunity from IPV probably lasts many years.

In 1988, the year that the World Health Assembly resolved to eradicate polio, there were 350,000 cases worldwide.[10] By 1994, the Region of the Americas was certified free of indigenous polio; by 2000 the Western Pacific Region was polio-free, by 2002 the European Region, by 2014 the South-East Asia Region, and by 2020 the African Region. In 2015 the world was declared free of polio type 2, and in April 2016, all countries switched to either 2-valent OPV or 3-valent IPV.[11] The reason—continued use of live attenuated type 2 vaccine would have meant continued risk of reversion to virulence and vaccine-associated polio, a risk not worth taking in a type 2 polio-free world. In 2019, the world was declared free of polio type 3,[12] and by April of that year, every country on the planet had introduced at least one dose of IPV into their routine immunization schedule.[13] It has been estimated that since 1960, polio immunization has prevented 30 million cases of paralysis worldwide,[14] and as of 2023, polio remained endemic in only two countries: Afghanistan and Pakistan.[15] It is important to remember that the early 21st century saw polio outbreaks in countries that had been polio-free, the result of importation, poor health infrastructure, and geopolitical unrest.

Safety

Minor local reactions, such as pain and redness, may occur following IPV. No serious adverse events have been associated with use of the currently available vaccine.

TABLE 24.1 — Polio Vaccine[a]

Trade name	IPOL
Abbreviation	IPV
Manufacturer/distributor	Sanofi
Type of vaccine	Non-live, whole agent
Composition	
Virus strain and amount	Type 1 (Mahoney), 40 D antigen units
	Type 2 (MEF-1), 8 D antigen units
	Type 3 (Saukett), 32 D antigen units
Propagation	Vero (African green monkey kidney) cells
Inactivation	Formalin
Adjuvant	None
Preservative	2-phenoxyethanol (0.5%)
	Formaldehyde (≤0.02%)
Excipients and contaminants	Neomycin (<5 ng)
	Streptomycin (<200 ng)
	Polymyxin B (<25 ng)
	Calf serum albumin (<50 ng)
Latex	None
Labeled indications	Prevention of poliomyelitis
Labeled ages	≥6 wk
Dose	0.5 mL
Route of administration	Intramuscular or subcutaneous
Labeled schedule (age)	2, 4, 6-18 mo and 4-6 y
Recommended schedule	Same
How supplied (number in package)	10-dose vial (1)
Cost per dose (USD, 2023)	
Public	15.98
Private	40.64
Reference package insert	May 2022

[a] IPV is available in combination with DTaP (Kinrix, GSK; Quadracel, Sanofi); DTaP and HepB (Pediarix; GSK); DTaP and Hib-T (Pentacel; Sanofi); and DTaP, HepB and Hib-OMP (Vaxelis; Merck and Sanofi). See *Chapter 35: Combination Vaccines*.

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- Pregnancy (theoretical risk to the fetus or attribution of birth defects to vaccination). No deleterious effects have been demonstrated from IPV administration during pregnancy, and the risk of adverse fetal effects from a non-live vaccine is extremely low.

Recommendations

All children should be vaccinated against polio. The primary series of IPV consists of 3 doses, usually given at 2, 4, and 6 to 18 months of age. Dose 4 is given at 4 to 6 years of age. The final dose should be given at ≥4 years of age and ≥6 months after the last dose; if Dose 4 is given at <4 years of age (as would be the case, for example, in a child who receives DTaP-IPV/Hib at 2, 4, 6, and 15 months of age), another dose of IPV should be given at 4 to 6 years of age. Dose 4 is not necessary if Dose 3 was given at ≥4 years of age and ≥6 months after the previous dose. In the first 6 months of life, the minimum age and minimum intervals should only be used if imminent exposure to polio is expected (as, for example, in the case of an infant traveling to an endemic area). Only 3-valent OPV and IPV are considered valid doses of polio vaccine in the US schedule; any OPV administered on or after April 1, 2016, would have been 2-valent and would not be considered valid. If both 3-valent OPV and IPV were administered as part of a series, the total number of doses should be the same as for an all-IPV schedule. If only 3-valent OPV was administered, and all doses were given at <4 years of age, one dose of IPV should be given at ≥4 years of age, ≥6 months after the last dose of OPV. Serological testing for polio immunity is not recommended because appropriate reagents are becoming increasingly unavailable.[16]

Persons ≥18 years of age who are unvaccinated—ie, did not receive ≥3 doses of 3-valent OPV or IPV (in any combination, with ≥4 weeks between doses, with the last dose given at ≥4 years of age and ≥6 months after the previous dose) should complete a primary series with IPV. A primary series of IPV consists of doses at 0, 1 to 2, and 6 to 12 months (an accelerated schedule consisting of doses at 0, 1, and 2 months can be used if necessary). It should be noted that most adults who were born and raised in the US were probably vaccinated against polio as children; those who received any childhood vaccines almost certainly received the polio vaccine.

Persons ≥18 years of age who have had <3 doses of either OPV or IPV should complete the primary series of 3 doses using IPV, regardless of the interval since the last dose and the type of vaccine that was previously given. Those who have received a primary series who are at increased risk of exposure may receive a single booster dose of IPV (this does not need to be repeated). Persons who are at increased risk include travelers to countries where polio is epidemic or endemic (see *Chapter 6: Vaccination in Special Circumstances—Travel*), laboratory and healthcare personnel (HCP) who handle specimens that might contain poliovirus, and HCP or caregivers who have close contact with a person who could be infected.

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Rabies

The Pathogen

Rabies virus is an enveloped, bullet-shaped, single-stranded RNA virus in the Rhabdoviridae family. The virion surface is covered with glycoprotein (G-protein) spikes, which mediate attachment to the heavily sialated gangliosides on neuronal cells. Attachment also may occur at nicotinic acetylcholine receptors in muscle, facilitating entry into peripheral nerves. The virus moves by retrograde axoplasmic flow from the site of inoculation to neuronal cell bodies, where it replicates and spreads to the brain; from there it may spread to other organs, including the salivary glands, facilitating transmission to another host. The virus spreads from neuron-to-neuron through synapses, and host defenses appear to be downregulated by the virus, enhancing spread. Gross pathologic changes in the brain include vascular congestion and edema, and characteristic eosinophilic inclusions (*Negri bodies*) are seen in the cytoplasm of neurons. The clinical severity of the disease is disproportionate to the degree of histopathologic derangement.

Clinical Features

Rabies has four stages: the incubation period, prodrome, acute neurologic phase, and coma/death.[1] Two thirds of patients present with the *furious form*, characterized by fluctuating consciousness, phobic spasms, dilated pupils, and hypersalivation. The rest present with the *paralytic form*, which is differentiated from Guillain-Barré syndrome by the presence of fever, intact sensation, and urinary incontinence. The incubation period is typically a few weeks to 2 months but may be many years. Animal bites to the head result in shorter incubation periods than bites to the extremities.

There are no symptoms during the *incubation phase*, but the *prodrome,* which lasts 2 to 10 days, is characterized by fever, headache, malaise, fatigue, anorexia, anxiety, agitation, irritability, insomnia, and depression; pain, pruritus, or paresthesia may occur at the site of the bite. The *acute neurologic phase*, which lasts 2 to 12 days, is characterized by hyperactivity, disorientation, hallucinations, bizarre behavior, aggressiveness, seizures, paralysis, aerophobia, hyperventilation, and cholinergic manifestations, including hypersalivation, lacrimation, mydriasis,

and hyperpyrexia. Agitation may be precipitated by tactile, auditory, visual, or other stimuli, and hydrophobia, characterized by painful spasms of the pharynx and larynx, may be precipitated by eating or drinking or even the sight of liquids. Paralysis occurs in 20% of cases. At the end of the neurologic phase, the patient may become comatose. Death from respiratory or cardiac arrest usually occurs within 7 days, although with supportive care, coma may last for months. There are only a handful of reported survivors, most of whom have neurologic sequelae. Successful treatment of a 15-year-old girl from Wisconsin was reported in 2005; the strategy included therapeutic coma using gamma-aminobutyric acid receptor agonists along with *N*-methyl-d-aspartate receptor antagonists.[2]

Epidemiology and Transmission

All mammals can be infected with rabies, but only carnivorous mammals and bats are considered true reservoirs. Transmission from animals to humans occurs by exposure to saliva, usually through an animal bite, scratch, or contact with mucous membranes. Infection by aerosol has been reported in laboratories that handle the virus and in caves inhabited by bats (here, direct infection of the olfactory apparatus is suspected). Rabies can also be transmitted by allografts. In nature, dogs, wolves, foxes, coyotes, jackals, raccoons, skunks, weasels, bats, and mongooses are most commonly infected.

There are an estimated 59,000 human rabies cases each year worldwide, almost all of which are from dog bites and almost all of which are fatal (in 2018, the World Health Organization and its partners launched a program to eliminate dog rabies by 2030[3]). In the US, where domestic animal rabies is well controlled through animal vaccination, only about 2 human cases occur per year; while insectivorous bats are the most common source of infection, almost a third of cases are acquired from dog bites during international travel.[4] Silver-haired bats have become a particular problem because the virus strains they carry may infect human skin more easily and their bites may be too small to see. In at least half of bat-associated cases, there is no known bite—a bite may simply have been imperceptible or might have occurred during sleep, or transmission might have occurred through bat saliva contacting a mucous membrane or break in the skin. Of note, there are about 175 mass bat exposures (>10 persons exposed to a potentially rabid bat) in the US every year.

Most animal contact in the US involves dogs, cats, and rodents, the vast majority of which carry a very low risk for rabies transmission; nevertheless, postexposure prophylaxis is commonly given.[5] Small rodents (eg, squirrels, rats, and mice) and lagomorphs (eg, rabbits and hares) rarely carry rabies. Oral vaccination of wildlife has proven effective in preventing spread of enzootic disease. Traditional approaches have utilized bait seeded with live attenuated rabies

strains. Another approach uses a vaccinia recombinant expressing the G protein of rabies virus.

Immunization Program

The long incubation period makes rabies uniquely suited to postexposure prophylaxis through both vaccination and passive immunization with human rabies immune globulin (HRIG); in this respect, rabies is similar to hepatitis B.[6] The common occurrence of animal contacts combined with the near certainty of death if rabies occurs leads to frequent consideration of postexposure prophylaxis. However, postexposure prophylaxis is considered *urgent*, not *emergent*—in other words, the time frame in which to administer prophylaxis is hours, not minutes, and in some cases may be days (eg, if signs of rabies develop in a domestic animal during quarantine). From the societal perspective, postexposure prophylaxis is cost saving when given to persons bitten by test-positive rabid animals or untested reservoir or vector animals. For other risk situations, cost-effectiveness varies widely. About 55,000 courses of postexposure prophylaxis are given each year in the US.

Pre-exposure vaccination of persons likely to encounter the virus can simplify postexposure treatment by eliminating the need for HRIG and reducing the number of vaccine doses needed. It also protects people who may have inapparent exposures or whose postexposure therapy might be delayed. Pre-exposure vaccination is particularly important for persons who are at high risk of exposure but who may be in situations where modern prophylaxis is not available.

Comprehensive recommendations for prevention of human rabies were published in 2008.[7] In 2010 the postexposure vaccine series was reduced from 5 to 4 doses for otherwise healthy persons,[8] and in 2022 the risk categories for exposure to rabies were redefined and the number of doses recommended for pre-exposure prophylaxis was reduced, among other updates.[9]

Vaccines

Characteristics of the rabies vaccines licensed in the US are given in **Table 25.1**. These are non-live, whole-virus vaccines, made much the same way as the Salk polio vaccine.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Essentially all persons given pre- or postexposure prophylaxis achieve protective concentrations of antibody.[10] Multiple studies have demonstrated that postexposure prophylaxis with cell culture-derived vaccine and HRIG provide excellent protection against

TABLE 25.1 — Rabies Vaccines[a]

Trade name	Imovax Rabies	RabAvert
Abbreviation	RAB-HDC (rabies-human diploid cell)	RAB-PCEC (rabies-purified chick embryo cell)
Manufacturer/ distributor	Sanofi	Bavarian Nordic[b]
Type of vaccine	Non-live, whole agent	Non-live, whole agent
Composition		
Virus strain	PM-1503-3M	Flury LEP
Propagation	Human diploid (MRC-5) cells	Purified chick embryo cells (fibroblasts)
Inactivation	Beta-propiolactone	Beta-propiolactone
Antigen content	≥2.5 IU	≥2.5 IU
Adjuvant	None	None
Preservative	None	None
Excipients and contaminants	Albumin (<100 mg)	Polygeline (processed bovine gelatin; ≤12 mg)
	Neomycin sulfate (<150 mcg)	Human serum albumin (≤0.3 mg)
	Phenol red (20 mcg)	Potassium glutamate (1 mg)
	Beta-propiolactone (<50 ppm)	Sodium ethylenediaminetetraacetic acid (0.3 mg)
		Ovalbumin (≤3 ng)
		Neomycin (≤10 mcg)
		Chlorotetracycline (≤200 ng)
		Amphotericin B (≤20 ng)
Latex	None	None
Labeled indications	Pre-exposure (primary series and booster dose) and postexposure prophylaxis	Pre-exposure (primary series and booster dose) and postexposure prophylaxis
Labeled ages	All ages	All ages
Dose	1 mL	1 mL
Route of administration	Intramuscular[c]	Intramuscular[c]
Labeled schedule		
Pre-exposure	Doses at 0, 7, and 21 or 28 d	Doses at 0, 7, and 21 or 28 d
	Periodic boosters	Periodic boosters
Postexposure (unvaccinated)[d]	Doses at 0, 3, 7, 14, and 28 d	Doses at 0, 3, 7, 14, and 28 d
Postexposure (previously vaccinated)	Doses at 0 and 3 d	Doses at 0 and 3 d
Recommended schedule		
Pre-exposure	See **Table 25.2**	See **Table 25.2**
Postexposure[d]	See **Table 25.4**	See **Table 25.4**
How supplied (number in package)	1-dose vial (1), lyophilized, with diluent	1-dose vial (1), lyophilized, with diluent
Cost per dose (USD, 2023)		
Public	—	—
Private	446.80	418.48
Reference package insert	December 2019	January 2021

HRIG, human rabies immune globulin

[a] Rabies Vaccine Adsorbed (BioPort) and Imovax Rabies I.D. (Sanofi) are no longer available in the US.

[b] GSK acquired this product from Novartis in 2015, and Bavarian Nordic acquired this product from GSK in 2020.

[c] The deltoid muscle should be used for older children and adults. The anterolateral thigh may be preferable for infants and small children. The gluteal muscle should never be used because this may result in lower antibody titers.

[d] HRIG should also be given to exposed, previously unvaccinated persons (see **Table 25.4**).

rabies. Whereas there has never been a reported failure of properly administered postexposure prophylaxis to an immunocompetent person in the US (failure has been reported in an immunocompromised person[11]), failures have been reported in other countries, mostly after severe injuries to heavily innervated areas like the head.[12]

Safety

Local reactions to RAB-HDC occur in 60% to 90% of vaccinees, with local pain occurring in 21% to 77%. Mild systemic symptoms, such as fever, headache, dizziness, and gastrointestinal complaints, occur in 7% to 56%. Systemic hypersensitivity, including urticaria, pruritic rash, and angioedema, may be seen in up to 6% of persons receiving booster doses. This is thought to be mediated by IgE antibodies to human albumin that is chemically altered by beta-propiolactone.

Local reactions to RAB-PCEC occur in 11% to 57% of vaccinees, with local pain occurring in 2% to 23%. Mild systemic symptoms are seen in up to 31%. From 1997 to 2005, the reporting rate to the Vaccine Adverse Event Reporting System was 30 adverse events per 100,000 doses distributed, and for serious adverse events it was 3 per 100,000 doses distributed.[13]

Contraindications

- In the event of exposure to rabies, there are no contraindications to vaccination or use of HRIG.

Precautions

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction). This is not listed as a contraindication, as it is for other vaccines, because rabies is considered universally fatal and therefore the risks of recurrent allergic reaction must be weighed against the possibility of death from rabies.
- Immunosuppressive agents should not be administered during postexposure prophylaxis unless absolutely essential. If possible, pre-exposure prophylaxis should be postponed until immunocompromising conditions are resolved. When an immunosuppressed person is given pre- or postexposure prophylaxis, antibody levels should be checked (≥0.5 IU/mL is considered protective).
- Consider avoiding chloroquine when RAB is being administered (potential for reduced immunogenicity).[14]

Recommendations

Table 25.2 gives recommendations for pre-exposure prophylaxis. **Table 25.3** lists the situations where postexposure prophylaxis should be considered, and **Table 25.4** gives the postexposure regimens. Cell culture-derived rabies vaccines are considered interchangeable, although situations where one would need to complete a series with a different vaccine are rare.

TABLE 25.2 — Pre-Exposure Rabies Prophylaxis

Risk Category	Nature of Exposure[a]	Typical Groups[b]	Biogeography[c]	Vaccination[d]
Note that pre-exposure prophylaxis does not eliminate the need for postexposure prophylaxis (Table 25.4).				
1	Unrecognized or recognized[e] Unusual (eg, aerosol) or high-risk High concentration of virus	Rabies research or vaccine production workers Persons performing tests for rabies	Laboratory[f]	Primary series[g] Serology every 6 mo Booster dose if antibody <0.5 IU/mL[h]
2	Typically recognized but could be unrecognized[e] Unusual exposure unlikely	Persons who handle bats, have contact with bats, or enter high-density bat environments Persons who perform animal necropsies	Regions where any rabies reservoir is present	Primary series[g] Serology every 2 y Booster dose if antibody <0.5 IU/mL[h]
3	Recognized[e] Sustained (>3 y)	Veterinarians and veterinary technicians Animal control officers Wildlife biologists, rehabilitators, and trappers Spelunkers	Regions where any rabies reservoir is present	Primary series[g] Serology one time in the 1 to 3 y after the primary series (booster dose if antibody <0.5 IU/mL[h])—or—booster dose on or after 21 d but no later than 3 y after primary series
		Selected travelers[i]	Regions where any rabies reservoir is present, particularly where dog rabies is endemic	
4	Recognized[e] Time-limited (≤3 y)	Short-term volunteers providing hands-on animal care	Regions where any rabies reservoir is present	Primary series[g]
		Infrequent traveler with no expected high-risk travel >3 years after prophylaxis	Regions where any rabies reservoir is present, particularly where dog rabies is endemic	
5	Low risk	Typical US resident[j]	—	None

[a] See **Table 25.3** for explanation of mechanisms of exposure.
[b] Examples of risk groups in each category are given. Risk category should be determined on a case-by-case basis and may change over time. Groups include students and trainees, where appropriate.
[c] Consult local or state health departments for current information.
[d] Consider avoiding chloroquine when RAB is being administered because of the potential for reduced immunogenicity.
[e] An example of an unrecognized exposure is a small scratch sustained during an inconspicuous personal protective equipment breach in a person who is testing neural tissue from a rabid animal. Examples of a recognized exposure include any contact with a bat and a bite, scratch, or splash from a potentially rabid animal.
[f] Determining relative risk and monitoring immunization status is generally the responsibility of the laboratory supervisor. Individual laboratories set rules about whether acceptable antibody titers should be confirmed for all personnel (not just those with altered immunity).

Continued

TABLE 25.2 — *Continued*

[g] The primary series consists of doses of RAB at 0 and 7 d. A systematic review in 2022 showed that priming from a 2-dose regimen was comparable to the historical 3-dose regimen (CDC Web site. ACIP grading of recommendations assessment, development and evaluation (GRADE) for 2-dose rabies vaccination schedule. https://www.cdc.gov/vaccines/acip/recs/grade/rabies-2-dose.html. Accessed June 6, 2023). Persons who previously received the 3-dose regimen and are in risk categories 1 or 2 should follow the given testing and boosting recommendations; those who are in risk category 3 need no further vaccine doses or serologies.

[h] Serology to verify a booster response is not needed for immunocompetent persons. For persons with temporary immunosuppression, vaccination should be deferred until immunosuppression can be reversed. For other immunocompromised persons, serology should be performed ≥1 wk (2 to 4 wk is preferred) after the primary series and each booster dose. If the antibody level is <0.5 IU/mL, a second booster dose should be given. If the antibody level after 2 booster doses is <0.5 IU/mL, public health authorities should be consulted and participation in high-risk activities should be suspended. In 2022, an antibody level of ≥0.5 IU/mL replaced the historical target of a serum dilution of ≥1:5 in the rapid fluorescent focus inhibition test.

[i] This includes persons who will be performing occupational or recreational activities that increase risk for exposure to potentially rabid animals (particularly dogs) and those who might have difficulty getting prompt access to postexposure prophylaxis.

[j] The risk of transmission from the body of an animal that has been deceased for an extended period is unknown but presumed to be low; therefore, hunters and taxidermists usually fall into risk category 5. Direct skin contact with saliva and neural tissue of mammals should be avoided regardless of profession.

Adapted from Rao AK, et al. *MMWR.* 2022;71:619-627.

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TABLE 25.3 — Indications for Postexposure Rabies Prophylaxis

Animal[a]	Animal Evaluation and Disposition	Recommendations
Dog, cat, ferret	Healthy and quarantined for 10 d observation period[b]	Institute prophylaxis at first sign of rabies in the animal
	Rabid or suspected rabid	Institute prophylaxis immediately[c]
	Unknown or not available for observation	Consult public health officials[d]
Skunk, raccoon, fox, other carnivore (eg, coyote, bobcat, wild-animal hybrid), bat[e]	Regard as rabid	Institute prophylaxis immediately[c]
Livestock, horse, small rodent (eg, squirrel, chipmunk, rat, mouse, hamster, guinea pig, gerbil), large rodent (eg, woodchuck or groundhog, beaver), lagomorph (eg, rabbit, hare), other mammal[f]	Consider individually	Consult public health officials[d]

[a] *Bite* exposures occur when there has been any penetration of the skin by teeth. *Nonbite* exposures include scratches, abrasions, open wounds, or mucous membranes contaminated with saliva or other potentially infectious material (eg, brain or neural tissue). Contact between intact skin and saliva does not constitute an exposure; neither does casual petting or handling or contact with blood, urine, or feces. However, any potential contact with a bat deserves evaluation because bat bites are small and can go unrecognized. Exposure is assumed to have occurred if a person in the same room as a bat might have been unaware that a bite or direct contact had occurred. Examples include a sleeping person who awakens to find a bat in the room or finding a bat in the room with an unattended child, mentally disabled person, or intoxicated person (awake or asleep). *Aerosol* exposure is rare but has been reported in laboratories that handle the virus and in caves infested with millions of bats. *Human-to-human* transmission occurs almost exclusively through tissue or organ transplantation.

[b] The animal should be quarantined and observed for 10 d. This usually takes place under the supervision of the local health department, which specifies approved facilities (private or government) and monitors the animal's behavior. If signs of rabies develop (eg, aggressive or combative behavior, irritability, hyper-reaction to stimuli, or paralysis), the animal should be euthanized, and the brain sent for detection of rabies virus (this is usually done at the state lab).

[c] If it is likely that the animal is rabid, prophylaxis should begin within 24 h and not await test results (prophylaxis can always be discontinued if tests return negative). **Table 25.4** gives the recommended prophylaxis regimens.

[d] The epidemiology of rabies is complex and varies from region to region. Local and state public health officials should be consulted to determine the likelihood of exposure in specific situations.

[e] These animals should be regarded as rabid unless proved negative by testing of the brain. Prophylaxis should be initiated unless the brain is known to be negative or expeditious testing is under way. Prophylaxis should be considered more urgent if the exposure was from an animal species in the area known to carry rabies; if the animal exhibited abnormal behavior or signs of illness, had an unexplained wound, attacked *without provocation* (bites that result from attempts to feed or handle an apparently healthy animal should generally be regarded as *provoked*); or if the person's wounds were severe or involved the head and neck. Every effort should be made by properly trained officials to obtain the animal for euthanization and testing; quarantine for observation is *not* recommended because signs of rabies in wild animals cannot be interpreted reliably.

[f] Bites of small rodents and lagomorphs almost never require prophylaxis. Large rodents, such as woodchucks, could survive an attack by a rabid animal and go on to develop rabies. This should be considered in areas where raccoon rabies is prevalent.

Adapted from Manning SE, et al. *MMWR*. 2008;57(RR-3):1-28; Rupprecht CE, et al. *MMWR*. 2010;59(RR-2):1-9.

TABLE 25.4 — Postexposure Rabies Prophylaxis Regimens[a]

Vaccination Status	Treatment	Regimen
Not previously vaccinated	Wound cleansing	Cleanse all wounds thoroughly with soap and water
		Use a virucidal agent like povidone-iodine solution if available
	HRIG[b]	Administer 20 IU/kg (0.133 mL/kg)[c]
		Infiltrate the full dose around the wound and give any remaining volume intramuscularly at another site[d]
		Do not exceed the recommended dose[e]
		Use separate syringes for HRIG and vaccine
	RAB	*Healthy person:* administer 1 mL intramuscularly at 0, 3, 7, and 14 d[f]
		Immunosuppressed person: administer 1 mL intramuscularly at 0, 3, 7, 14, and 28 d[f]
Previously vaccinated[g]	Wound cleansing	Cleanse all wounds thoroughly with soap and water
		Use a virucidal agent like povidone-iodine solution if available
	HRIG	Not recommended
	RAB	Administer 1 mL intramuscularly at 0 and 3 d[f]

HRIG, human rabies immune globulin

[a] If the likelihood of exposure is high, prophylaxis should begin immediately (within 24 h) and not await test results on the animal. Both HRIG and vaccine are recommended for prophylaxis, *regardless of the interval between exposure and initiation of treatment*. State or local health departments should be contacted for patients whose postexposure prophylaxis was initiated outside of the US, because the regimens and products used may be suboptimal. For bites, the need for tetanus immunization and prophylactic antibiotics should be assessed. Wound closure should be avoided if possible.

[b] HRIG is used in conjunction with vaccination for postexposure prophylaxis. Three products—HyperRAB (Grifols), Kedrab (Kedrion/Kamada), and Imogam Rabies—HT (Sanofi)—are available in the US. They consist of IgG derived from pooled plasma of human donors who have been hyperimmunized with RAB; they are therefore polyclonal (contain a variety of antibodies, including antibodies to other organisms). Patients with selective IgA deficiency may be at increased risk for anaphylactic reactions to HRIG because it may contain minute amounts of IgA.

[c] HRIG should be given at the same time the vaccine series is initiated. If not given on the day of Dose 1 of vaccine, it may be given up to 7 d later. Beyond this it is not indicated because the vaccine is presumed to have induced antibodies by then.

[d] The intramuscular site, if used, should be different from the site where the first dose of vaccine is given. Subsequent doses of the vaccine may be given in the same muscle where the HRIG was given if that is a preferred site for vaccination.

[e] Exceeding the dose of HRIG may suppress the antibody response to vaccination.

[f] In 2010, the recommended number of doses was reduced from 5 to 4 for otherwise healthy persons (off-label recommendation). The deltoid area is the only acceptable site for adults and older children. The anterolateral thigh can be used for young children (see **Table 4.10**), and the dose is the same as for adults. The gluteal area should never be used. The series does not need to be reinitiated because of minor interruptions of the vaccine schedule—just pick up at the point it was discontinued, maintaining the proper intervals between doses specified in the schedule. If major deviations occur, and for all immunosuppressed persons, test for antibody after completing postexposure prophylaxis. Note that in 2022, an antibody level of ≥0.5 IU/mL replaced the historical target of a serum dilution of ≥1:5 in the rapid fluorescent focus inhibition test.

[g] This includes: 1) persons who received a full pre- or postexposure series of one of the currently licensed cell culture-derived vaccines or of Rabies Vaccine Adsorbed (which is no longer available in the US); and 2) persons who received another type of rabies vaccine and had a documented antibody response. Serologic testing at the time of exposure is not recommended.

Adapted from Manning SE, et al. *MMWR*. 2008;57(RR-3):1-28; Rupprecht CE, et al. *MMWR*. 2010;59(RR-2):1-9.

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Respiratory Syncytial Virus

The Pathogen

Respiratory syncytial virus (RSV), which belongs to the Pneumoviridae family, has a non-segmented, single-stranded RNA genome and a lipid envelope supported by matrix proteins.[1] Two major surface glycoproteins mediate infection. The G-protein, which is antigenically diverse and determines classification of strains into subtypes A and B, mediates attachment to cells and plays a role in modulating the immune response. After attachment, the fusion (F) protein, which is highly conserved between strains, binds to cell surface receptors and undergoes a conformational change that induces fusion between the viral and cellular membranes, allowing the ribonucleoprotein complex to enter the cytoplasm and begin the process of replication. The F-protein is the dominant antigen that elicits neutralizing antibodies. The most potent neutralizing epitopes are exposed on the prefusion conformation of the F-protein; however, this conformation is metastable and reverts to the postfusion conformation in solution and even on the surface of virions and cells.[2] A critical step in vaccine development was the introduction of amino acid sequence changes that "lock" the F-protein in its prefusion ("pre-triggered") conformation[3]; this results in constitutive presentation of the major neutralizing epitopes, especially "site Ø", which is not accessible on the postfusion molecule, enhancing the induction of neutralizing antibody many-fold (similar technology was used to stabilize the SARS-CoV-2 S-protein for use in vaccines; see *Chapter 12: COVID-19*).[4]

RSV initially targets the nasal epithelium and spreads to the lower respiratory tract by infecting ciliated epithelial cells in the bronchial epithelium and type 1 pneumocytes in the alveoli.[5] The virus itself is not cytopathic[6]; rather, it causes superficial damage that leads to capillary leak, inflammation, reduced surfactant activity, bronchoconstriction, and mucociliary dysfunction, ultimately resulting in small airways that are clogged with mucus, fibrin, and cellular debris; clinical manifestations include increased airway resistance, air trapping, atelectasis, and hypoxemia.

Natural immunity is incomplete; this is less due to strain variation than to immunomodulatory effects of the virus, which lead to poor immune memory.[7]

Clinical Features

The incubation period is 4 to 7 days. Most infections are either asymptomatic or result in self-limited upper respiratory tract symptoms like rhinorrhea, congestion, sneezing, coughing and sore throat, with or without fever. The classic manifestation of lower respiratory tract disease (LRTD) in infants is *bronchiolitis*,[8] characterized by persistent cough, tachypnea, increased work of breathing, intercostal and subcostal retractions, grunting, nasal flaring, wheezing, and poor feeding; rales may be apparent on auscultation. Symptoms peak on days 3 to 5 of illness, but cough may persist for weeks. RSV can also cause *pneumonia*, more commonly diagnosed in hospitalized older children.[9] Risk factors for severe disease include prematurity, age <6 months, chronic lung disease, congenital heart disease, immunosuppression, neuromuscular disorders, and cystic fibrosis. The case-fatality rate among hospitalized infants <6 months of age in industrialized countries is <0.05% but may be as high as 2.4% in low-income countries.[10] There is an association between RSV infection in infancy and the later development of recurrent wheezing and asthma, although a definitive causal relationship has not been established.[11,12]

Asymptomatic infection is unusual in adults.[13] Initial symptoms include nasal congestion, rhinorrhea, sore throat, and fever; signs of LRTD include cough, wheezing and dyspnea, and complications may include pneumonia, acute bronchitis, exacerbations of chronic obstructive pulmonary disease and asthma, and secondary bacterial infection.[14] RSV can cause particularly severe disease in the elderly and in those with high risk conditions such as congestive heart failure or chronic pulmonary disease; the illness usually lasts about 2 weeks and up to half of patients may be unable to perform the normal activities of daily living at some point.[15] Short-term morbidity and mortality are comparable to, or more severe than, that seen with influenza, and long-term survival may be affected to a greater degree.[16] The case-fatality rate among persons ≥60 years of age in high income countries is estimated to be around 7%.[17]

Epidemiology and Transmission

RSV occurs worldwide. It is transmitted from person to person by airborne droplets and contaminated fomites, and infected people may be contagious before they develop symptoms. Infection is essentially universal in early childhood, and reinfections occur throughout life. Epidemics usually follow a characteristic seasonal pattern; in the US, infections typically begin in October, peak in December, and end in April.[18] Interestingly, the characteristic seasonal epidemic did not occur in the winter of 2020-2021, but instead the RSV "season" started in May of 2021 and ended in January of 2022, peaking in July; these changed were thought to be due, in part, to school closings, masking and social distancing implemented during the COVID-19 pandemic.

RSV is one of the most common causes of LRTD worldwide.[19] It was estimated that in 2005 nearly 34 million cases of RSV-associated acute LRTD occurred globally in children <5 years of age[20]; approximately 10% of these cases were severe, and there were 66,000 to 199,000 deaths, almost all of which were in developing countries. A 2015 estimate placed the number of RSV-associated hospitalizations among persons ≥65 years of age at 336,000, with about 14,000 in-hospital deaths.[21] **Figure 26.1** shows hospitalization rates by age in the US for the 2022-2023 season. The rates for infants are as high as 50 per 1000,[22] making RSV one of the most common causes of hospital admission in the first year of life. The average annual number of RSV-associated infant hospitalizations is about 80,000 and the number of Emergency Department visits exceeds 130,000.[23,24] The annual direct cost of RSV-associated hospitalizations and ambulatory visits is $710 million (2000 dollars).[25]

A 2022 systematic review and meta-analysis suggested that the rate of RSV-associated hospitalization among adults ≥65 years of age in the US is approximately 3 per 1000; the rate of ED visits is 2 per 1000 and outpatient visits 23 per 1000.[26] This translates into roughly 159,000 hospitalizations, 119,000 ED visits, and 1.4 million outpatient visits per year, with an estimated 9500 to 12,700 deaths. Estimates of the direct annual costs of RSV-associated hospitalization among persons ≥60 years of age range from $1.5 billion to $4 billion.[27]

Immunization Program

In the late 1960s, a whole agent, formalin-inactivated RSV vaccine was found to cause enhanced disease in seronegative children.[28] The mechanism was thought to involve the generation of low-affinity, non-neutralizing antibodies and Th-cell priming in the absence of cytotoxic T-cell production, leading to Th2 polarization of the immune response; subsequent natural RSV infection lead to immune complex deposition and inflammatory infiltrates in the lung. A similar phenomenon was seen with a formalin-inactivated measles vaccine.[29]

While the occurrence of enhanced disease set active vaccination strategies back for decades, the need to address prevention of RSV LRTD in infants spurred the development of passive immunization strategies. RSV-intravenous immune globulin (IGIV) (RespiGam, MedImmune), a polyclonal hyperimmune globulin, was licensed in 1996. Palivizumab (Synagis, MedImmune and later Astrazeneca and then Sobi), a monoclonal antibody, was licensed in 1998. Both products were labeled for monthly administration during RSV season, and neither was indicated for use in infants who were not at high risk. The American Academy of Pediatrics has provided guid-

FIGURE 26.1 —RSV Hospitalizations in the United States, 2022-2023

Data are from the Respiratory Syncytial Virus Hospitalization Network, which conducts active, population-based surveillance for laboratory-confirmed RSV-associated hospitalizations in 58 counties in 12 states. Because hospitalization rates are much higher in young children, the rate for children 0 to 4 y is plotted on the left axis (solid black line) and the rates for age groups ≥5 y (dashed or dotted gray lines) are plotted on the right axis (note that the scale on the right axis is 10-fold lower than the left axis).

Adapted from RSV-NET. CDC Web site. https://www.cdc.gov/rsv/research/rsv-net/dashboard.html. Accessed June 20, 2023.

ance on the use of these products for high-risk infants since their licensure.[30,31] Note that use of RSV-IGIV was discontinued in 2003 and that palivizumab was still available as of September 2023.[32]

The Advisory Committee on Immunization Practices (ACIP) did not issue recommendations regarding prevention of RSV disease in any population until 2023. In that year, nirsevimab (Beyfortus, Sanofi and Astrazeneca), a long-acting monoclonal antibody, was licensed for use in infants and children <24 months of age. Shortly thereafter, the ACIP recommended nirsevimab for universal use based on the high burden of disease, safety and efficacy of the product, feasibility of administering a single intramuscular dose to every infant, cost on par with (traditional) vaccines, and beneficial impact on health equity.[33] Use of nirsevimab for all infants <8 months of age born during or entering their first RSV season was estimated to cost $102,811 per quality-adjusted life year (QALY) gained.[34] While nirsevimab is not a *vaccine* in the technical sense (see *Chapter 1: Introduction to Vaccinology—Immunization*), it has been handled like a vaccine by the ACIP, which also voted to include it in the Vaccines for Children Program (VFC)[35]; likewise, nirsevimab is considered an "ACIP-recommended immunization" under the Affordable Care Act (see *Chapter 2: Vaccine Infrastructure in the United States—Financing*) and is covered by insurance without cost sharing by the patient.[36]

Two prefusion F-protein based vaccines—one from Pfizer and the other from GSK—were licensed in 2023 for prevention of LRTD in adults ≥60 years of age. Shortly thereafter, the ACIP recommended vaccination of adults ≥60 years of age based on shared clinical decision-making.[37] The Pfizer vaccine was also labeled for administration to pregnant women at 32 to 36 weeks' gestation in order to prevent LRTD in their infants during the first 6 months of life, and in September 2023, the ACIP recommended the Pfizer vaccine during pregnancy.[38] Use of RSV vaccine in adults ≥60 years of age is expected to cost $24,000 to $206,000 per QALY gained,[39] and maternal vaccination is expected to cost $85,000 to $400,000 per QALY gained[40]; these estimates are heavily dependent on the input assumptions and models used. RSV vaccine for older adults is covered by Medicare under Part D (outpatient prescription drug coverage). In September 2023, the ACIP voted to include RSV vaccine for pregnant women <19 years of age in the VFC; also note that vaccination of pregnant women ≥19 years of age should be covered by insurance and, as of October 1, 2023, Medicaid programs (see *Chapter 2: Vaccine Infrastructure in the United States—Financing*).

Vaccines

Characteristics of the RSV vaccines licensed in the US are given in **Table 26.1**. Both are non-live, subunit, in vitro-expressed vaccines that contain the prefusion stabilized F-protein (see above). RSV (Pfizer) contains 2 different F-proteins, one from strain A and

TABLE 26.1 — Respiratory Syncytial Virus Vaccines

Trade name	Abrysvo	Arexvy
Abbreviation	RSV (Pfizer)	RSV (GSK)
Manufacturer/ distributor	Pfizer	GSK
Type of vaccine	Non-live, subunit, in vitro-expressed	Non-live, subunit, in vitro-expressed
Composition		
Antigen	Prefusion-stabilized fusion protein (preF) from RSV strains A and B	Prefusion-stabilized fusion protein (preF3) from RSV strain A
Expression system	Genetically engineered Chinese Hamster Ovary (CHO) cells	Genetically engineered Chinese Hamster Ovary (CHO) cells
Antigen content	60 mcg of preF from RSV strain A and 60 mcg of preF from RSV strain B	120 mcg of preF3 from RSV strain A
Adjuvant	None	$AS01_E$ (3-*O*-desacyl-4′-monophosphoryl lipid A from *Salmonella minnesota* [25 mcg] and QS-21, a saponin purified from plant extract *Quillaja saponaria* Molina [25 mcg]; liposomal formulation using dioleoyl phosphatidylcholine [0.5 mg] and cholesterol [0.125 mg])
Preservative	None	None
Excipients and contaminants	Tromethamine (0.11 mg)	Trehalose (14.7 mg)
	Tromethamine hydrochloride (1.04 mg)	Sodium chloride (4.4 mg)
	Sucrose (11.3 mg)	Potassium dihydrogen phosphate (0.83 mg)
	Mannitol (22.5 mg)	Dipotassium phosphate (0.26 mg)
	Polysorbate 80 (0.08 mg)	Polysorbate 80 (0.18 mg)
Excipients and contaminents (*continued*)	Sodium chloride (1.1 mg)	Disodium phosphate anhydrous (0.15 mg)
	Host cell proteins (≤0.1%)	Host cell proteins (≤2.0%)
	Host cell DNA (<0.40 ng/mg)	Host cell DNA (≤0.80 ng/mg)
Latex	None	None
Labeled indications	Prevention of LRTD caused by RSV in adults Prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 mo when given to pregnant women	Prevention of LRTD caused by RSV in adults
Labeled ages	≥60 y Pregnant women (any age)	≥60 y
Dose	0.5 mL	0.5 mL
Route of administration	Intramuscular	Intramuscular
Labeled schedule	1 dose	1 dose
Recommended schedule	Same	Same
How supplied (number in package)	1-dose vial (1, 5, 10), lyophilized, with diluent in prefilled syringe	1-dose vial (10), lyophilized, with adjuvant/ diluent
Cost per dose (USD, 2023)		
Public	219.72	198.40
Private	295.00	280.00
Reference package insert	August 2023	May 2023

LRTD, lower respiratory tract disease.

one from strain B; RSV (GSK) contains the F-protein from strain A and is adjuvanted.

Palivizumab is a humanized mouse monoclonal antibody that is directed against antigenic site A of the F-protein. Nirsevimab is a human monoclonal antibody that has high affinity for the well-conserved neutralizing site Ø epitope on the prefusion F-protein.[41] To increase the half-life of the antibody, a 3 amino acid substitution was introduced into the Fc portion, increasing affinity for the neonatal Fc receptor, which protects IgG molecules from degradation after pinocytosis and facilitates recycling back into the extracellular environment.[42] Nirsevimab neutralizes RSV A and B strains with >50 times the potency of palivizumab and the half-life is about 70 days, ensuring active serum levels for the typical 5-month RSV season after a single intramuscular dose.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

RSV (GSK) was evaluated in a 17-country, placebo-controlled Phase 3 study (AReSVi-006) involving 12,467 vaccinees and 12,499 placebees from 2021 to 2023.[43] RSV (Pfizer) was evaluated in a similar study called RSV Efficacy Study in Older Adults Immunized Against RSV Disease (RENOIR), which was conducted in 7 countries from 2021 to 2022 and involved 17,215 vaccinees and 17,069 placebees.[44] Both studies enrolled persons ≥60 years of age and both were ongoing at the time the interim results were published. Efficacy against RSV-associated LRTD for both vaccines is shown in **Table 26.2**.

In the Maternal Immunization Study for Safety and Efficacy (MATISSE) trial, 3682 pregnant women (3570 infants evaluated) received RSV (Pfizer) and 3676 (3558 infants) received placebo.[45] In the first 90 days of life, medically attended severe LRTD occurred in 6 infants of vaccinee mothers and 33 infants of placebee mothers, for a vaccine efficacy of 81.8%; in the first 180 days of life, the case split was 19 and 62, for an efficacy of 69.4%. Whereas the prespecified criterion for efficacy against any medically attended RSV LRTD at 90 days was not met (57%), it was met at 180 days (51%). In a subgroup analysis of women vaccinated at 32 to 36 weeks, which corresponds to the labeled age indication, efficacy against severe RSV LRTD in the infants was 91% at 90 days and 77% at 180 days.

Efficacy of nirsevimab was assessed by combining the results of 2 pivotal trials, one in preterm infants[46] and one in healthy late preterm and term infants (the MELODY trial).[47,48] Medically attended RSV-associated LRTD occurred in 31 of 2579 nirsevimab recipients and 80 of 1293 placebo recipients, for an efficacy of 79.0%. The case split for hospitalization was 12 and 33, for an efficacy of 80.6%, and for intensive care unit admission 1 and 6, for an efficacy of 90.0%.

TABLE 26.2 — Vaccine Efficacy Against RSV-Associated Outcomes in Persons ≥60 Years of Age

Evaluation Period	RSV (GSK)		RSV (Pfizer)	
	LRTD	Medically attended LRTD	LRTD	Medically attended LRTD
Season 1	82.6%	87.5%	88.9%	84.6%
Season 2	56.1%	*Footnote a*	78.6%	*Footnote a*

LRTD, lower respiratory tract disease

[a] Interim analysis underpowered to estimate efficacy.

Adapted from Melgar M, et al. *MMWR*. 2023;72:793-801.

Safety

RSV Vaccine

The safety database for each vaccine derived from the above referenced pivotal clinical trials plus earlier Phase 1/Phase 2 trials.[49,50] Severe reactogenicity events (injection site pain, redness, or swelling; fever, fatigue, myalgia, headache, arthralgia) occurred in 3.8% of vaccinees versus 0.9% of placebees for RSV (GSK) and in 1.0% versus 0.7% for RSV (Pfizer). The occurrence of severe adverse events was around 4% for both vaccinees and placebees for both vaccines. Across all vaccinees in all clinical trials for both vaccines (a total of almost 40,000 participants), there were 6 inflammatory neurologic events, including Guillain-Barré syndrome and acute disseminated encephalomyelitis; it is unclear whether these events occurred by chance or were related to vaccination.

In the MATISSE trial, 13.8% of mothers and 37.1% of infants in the RSV (Pfizer) group reported adverse events within 1 month of vaccination; the respective proportions for the placebo group were 13.1% and 34.5%. The incidence of serious adverse events among mothers (preeclampsia, arrested or prolonged labor, gestational hypertension, among others) and infants (neonatal jaundice, respiratory distress, atrial septal defect, among others) was similar in the vaccine and placebo groups. The incidence of adverse events of special interest among infects (low birth weight, prematurity, developmental delay, and positive COVID-19 test) was also similar in the vaccine and placebo groups. Preterm birth occurred in 5.7% of the vaccine group and 4.7% of the placebo group, but the data were insufficient to establish or exclude a causal relationship between the vaccine and preterm birth.

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)

Nirsevimab

In the MELODY trial, drug-related adverse events were seen in 1.3% of nirsevimab recipients and 1.5% of placebo recipients through 360 days after injection, and only 0.1% in each group were considered severe. No safety signal has been seen in an ongoing study (the MEDLEY trial) in which high-risk infants are being randomized to nirsevimab or palivizumab.[51]

Because nirsevimab is classified as a drug, adverse reactions should be reported to MedWatch (https://www.fda.gov/medwatch) as opposed to the Vaccine Adverse Events Reporting System.

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of product or any product component (risk of recurrent allergic reaction)

Precautions

- Follow best practice guidelines for children with bleeding diatheses (see **Table 6.7**)

Recommendations

Adults ≥60 years of age may be vaccinated based on shared clinical decision-making. **Table 26.3** offers considerations to inform that process. Vaccination should occur before the onset of RSV season. For the 2023-2024 season, providers should offer vaccine as soon as it is available, and they should continue to offer it to eligible adults who have not been vaccinated. Other adult vaccines may be given at the same visit.

Seasonal (September through January in most of the continental United States) vaccination of pregnant women with RSV (Pfizer), regardless of age, from 32 through 36 weeks' gestation is recommended to prevent LRTD in their infants during the first 6 months of life. Simultaneous administration of other indicated vaccines is acceptable. There is no current recommendation for RSV vaccine during subsequent pregnancies.

Nirsevimab is recommended for all infants <8 months of age born during or entering their first RSV season. Nirsevimab is also recommended for children 8 to 19 months of age who are at increased risk for severe RSV disease and are entering their second RSV season (the dosing is shown in **Table 26.4**). Children at increased risk include those with chronic lung disease of prematurity who required medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) any time during the 6-month period before the start of the second RSV season; those with severe immunocompromise; cystic fibrosis patients who have either 1) manifestations of severe lung disease (hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest imaging that persist when stable), or 2) weight-for-length <10th percentile; and American Indian or Alaska Native children. Clinical considerations for use of nirsevimab are given in **Table 26.5**.

Table 26.6 provides guidance on navigating the two options of vaccinating pregnant women and administering nirsevimab to infants for prevention of RSV LRTD.

TABLE 26.3 — Shared Clinical Decision-Making Around RSV Vaccine for Persons ≥60 y

Talking Points		
The disease is serious	**Safe and effective vaccines are available**	**There are reasons why a person might want to be vaccinated**
■ Exposure to RSV during typical seasonal epidemics is unavoidable ■ RSV causes or contributes to 1.4 million medical encounters, 160,000 hospitalizations, and 10,000 deaths per year among persons ≥65 y[a] ■ 18% of hospitalizations for RSV involve a stay in the intensive care unit[b]	■ The two available vaccines have an efficacy of 80%-90% in preventing RSV-associated medical visits and LRTD in the first season after vaccination ■ Severe reactogenicity events are unusual ■ Rare inflammatory neurologic conditions have been seen after vaccination, but causality has not been established ■ Medicare Part D (outpatient prescription drug coverage) covers, without cost sharing, vaccines that are recommended by the ACIP for prevention of disease in adults[c] ■ Vaccination should be discussed with all adults ≥60 y	■ Certain conditions increase the risk of severe RSV disease: – Lung disease (eg, COPD, asthma) – Cardiovascular disease (eg, CHF and CAD) – Moderate or severe immunocompromise[d] – Diabetes – Neurologic or neuromuscular condition – Kidney disorder – Liver disorder – Hematologic disorder ■ Frailty[e] increases the risk of severe RSV disease ■ The incidence of RSV increases with advancing age ■ Living in a nursing home or other long-term care facility increases risk ■ A health care provider may identify other factors that increase the risk of severe RSV disease

ACIP, Advisory Committee on Immunization Practices; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LRTD, lower respiratory tract disease

[a] Melgar M. Evidence to Recommendations Framework: Respiratory Syncytial Virus (RSV) in Adults. CDC Web site. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-23/RSV-Adults-04-Melgar-508.pdf.

[b] Ackerson B, et al. *Clin Infect Dis*. 2019;69:197-203.

[c] Patients may have to pay administration fees up front, but these are reimbursable under the plan. Vaccines that are covered under Medicare Part B are not covered under Part D. (Medicare Part D Vaccines. Centers for Medicare & Medicaid Services Web site. https://www.cms.gov/outreach-and-education/medicare-learning-network-mln/mlnproducts/downloads/vaccines-part-d-factsheet-icn908764.pdf. Accessed September 22, 2023.)

[d] Active cancer therapy; hematologic malignancy associated with poor vaccine response regardless of treatment status (eg, chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia); solid-organ or islet transplant on immunosuppressive therapy; CAR-T therapy or HCT (within 2 y or taking immunosuppressive therapy); moderate or severe primary immunodeficiency (eg, common variable immunodeficiency, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome); advanced or untreated HIV infection (CD4 count less than 200/mm^3, history of AIDS-defining illness without immune reconstitution, symptomatic HIV); high-dose corticosteroids (ie, ≥20 mg of prednisone or equivalent per day for ≥2 wk); alkylating agents; antimetabolites; transplant-related immunosuppressive drugs; cancer chemotherapeutic agents classified as severely immunosuppressive; tumor necrosis factor (TNF) blockers or other biologic agents that are immunosuppressive or immunomodulatory.

[e] Frailty is a geriatric syndrome that results from progressive, cumulative loss of physiological reserve in multiple organ systems. The Fried frailty phenotype (Fried LP, et al. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146-M156) assesses frailty using the following criteria: shrinking (unintentional weight loss), weakness, poor endurance, and energy (self-reported exhaustion), slowness, and low physical activity level.

Adapted from RSV vaccination for adults 60 years and older. CDC Web site. https://www.cdc.gov/vaccines/vpd/rsv/downloads/provider-job-aid-for-older-adults-508.pdf; Melgar M, et al. *MMWR*. 2023;72:793-801. All Web sites accessed September 20, 2023.

TABLE 26.4 — Passive Immunization Against Respiratory Syncytial Virus[a]

Trade name	Beyfortus
Generic name	Nirsevimab
Manufacturer/ distributor	Astrazeneca and Sanofi
Type of product	Human IgG1-kappa monoclonal antibody directed against antigenic site Ø of the RSV F-protein (molecular weight 146.3 kDa) expressed in Chinese Hamster Ovary (CHO) cells (50 mg/0.5 mL)
Preservative	None
Excipients and contaminants (0.5 mL dose)	Arginine hydrochloride (8 mg)
	Histidine (1.1 mg)
	L-histidine hydrochloride monohydrate (1.6 mg)
	Polysorbate 80 (0.1 mg)
	Sucrose (21 mg)
Latex	None
Labeled indications	Prevention of LRTD caused by RSV in neonates and infants born during or entering their first RSV season Prevention of LRTD caused by RSV in children ≤24 mo who remain vulnerable to severe disease through their second season
Labeled ages	≤24 mo
Dose	Neonates and infants born during or entering their first season: <5 kg: 50 mg (1 x 50 mg/0.5 mL dose) ≥5 kg: 100 mg (1 x 100 mg/1 mL dose) Children who remain vulnerable through their second season: 200 mg (2 x 100 mg/1 mL dose, separate sites)
Route of administration	Intramuscular
Labeled schedule	1 dose
Recommended schedule (age)	Same

Continued

TABLE 26.4 — *Continued*

Trade Name	Beyfortus
How supplied (number in package)[b]	Prefilled syringe, 50 mg/0.5 mL (1, 5) Prefilled syringe, 100 mg/mL (1, 5)
Cost per dose (USD, 2023)	
Public	395.00
Private	495.00 (50 mg/0.5 mL or 100 mg/mL)
Reference package insert	July 2023

LRTD, lower respiratory tract disease

[a] Note that palivizumab (Synagis, Sobi), a humanized mouse monoclonal antibody against the RSV F-protein, was still available as of September 2023, but was indicated only for high-risk children and only if nirsevimab was not available.

[b] Store in refrigerator. May be kept at room temperature for ≤8 hr.

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TABLE 26.5 — Clinical Considerations for Use of Nirsevimab in Infants and Toddlers

- Administration should begin shortly before the start of the RSV season, which is usually in October
- Infants born shortly before or during RSV season should receive a dose within 1 wk of birth
- Nirsevimab may be given during the birth hospitalization or in the outpatient setting
- Eligible children who have not yet received a dose may receive one at any time during RSV season, which usually lasts until March
- Only 1 dose is indicated during a given RSV season
- Infants who are hospitalized for a prolonged time after birth should receive a dose shortly before or promptly after discharge
- Nirsevimab may be given at the same time as routine vaccines
- Children who have received nirsevimab should not receive palivizumab in the same RSV season
- If palivizumab was given initially for the season and <5 doses were received, the infant should receive 1 dose of nirsevimab (no further doses of palivizumab should be given)
- If palivizumab was administered in the first season and the child is eligible for prophylaxis in the second season, they should receive nirsevimab in the second season
- If nirsevimab is not available or not feasible to administer, high-risk infants in the first or second year of life should receive palivizumab

Adapted from Jones JM, et al. *MMWR*. 2023;72:920-925; ACIP and AAP recommendations for nirsevimab. American Academy of Pediatrics Web site. https://publications.aap.org/redbook/resources/25379?autologincheck=redirected. Accessed September 26, 2023.

TABLE 26.6 — Navigating the Options for Prevention of RSV LRTD in Infants

- Both maternal vaccination with RSV (Pfizer) and passive immunization of infants with nirsevimab are not necessary in most situations
- Coordination between obstetric and pediatric providers is essential
- Nirsevimab is recommended for infants in the following situations:
  - Born <14 d after maternal vaccination
  - Born at <34 wks' gestation
  - Mother not vaccinated
  - Mothers' vaccination status unknown
- Nirsevimab may be considered in addition to maternal vaccination in the following situations:
  - Mother is immunocompromised and at risk of poor vaccine response
  - Mother has a condition associated with reduced transfer of transplacental antibodies (eg, HIV infection)
  - Infant might have lost maternal antibodies (eg, cardiopulmonary bypass or ECMO)
  - Infant has increased risk for severe RSV disease (eg, hemodynamically significant congenital heart disease, or intensive care admission requiring oxygen at hospital discharge)
  - Children 8-19 mo who are at increased risk for severe RSV disease and are entering their second RSV season should receive nirsevimab regardless of maternal vaccination status

ECMO, extracorporeal membrane oxygenation; LRTD, lower respiratory tract disease

Adapted from Jones JM, et al. *MMWR*. 2023;72:920-925; Fleming-Dutra KE, et al. *MMWR*. 2023;72:1115-1122; ACIP and AAP Recommendations for Nirsevimab. American Academy of Pediatrics Web site. https://publications.aap.org/redbook/resources/25379?autologincheck=redirected. Accessed September 26, 2023.

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Rotavirus

The Pathogen

Rotavirus is a nonenveloped virus in the Reoviridae family that has a wheel-like appearance.[1] The genome is divided into 11 double-stranded RNA segments, most of which encode only one viral protein. Infection of the gastrointestinal tract causes diarrhea by increased fluid secretion due to a virus-encoded enterotoxin (NSP4) and stimulation of the enteric nervous system, as well as increased osmotic load caused by destruction of villus epithelial cells, decreased absorption of salt and water, and decreased disaccharidase activity. Protection against disease is mediated by immune responses to the G protein, also known as VP7 or the *coat* protein, and the P protein, also known as VP4 or the *spike* protein. Any given rotavirus strain has a specific G type, designated by a serotype number (as in "G1"), and a P type, designated by a serotype number (as in "P1") and/or a genotype number in brackets (as in "P[8]"). Certain combinations of G and P types, such as G1P[8] and G2P[4], are found more commonly than others.

Clinical Features

The incubation period is 1 to 4 days. Fever and vomiting begin abruptly, and diarrhea ensues shortly thereafter. There may be >20 daily episodes of vomiting and/or diarrhea during the peak of the illness. Severe vomiting may lead to dehydration even before the diarrhea begins, and associated symptoms include irritability and lethargy. The illness lasts for about a week and is more severe than other forms of gastroenteritis in infants.[2] Risk factors for hospitalization include low birth weight, childcare attendance, and absence of breast-feeding.[3] Common complications of severe rotavirus infection include isotonic dehydration, electrolyte disturbances, metabolic acidosis, and temporary milk intolerance. Rare complications include necrotizing enterocolitis and hemorrhagic gastroenteritis. Immunocompromised patients may develop particularly severe or fatal illness and may shed virus in the stool for months.[4]

Epidemiology and Transmission

Transmission occurs from person to person by the fecal-oral route, airborne droplets, and contaminated fomites. It takes only one ten-millionth of a milliliter of stool to transmit the infection, making rotavirus one of the more contagious forms of gastroenteritis. Because rotavirus is not spread through contaminated food or water, improvements in sanitation and public hygiene do not affect the incidence of disease.

In the prevaccine era, virtually all children experienced at least one rotavirus infection by 5 years of age. In the US, rotavirus caused up to 410,000 annual office visits, 272,000 emergency department visits, 70,000 hospitalizations, and 60 deaths.[5] Outbreaks and nosocomial spread occurred frequently in day care centers, pediatric hospital wards, and nurseries. Annual epidemics began in the late fall in the Southwest and spread to the North and East by early spring, and most disease was caused by G1P[8] strains.[6]

Early in the postvaccine era, G3P[8] predominated but was later replaced by G12P[8].[7] Along with dramatic declines in disease incidence (*see below*), spatiotemporal patterns of rotavirus activity changed—the earliest peak week of rotavirus activity shifted from the Southwest to Arkansas, Oklahoma, and the western Gulf Coast, likely driven by high birth rates and low vaccine coverage in those regions.[8,9] Herd effects were evident[10] and there were sharp declines in rotavirus-associated outpatient visits[11,12] and diarrhea-associated health care utilization as a whole, including Emergency Department visits.[13,14]

Before vaccination was available, rotavirus caused 25 million annual outpatient visits, 2 million hospitalizations and over 500,000 deaths worldwide—most of those in developing countries.[15] Globally, G1P[8] strains predominate, but there is wide variation from year to year and from region to region.[16]

Immunization Program

Oral rhesus rotavirus vaccine, tetravalent (RRV-TV [RotaShield]; Wyeth) was licensed in 1998 and recommended for all infants in the US. The vaccine included a G3-like rhesus rotavirus strain that was naturally attenuated for humans, as well as three rhesus-human reassortants representing serotypes G1, G2, and G4 (each strain also expressed the rhesus P[3]). The vaccine was 70% to 95% effective at preventing severe rotavirus gastroenteritis,[17] but within a year of licensure was found to cause intussusception and was pulled from the market (see *Chapter 7: Addressing Concerns About Vaccination—Intussusception*).

The rotavirus disease burden and cost, however, continued to justify a vaccination program. It was estimated that a universal vaccination program instituted in a single US birth cohort—assuming only 70% coverage and looking at outcomes over 5 years—would reduce the number of domiciliary episodes of rotavirus gastroenteritis by 48%, office visits by 60%, emergency department visits by 64%, hospitalizations by 66%, and deaths by 44%. The cost per case averted would be $138, cost per serious case averted would be $3024, and cost per year of life saved would be $197,190 (2004 dollars).[18]

RV5 was licensed in 2006 and RV1 in 2008. Comprehensive recommendations for prevention of rotavirus disease were published in 2009,[19] and updates were published in 2010[20] and 2011.[21]

Vaccines

Characteristics of the rotavirus vaccines licensed in the US are given in **Table 27.1**. Both are live attenuated vaccines that are given orally. RV5 is a mixture of five different reassortant viruses, each of which is a (naturally attenuated) bovine rotavirus strain that has been engineered to express a different immunogenic protein (G1, G2, G3, G4, or P[8]) from human rotavirus. RV1 is a single human rotavirus strain (G1P[8]) that was attenuated by serial passage in tissue culture, much the same way as the Sabin polio vaccine.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Prelicensure studies of RV5 involved >70,000 infants. In the pivotal trial, efficacy against rotavirus gastroenteritis of any severity due to serotypes G1 through G4 during the first season was 74%, and efficacy against severe disease was 98%.[22] Emergency department visits due to rotavirus serotypes G1 through G4 were reduced by 94% during the 2 years following Dose 3, and hospitalizations were reduced by 96%. Efficacy against rotavirus-associated hospitalizations and emergency department visits, regardless of serotype, was 94% for >3 years following vaccination.[23] In a postlicensure study utilizing a national health insurance claims database that compared 33,140 infants who received 3 doses of RV5 to 26,167 unimmunized controls, effectiveness was estimated to be 100% against rotavirus hospitalizations and emergency department visits and 96% against outpatient visits.[24]

Prelicensure studies of RV1 also involved >70,000 infants. Efficacy in a European study[25] against rotavirus gastroenteritis of any severity through one season was 87% and through two seasons was 79%; the respective efficacies against severe disease were 96% and 90%. Hospitalizations were reduced by 100% through one season and 96% through two seasons. In a study conducted in Latin America and Finland,[26,27] efficacy against severe rotavirus gastroenteritis through one season was 85% and through two seasons was 81%; hospitalizations were reduced by 85% and 83%, respectively. In an integrated analysis, efficacy against severe disease

TABLE 27.1 — Rotavirus Vaccines

Trade name	Rotarix	RotaTeq
Abbreviation	RV1 (rotavirus vaccine, monovalent)	RV5 (rotavirus vaccine, 5-valent)
Manufacturer/distributor	GSK	Merck
Type of vaccine	Live, attenuated, classical	Live, attenuated, engineered
Composition		
Virus strain	Human rotavirus strain 89-12, serotype G1P1[8]	5 naturally attenuated bovine rotavirus reassortants expressing the following serotypes
		Human G1, bovine P7[5]
		Human G2, bovine P7[5]
		Human G3, bovine P7[5]
		Human G4, bovine P7[5]
		Bovine G6, human P1[8]
Propagation	Vero (African green monkey kidney) cells	Vero (African green monkey kidney) cells
Amount	10^6 median cell culture infective dose	2.0 - 2.8 × 10^6 infectious units of each virus
Adjuvant	None	None
Preservative	None	None
Excipients and contaminants	Dulbecco's Modified Eagle Medium	Sucrose
	Sucrose	Sodium citrate
	Disodium adipate	Sodium phosphate monobasic monohydrate
		Sodium hydroxide
		Polysorbate 80
		Cell culture media
		Fetal bovine serum (trace)
Latex	Tip cap contains latex	None
Labeled indications	Prevention of rotavirus gastroenteritis caused by serotype G1 and non-G1 serotypes G3, G4, and G9	Prevention of rotavirus gastroenteritis caused by serotypes G1, G2, G3, G4, and G9
Labeled ages	6-24 wk	6-32 wk
Dose	1.5 mL	2 mL
Route of administration	Oral[a]	Oral[a]
Labeled schedule (age)		
Dose 1	6-20 wk	6-12 wk
Dose 2	≥4 wk after Dose 1 but <24 wk	≥4 wk after Dose 1 but ≤32 wk
Dose 3	—	≥4 wk after Dose 2 but ≤32 wk

Continued

TABLE 27.1 — *Continued*

Trade name	Rotarix	RotaTeq
Recommended schedule (age)[b]	2 and 4 mo	2, 4 and 6 mo
Dose 1	6 wk-14 wk 6 d	6 wk-14 wk 6 d
Dose 2	≥4 wk after Dose 1 but ≤8 mo 0 d	≥4 wk after Dose 1 but ≤8 mo 0 d
Dose 3	—	≥4 wk after Dose 2 but ≤8 mo 0 d
How supplied (number in package)	1-dose oral applicator (10)[c]	1-dose squeezable, plastic tube (10, 25)
Cost per dose (USD, 2023)		
Public	105.45	79.24
Private	134.72	93.19
Reference package insert	November 2022	April 2023

[a] The dose should not be repeated if it is spit out or regurgitated. Administration through a gastrostomy tube is considered acceptable.

[b] The series should be completed with the same product, but vaccination should not be deferred if the same product is unknown or not available. If any dose in the series is RV5 or unknown, a total of 3 doses should be given. If Dose 1 is inadvertently given after 15 wk, the remaining doses should be given at the recommended intervals, although no doses should be given after 8 mo 0 d. For example, if Dose 1 of RV5 is inadvertently given at 6 ½ mo, Dose 2 should be given at 7 ½ mo (the minimum interval between Dose 1 and Dose 2 is 4 wk), but no doses should be given after that.

[c] Rotarix was historically supplied as a 1-dose vial, lyophilized, with diluent in a prefilled oral applicator. In late 2022, a fully-liquid presentation was approved, and the lyophilized version was phased out in 2023.

caused by G1P[8] strains (which share both G and P types with the vaccine) was estimated at 87%.[28] Efficacy against severe disease caused by G2P[4] strains was estimated at 71%; since these strains share neither G nor P types with the vaccine, these data indicate cross-protection.

A postlicensure study involving 165 cases and 428 controls showed that the effectiveness of both RV1 and RV5 was just over 90%.[29] Clinical trials[30] and postlicensure studies[31] support the efficacy of mixed schedules of RV1 and RV5.

Dramatic declines in rotavirus activity and hospitalizations for acute gastroenteritis were seen after implementation of the universal vaccination program in the US (**Figure 27.1**).[32-34] The reduction was so pronounced that in some seasons, the country as a whole failed to cross the epidemiologic threshold that defines the beginning of rotavirus season. When rotavirus seasons did occur, they started later, became shorter, and were less intense than they had been.[35-37]

In a systematic review of 48 studies that included 22 randomized controlled trials, efficacy against severe rotavirus diarrhea ranged from about 91% in developed regions to 46% in sub-Saharan Africa,[38] and another systematic review and meta-analysis confirmed

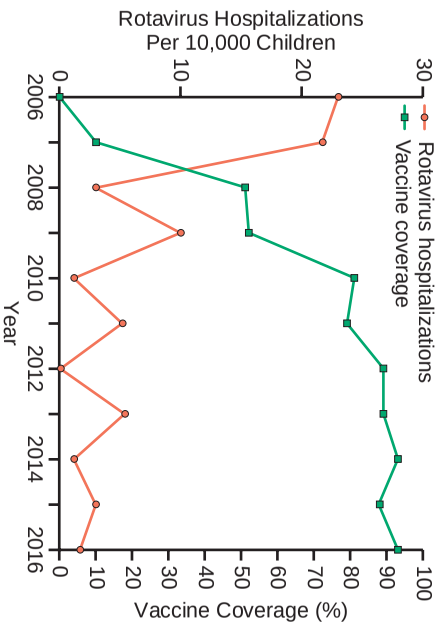

FIGURE 27.1 — Impact of Rotavirus Vaccination Among Children <3 y in the United States

Data are from the New Vaccine Surveillance Network. As RV uptake increased, rotavirus hospitalizations decreased rapidly and took on a biennial pattern, which dampened overtime; this is hypothesized to have been due to the accumulation of susceptible older children every other year.

Adapted from Staat MA, et al. *Clin Infect Dis*. 2020;71:e421-e429.

lower efficacy in low income countries.[39] Potential explanations for these regional differences include interference by maternal antibodies, breast-feeding, malnutrition, concomitant enteric infection, coadministration of oral polio vaccine, differences in the gut microbiome, and environmental enteropathy, among others.

Safety

Prelicensure trials of RV5 showed a slight excess of vomiting and diarrhea after Dose 1 and a slight excess of diarrhea after Dose 2. In prelicensure trials of RV1, solicited adverse events occurred at similar rates among vaccinees and placebees, although there were slightly increased unsolicited reports of irritability and flatulence among vaccinees. An integrated safety summary of eight randomized, double-blind trials of RV1 involving a total of 71,209 infants demonstrated no differences in solicited adverse events or serious adverse events.[40]

RV1 is shed in about 50% of vaccinees, more commonly after Dose 1; RV5 is shed in about 10% of vaccinees after Dose 1, but very rarely after subsequent doses. Horizontal transmission has been documented for both vaccines. For a discussion of rotavirus vaccines and intussusception, see *Chapter 7: Addressing Concerns About Vaccines—Intussusception.*

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction). Because RV1 may cause latex sensitization, some experts recommend RV5 for infants with spina bifida or bladder exstrophy; however, if only RV1 is available, it should be given.
- Severe combined immunodeficiency disease (risk of disease caused by live virus)
- History of intussusception (risk of recurrent intussusception)

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- Moderate or severe acute gastroenteritis (risk of impaired immune response)
- Immunodeficiency or immunosuppression (risk of disease caused by live virus). Adverse events are unlikely in HIV-infected infants because the vaccine strains are attenuated.

Recommendations

All infants should be vaccinated against rotavirus. The usual schedule is doses at 2, 4, and, if RV5 is used, 6 months of age. There is no preference for one vaccine over the other. The following circumstances *do not* preclude vaccination:

- Infants who have already had an episode of rotavirus gastroenteritis
- Breast-feeding
- Premature infants who are clinically stable and are being or have been discharged from the nursery (the current recommendation is not to immunize infants who are hospitalized in intensive care settings, although nosocomial transmission appears to be rare[41])
- Infants living in the home of immunocompromised or pregnant individuals (standard precautions should be followed to minimize the potential for transmission)
- Infants who have received antibody-containing blood products (there is the theoretical risk that passively acquired antibodies could inactivate a dose of the vaccine, but this should not be an issue since it is a multiple-dose series)
- Infants with pre-existing gastrointestinal conditions such as malabsorption syndromes, Hirschsprung's disease, or short-gut syndrome. The RV1 package insert lists as a contraindication uncorrected congenital malformation of the gastrointestinal tract that would predispose to intussusception. The RV5 package insert lists history of congenital abdominal disorders and abdominal surgery under Warnings and Precautions.

The series should be completed with the same product, but vaccination should not be deferred if the same product is not available (if a mixed schedule is used, or if a previous product is unknown, a total of 3 doses should be given). Standard precautions should be used for infants who are hospitalized after vaccination.

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Smallpox, Mpox, and Other Orthopoxvirus Diseases

The Pathogen

Variola virus (the cause of smallpox) and other orthopoxviruses (monkeypox virus [MPXV], cowpox, and vaccinia) are large, brick-shaped, enveloped DNA viruses in the Poxviridae family (genus *Orthopoxvirus*) that replicate in the cytoplasm. Direct organ damage from variola virus is unusual, as is secondary bacterial infection. Instead, morbidity results from toxemia associated with circulating immune complexes and viral antigens. Encephalitis can occur and is like the acute perivascular demyelination syndromes that may complicate measles and varicella infection or smallpox vaccination. The pathogenesis of mpox, the disease caused by MPXV, is thought to be similar.

Clinical Features

Initial infection with variola virus takes place at mucosal surfaces of the oropharynx or respiratory tract.[1] Three to 4 days later, viremia leads to asymptomatic visceral dissemination. Secondary viremia leads to a marked *prodromal illness*, which begins 12 to 14 days after infection and is characterized by high fever, malaise, headache, backache, prostration, chills, vomiting, delirium, and/or abdominal pain. *Rash* begins 1 to 4 days into the prodrome and is coincident with a decrease in fever; maculopapular lesions initially appear in the mouth and on the face and forearms, spreading to the trunk and legs. The lesions evolve slowly into *vesicles* and *pustules*, which are characteristically deep-seated, round, firm, and discrete, although some may coalesce. Eventually, the lesions develop an umbilicated appearance with a central dimple. Fever usually continues until scabs form, about 2 weeks into the illness. Scars are evident after the scabs separate.

The mortality rate for *variola major,* the typical smallpox syndrome, is around 30%. *Hemorrhagic smallpox* follows a shorter incubation period and is characterized by an extreme prodrome, the development of dusky erythema, and the eruption of petechiae and hemorrhage into skin and mucous membranes. Pregnant women are disproportionately affected, and the syndrome is uniformly fatal. In *malignant (flat) smallpox*, the onset is equally abrupt, but the initial confluent

lesions never evolve into pustules, instead remaining flat, soft, and velvety; mortality approaches 100%. *Modified smallpox* occurs in previously vaccinated persons, and although the prodrome may be severe, the lesions are fewer in number, more superficial, and evolve more rapidly; death is rare. *Variola minor* (*alastrim*), caused by a less-pathogenic strain of the virus, is differentiated by fewer constitutional symptoms, sparse rash, and excellent prognosis. *Variola sine eruptione* is asymptomatic or self-limited with fever and flu-like symptoms; it occurs in previously vaccinated persons or infants with maternal antibodies. **Table 28.1** provides clues to diagnosing smallpox and differentiating it from chickenpox.

MPXV inoculation takes place through the skin, respiratory tract, or mucous membranes.[2] Virus spreads either directly or via migrating antigen-presenting cells to regional lymph nodes, leading to low-grade viremia and infection of large organs, including the spleen and liver; amplification and secondary viremia ensue, resulting in infection of other organs and skin. During the 2022 outbreak, sexual acquisition of MPXV caused local oral and anogenital lesions, and extensive disseminated lesions were rare.

Mpox is less severe than smallpox. The occurrence of firm, tender maxillary, cervical and inguinal lymphadenopathy is a distinguishing characteristic, and scarring of the skin is common. Clinical features of the 2022 outbreak are given below. The case-fatality rate for clade 1 MPXV infections (seen in central Africa and the Congo Basin) is 1% to 12% and for clade 2 the case-fatality rate is <0.1%.

Epidemiology and Transmission

Natural smallpox has been *eradicated*, but the variola virus itself is not *extinct* (see *Chapter 1: Introduction to Vaccinology—Goals of Immunization Programs*). Certain features of smallpox make it attractive as a weapon, including the small infectious dose, high mortality rate, absence of natural and vaccine-induced immunity at the population level, lack of established therapy, historical fear and panic related to the disease, and person-to-person spread, which would amplify the effect of a primary release.[3] Epidemic disease in developed countries today would have the potential for great devastation because of the high point prevalence of atopic skin disease, use of immunosuppressive therapies, chronic conditions, HIV infection, as well as aging of the population.

Transmission of variola occurs through direct contact with body fluids and inhalation of aerosols and droplet nuclei expelled from the oropharynx of infected persons. Close contact is usually required. Distant airborne transmission is rare, but fomites such as bedding or clothing can transmit the virus. Transmission does not occur through insects or animals. Patients are most infectious 7 to 10 days after the rash develops; since this occurs after a debilitating prodromal illness, patients are likely to be easily recognized and bedridden at the time they are most contagious. Transmission from subclinical cases is of little epidemiologic importance.

The old term "monkeypox" is a misnomer because MPXV infects a wide variety of mammals, including rodents (the reservoir in nature is not known). Animal-to-human transmission can occur from touching, cage cleaning, hunting and processing meat, or from bites and scratches. Human-to-human transmission occurs through direct contact or large droplet aerosols.[4]

It has been suggested that the eradication of smallpox and the cessation of routine vaccination might have opened an ecological niche for MPXV to fill.[5] Mpox outside of Africa came to attention in 2003 when about 50 cases occurred in the US; this outbreak was caused by exposure to North American prairie dogs that had been purchased as exotic pets (the prairie dogs had themselves been infected during shipping by rodents from Ghana, also intended for the exotic pet industry).[6] Cases in Africa had been increasing before 2022, the highest number being just over 6000 in the Democratic Republic of the Congo in 2020[7]; there had also been a handful of cases outside of Africa, most related to travel. However, in early 2022 the number of cases outside of Africa skyrocketed, and on July 23, 2022, the World Health Organization declared a public health emergency of international concern[8] (the emergency declaration was rescinded on May 11, 2023). By August 2023, there had been almost 90,000 cases reported worldwide (30,000 in the US) and 153 deaths (46 in the US).[9] This outbreak was caused by a new lineage of clade 2 and was distinguished by 1) a short incubation period of 7 to 10 days; 2) transmission via skin/mucus membrane-to-skin/mucus membrane contact associated with intimate sexual contact; 3) localized anogenital lesions and localized complications; 4) a majority of cases occurring in men who have sex with men; and 5) a low case fatality rate of <0.1%.

Immunization Program

Smallpox vaccine was given in the US at 1 year of age until 1972, when the program was abandoned because of global eradication. Since the 1980s, the vaccine has been recommended for persons involved in orthopoxvirus research and health care personnel (HCP) involved in clinical trials of vaccinia recombinants.[10] The remaining interest in smallpox vaccination resides in preparing for the possibility of bioterrorism as well as emerging orthopoxviruses like MPXV.

Universal pre-event vaccination would constitute an absolute deterrent to a smallpox attack.[11,12] However, the overall risk of an attack is low, the population at risk cannot be determined, and the risks of vaccination are substantial. *Surveillance and containment*, or *ring vaccination*, involves the isolation of cases and the identification, vaccination, and monitoring of their contacts. Vaccination

TABLE 28.1 — Diagnosis of Smallpox

Clinical Finding	Smallpox[a]	Chickenpox[b]
Major Criteria		
Prodrome	Fever ≥101°F (38.3°C) beginning 1-4 d before rash and at least one of the following: prostration, headache, backache, chills, vomiting, severe abdominal pain	None or mild
Lesion morphology	Deep-seated, firm, round, well-circumscribed vesicles or pustules, may be umbilicated or confluent	Superficial vesicles (resembling dew drops on rose petals)
Lesion development	Same stage of development on any one part of the body	Crops at different stages of development on any one part of the body
Minor Criteria		
Distribution	Centrifugal (concentrated on face and distal extremities)	Centripetal (concentrated on trunk)
Initial lesions	Oral mucosa, palate, face, forearms	Face or trunk
General appearance	Toxic or moribund	Well
Evolution	Slow (from macules to papules to pustules over days)	Rapid (from macules to papules to vesicles to pustules to crusts in <24 h)
Palms and soles	Involved	Spared

Continued

can be extended to people with indirect exposure and the strategy can be supplemented by quarantine and travel restrictions. This strategy, which was highly successful during the global eradication campaign, is workable because vaccination is effective if given soon after exposure; however, the strategy might be difficult to implement in a highly mobile population experiencing a multisite intentional release, especially if there was public panic. *Universal post-event vaccination* would be logistically difficult and would provide little

TABLE 28.1 — *Continued*

CDC, Centers for Disease Control and Prevention

[a] Failure to diagnose the first wave of cases during a smallpox attack would have grave consequences. Suspected cases should immediately be reported to state or local health departments. The CDC also maintains a 24/7 Emergency Operations Center—the main CDC phone number is (800) 232-4636. If the patient has all three major criteria, the risk of smallpox is high, and authorities should be notified immediately. If the patient has a febrile prodrome and one other major criterion or ≥4 minor criteria, the risk is moderate and urgent evaluation is indicated. Other conditions to be considered in the differential diagnosis include disseminated herpes zoster or herpes simplex, impetigo, drug eruptions, erythema multiforme, Stevens-Johnson syndrome, enterovirus infection, scabies, secondary syphilis, bullous pemphigoid, and molluscum contagiosum. Mpox is difficult to distinguish from smallpox on clinical grounds, but a history of close exposure to rodents or human cases might be expected. The differential diagnosis of hemorrhagic smallpox includes meningococcemia, hemorrhagic varicella, Rocky Mountain spotted fever, ehrlichiosis, and gram-negative sepsis.

[b] Other clues to the diagnosis of chickenpox include absence of a personal history of varicella or varicella vaccination and exposure to chickenpox or shingles. Most cases will occur in children because most adults are immune. The lesions are usually intensely pruritic, and scarring is unusual.

Adapted from CDC Web site. Evaluating patients for smallpox. https://www.cdc.gov/smallpox/clinicians/algorithm-protocol.html. Accessed August 21, 2023.

additional benefit to ring vaccination. Protocols exist for simultaneous delivery of vaccine to every state and territory within 24 hours of an event.[13]

In the wake of the anthrax attacks of October 2001, recommendations were made to vaccinate smallpox response teams in each state and smallpox health care teams at predesignated isolation and care facilities.[14] The federal plan called for voluntary vaccination of up to 500,000 health and safety workers.[15] By mid-2003, only 40,000 civilians had been vaccinated, and the Centers for Disease Control and Prevention (CDC) effectively ceased efforts to vaccinate additional people. However, by 2005 over 700,000 military service members had been vaccinated.

Updated recommendations for post-event smallpox immunization, focusing on identifying and immunizing exposed persons, were published in 2015.[16] Recommendations for immunization of certain laboratory workers and HCP were updated in 2016,[17] and recommendations for use of the third-generation vaccine Jynneos were published in 2022.[18] Mpox was declared a public health emergency in the US on August 4, 2022, and guidance for use of smallpox vaccines to control the 2022 mpox outbreak is posted on the CDC Web site.[19] On August 9, 2022, Emergency Use Authorization (EUA; see *Chapter 2: Vaccine Infrastructure in the United States—Emergency Preparedness and Response*) was granted for intradermal use of Jynneos at a reduced dose. A preference for use of Jynneos in persons with HIV infection was published in August 2022.[20]

US military personnel continue to be vaccinated against smallpox.

Vaccines

Vaccinia virus—which confers immunity to smallpox through cross-protection—is not found in nature. Its origins are obscure; recent evidence suggests that it is more closely related to horsepox than to cowpox, as was originally thought.[21] In 2002, the US Food and Drug Administration (FDA) relicensed Dryvax (Smallpox Vaccine, Dried, Calf Lymph Type), a first-generation product manufactured until 1982 and held in storage at the CDC since then. Relicensure was intended to facilitate administration of the vaccine outside of investigational protocols. Dryvax was a lyophilized preparation of the New York City Board of Health strain of vaccinia harvested from lymph contained in skin lesions that develop after scarification of calves. A second-generation vaccine called ACAM2000, which is propagated in cell culture, was licensed in 2007 and replaced Dryvax in the Strategic National Stockpile.[22,23] ACAM2000 consists of live vaccinia virus that was plaque purified from Dryvax. A third-generation vaccine, Jynneos, was licensed in 2019. This was derived from chorioallantois vaccine virus Ankara through serial passage in chick embryo fibroblasts, which resulted in major deletions, mutations affecting virulence and immune evasion functions, and host restriction to avian cells.[24] Because it is live but does not replicate in mammalian cells, it is thought to be safer than previous vaccines. The available licensed smallpox vaccines are shown in **Table 28.2** and differences between them are shown in **Table 28.3**.

Administration of first- and second-generation vaccines is different from all other vaccines because they are delivered percutaneously using a special bifurcated needle (this referred to as *scarification*; guidance can be found on the CDC Web site[25]). The pustular lesion that eventually develops contains live virus that is contagious (failure to develop a lesion indicates failure of vaccination). Jynneos is licensed for subcutaneous administration and can be given intradermally under EUA.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Antibody levels after receipt of Dryvax decline 5 to 10 years following vaccination; while detectable cellular responses may persist, it is assumed that protection against smallpox wanes. Revaccination even one time results in boosted antibody levels that may persist for 30 years.

Two randomized, multicenter studies were conducted comparing ACAM2000 with Dryvax. One looked at 1647 persons who had been vaccinated over 10 years earlier; 1242 received ACAM2000 and 405 received Dryvax. Successful revaccination was slightly less common in the ACAM2000 group, but antibody titers were noninferior. The second study looked at 1037 vaccinia-naïve subjects; 780 received ACAM2000 and 257 received Dryvax. In this case, vaccination success rates were noninferior, although antibody titers were lower. Overall, ACAM2000 was noninferior to Dryvax where it counts most—major cutaneous reaction in vaccinia-naïve subjects and strength of antibody response in vaccinia-experienced subjects (whose pre-existing immunity might have modified the cutaneous reaction).

In a randomized, open-label study conducted at US military facilities in South Korea, the geometric mean titer of vaccinia-neutralizing antibody among 185 recipients of Jynneos (2 doses) was noninferior to that of 186 who received ACAM2000 (one dose). Effectiveness against mpox was initially inferred from animal challenge studies but was later confirmed during the 2022 outbreak. For example, in a study conducted from August 2022 to November 2022, 25 of 2193 cases of medically-attended mpox and 335 of 8319 controls were found to have received 2 doses of Jynneos, for an adjusted effectiveness of 66%.[26] Likewise, in a matched case-control study conducted among men who have sex with men and transgender persons 18 to 49 years of age from August 2022 to March 2023, adjusted effectiveness of 2 doses was 86%, and there was little difference between subcutaneous, intradermal, and mixed routes of administration.[27] The effectiveness of a single subcutaneous dose of Jynneos in an observational, retrospective cohort study from Israel was 86%.[28]

Safety

First- and second-generation smallpox vaccines are the most reactogenic and dangerous of all licensed vaccines. Severe local reactions and associated systemic complaints occur in about a third of vaccinees. Transmission to persons who are pregnant, immunocompromised, or have chronic skin problems can lead to serious complications. Persons who are to receive ACAM2000 are required to receive a Medication Guide from the FDA.[29]

Potential complications of vaccination include inadvertent inoculation, generalized vaccinia, erythema multiforme, eczema vaccinatum, postvaccinal encephalitis or encephalomyelitis, progressive vaccinia, contact vaccinia, and fetal infection. Nearly 800,000 vaccinees were included in a review of the safety of Dryvax in the post-9/11 campaign—no cases of eczema vaccinatum, progressive vaccinia, fetal vaccinia, or workplace contact transmission were reported, suggesting that education and screening procedures were successful. However, there were 107 cases of myopericarditis; among military personnel alone, the observed incidence within 30 days of vaccination (16.11 per 100,000) was 7.5-fold higher than the background rate. A causal relationship was suggested by temporal

TABLE 28.2 — Smallpox Vaccine

Trade name	ACAM2000[a]	Jynneos
Abbreviation	—	—
Manufacturer/ distributor	Sanofi	Bavarian Nordic
Type of vaccine	Live, attenuated, classical	Non-live, viral, non-replicating
Composition	Vaccinia, New York Board of Health strain	Vaccinia, Modified Ankara-Bavarian Nordic strain
	Propagated in Vero (African green monkey kidney) cells	Propagated in primary chicken embryo fibroblasts
	2.5 - 12.5 × 10^5 plaque-forming units/dose	0.5 - 3.95 x 10^8 infectious units/dose
Adjuvant	None	None
Preservative	None	None
Excipients and contaminants	HEPES (pH 6.5-7.5; 6-8 mM)	Tromethamine (10 mM)
	Human serum albumin (2%)	Sodium chloride (140 mM)
	Sodium chloride (0.5%-0.7%)	Residual host cell DNA (≤20 mcg)
	Mannitol (5%)	Protein (≤500 mcg)
	Neomycin (trace)	Benzonase (≤0.0025 mcg)
	Polymyxin B (trace)	Gentamicin (≤0.4 mcg)
	Glycerin (50% v/v)	Ciprofloxacin (≤0.005 mcg)
	Phenol (0.25% v/v)	
Latex	None	None
Labeled indications	Prevention of smallpox	Prevention of smallpox and mpox
Labeled ages	All ages	≥18 y <18 y (EUA)[b]
Dose	15 punctures	0.5 mL subcutaneous 0.1 mL intradermal (EUA)[c]
Route of administration	Percutaneous (scarification)[d]	Subcutaneous Intradermal (EUA)[c]
Labeled schedule	1 dose	Doses at 0 and 4 wk
	Booster doses every 3 y (for persons at continued high risk of exposure)	
Recommended schedule	*See text*	*See text*
How supplied (number in package)	100-dose vial, lyophilized, with diluent, bifurcated needles, and tuberculin syringe for reconstitution	1-dose vial (10, 20)
Reference package insert	March 2018	March 2023

EUA, Emergency Use Authorization

[a] ACAM2000 and Jynneos are not commercially available but rather are purchased by the federal government for inclusion in the Strategic National Stockpile. Dryvax (Smallpox Vaccine, Dried, Calf Lymph Type; Wyeth) is no longer available.

[b] In August 2022, Jynneos was approved under EUA (see *Chapter 2: Vaccine Infrastructure in the United States—Emergency Preparedness and Response*) for administration subcutaneously to persons <18 y.

[c] In August 2022, Jynneos was approved under EUA (see *Chapter 2: Vaccine Infrastructure in the United States—Emergency Preparedness and Response*) for intradermal administration in persons ≥18 y. This regimen was preferred during the mpox outbreak in 2022 because it increased the number of available doses. Mixed schedules of subcutaneous and intradermal administration are acceptable.

[d] This technique involves multiple punctures of the skin using a bifurcated needle that has been dipped in the vaccine preparation. Video demonstrations are available on the Centers for Disease Control Web site at https://www.cdc.gov/smallpox/clinicians/administering-acam2000.html. Accessed August 21, 2023.

clustering as well as the wide geographic and cross-seasonal distribution. Clinical myocarditis occurred in 1 of every 6300 persons who received ACAM2000 in a study of service military service members from 2009 to 2017; the rates were higher for males (1 in 4600) than females (1 in 11,800) and for persons <40 years of age (1 in 4700) than those ≥40 years of age (1 in 15,900).[30] Other vaccines have not been associated with inflammatory heart disease,[31] with the exception of some COVID-19 vaccines (see *Chapter 12—COVID-19*).

In an integrated pooled analysis that involved 7093 vaccinees and 1206 placebees, all of whom were smallpox vaccine-naïve and received at least one dose of Jynneos, serious adverse events were reported in 1.5% and 1.1% of subjects, respectively. Cardiac events of special interest (mostly asymptomatic elevation of troponin-I) occurred in 1.3% of Jynneos recipients. Only 6 cardiac events were thought to be causally related to vaccination, and none of these

TABLE 28.3 — Characteristics of Vaccines for Prevention of Smallpox

Characteristic	ACAM2000	Jynneos
Vaccine virus	Replication-competent	Replication-deficient
Development of skin lesion ("take") at site of inoculation	Yes[a]	No
Risk for inadvertent inoculation and autoinoculation	Yes	No
Risk for serious adverse event	Yes	Not identified during clinical trials
Risk for cardiac events	Yes	Not identified during clinical trials
Timing of optimal protection	28 d after dose	2 wk after Dose 2
Boosters for persons at ongoing risk for occupational exposure to more virulent orthopoxviruses (eg, variola or MPXV)[b]	Every 3 y	Every 2 y
Boosters for persons at ongoing risk for occupational exposure to less virulent orthopoxviruses (eg, vaccinia or cowpox)[b]	Every 10 y	

MPXV, mpox virus

[a] This is considered a marker of successful vaccination.

[b] ACAM2000 recipients who transition to Jynneos boosters should continue to receive Jynneos boosters at the appropriate intervals.

Adapted from Rao AK, et al. *MMWR*. 2022;71:734-742.

were considered serious. From May 2022 to October 2022, nearly 1 million doses of Jynneos were given in the US, at least half of which were given intradermally; monitoring through the Vaccine Adverse Event Reporting System, the Vaccine Safety Datalink, and Emergency Investigational New Drug procedures did not identify any new or unexpected safety concerns, including among vaccinees <18 years of age.[32]

Table 28.4 lists *contraindications* to pre-event administration of smallpox vaccines; *precautions* include moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction) and, for ACAM2000, inflammatory eye disease requiring steroid therapy (risk of disease from live virus). In addition, consideration should be given to delaying administration of some COVID-19 vaccines for ≥4 weeks after receipt of ACAM 2000 or Jynneos—especially in adolescent and young adult males—given the association of both live, attenuated smallpox vaccine and some COVID-19 vaccines with myocarditis. *In the event of exposure to smallpox, there are no absolute contraindications to vaccination and no precautions, although relative contraindications, such as severe immunodeficiency, may be considered in the public health response.*

Replication of ACAM2000 could theoretically suppress the response to a tuberculin skin test (TST) and may cause false negative results in an interferon-gamma release assay (IGRA). If testing for tuberculosis is warranted, the preferred option is to place a TST or perform an IGRA before or on the same day as vaccination (any immunosuppression would occur later, at the peak of viral replication). Otherwise, the tuberculosis test should be delayed ≥4 weeks.

Ticovirimat (SIGA Technologies) was licensed for treatment of smallpox in 2018 and brincidofovir (Chimerix) was licensed in 2021. Vaccinia immune globulin intravenous, a polyclonal immune globulin product made from blood of recently vaccinated donors, is available from the CDC under an Investigational New Drug (IND) protocol to treat complications of vaccination.[33] The Public Readiness and Emergency Preparedness Act provides compensation to persons for serious physical injuries or deaths resulting from pandemic, epidemic, or security countermeasures—including smallpox vaccination—in the event of designated public health emergencies (see *Chapter 3: Standards, Principles, and Regulations—Public Readiness and Emergency Preparedness* [*PREP*] *Act*).[34]

Recommendations

Smallpox

Vaccination is recommended for the following:

- Research laboratory personnel who handle cultures or animals contaminated or infected with replication-competent vaccinia virus, recombinant vaccinia viruses derived from replication-competent strains, or other orthopoxviruses that infect humans (this includes MPXV, cowpox, and variola)
- Clinical laboratory personnel who perform diagnostic testing for orthopoxviruses (this does not include personnel who perform routine clinical laboratory tests)
- Designated response team members (as determined by public health authorities)

TABLE 28.4 — Contraindications to Nonemergency Use of Smallpox Vaccines[a]

Condition	ACAM2000			Jynneos
	Primary Vaccination	Revaccination	Household Contact With Condition[b]	
History or presence of atopic dermatitis	✓	✓	✓	
Active exfoliative skin condition[c]	✓	✓	✓	
Immunosuppression[d]	✓	✓	✓	
Pregnancy[e]	✓	✓	✓	
Age <1 y[f]	✓	✓	✓	
Breast-feeding	✓	✓		
Serious allergic reaction to vaccine or vaccine component	✓	✓		✓
Heart disease[g]	✓	✓		
≥3 major cardiac risk factors[h]	✓			

[a] Check marks indicate where the given condition is a contraindication. For most of these conditions, the risk of ACAM2000 is disease caused by the live virus in vaccinees or their contacts. Jynneos, a non-live, viral, non-replicating vaccine, is safe in immunocompromised persons, although immune responses may be diminished. This vaccine should not present a risk of transmission to contacts.

[b] Persons with prolonged contact with the potential vaccinee (eg, sexual contacts) and others who might have direct contact with the vaccination site or contaminated materials (eg, dressings or clothing).

[c] Eczema, burns, impetigo, varicella-zoster virus infection, herpes, severe acne, severe diaper dermatitis with extensive areas of denuded skin, psoriasis, or Darier disease (keratosis follicularis).

[d] Leukemia, lymphoma, generalized malignancy, solid organ transplantation, therapy with alkylating agents, antimetabolites, radiation, tumor necrosis factor inhibitors, or high-dose corticosteroids (≥2 mg/kg body weight or ≥20 mg/day of prednisone or equivalent for ≥2 wk), hematopoietic cell transplantation (<24 mo post-transplant or ≥24 mo post-transplantation but with graft-versus-host disease or disease relapse), autoimmune disease associated with immunodeficiency, and HIV infection (routine testing is not recommended, but should be done in persons with risk factors, those who are unsure of their status and those who are concerned that they could have HIV infection).

Continued

TABLE 28.4 — *Continued*

[e] Women who receive ACAM2000 should not be pregnant and should not become pregnant for 4 wk. For reassurance, women can perform a urine pregnancy test on the first morning void on the day of vaccination. Routine pregnancy testing is not recommended. Inadvertent vaccination during pregnancy is not ordinarily a reason to terminate the pregnancy, although the mother should be aware of the extremely rare occurrence of fetal vaccinia. There are insufficient data on use of Jynneos in pregnancy, although animal models show no evidence of harm to the developing fetus.

[f] ACAM2000 is contraindicated in infants <1 y. Caution should be used when considering the administration of ACAM2000 or Jynneos to persons <18 y.

[g] Examples include coronary artery disease and cardiomyopathy.

[h] Hypertension, diabetes (type 1 or 2), hypercholesterolemia, heart disease at 50 y in a first-degree relative, and tobacco smoking.

Adapted from Rao AK, et al. *MMWR*. 2022;71:734-742.

- HCP who administer ACAM2000 or care for patients infected with orthopoxviruses, including patients in clinical trials of replication-competent orthopoxvirus vaccines (shared clinical decision-making; see *Chapter 2: Vaccine Infrastructure in the United States—Policy and Recommendations* and **Table 2.7**)

Either ACAM2000 or Jynneos may be used; factors that may inform the choice of vaccine are given in **Table 28.3**. Persons who are at ongoing risk of occupational exposure to orthopoxviruses should be revaccinated every 2 or 3 years, depending on which vaccine is used (**Table 28.3**). Revaccination of response personnel, including persons who were initially vaccinated under the 2003 US Civilian Smallpox Preparedness and Response Program,[35] is recommended only on an "out-the-door" basis, ie, only after there is determination of a credible threat to public health and prior to engaging in activities involving a risk for exposure.[36]

In the case of a smallpox event, vaccination would be deployed to stop the chain of transmission and achieve epidemic control. Smallpox vaccine will completely prevent or significantly modify the disease if given 3 to 4 days after exposure; vaccination 4 to 7 days postexposure probably modifies the severity of the disease.

Mpox

Table 28.5 lists persons who are at increased risk of mpox and should be offered vaccination. **Table 28.6** provides vaccination guidance for specific populations.

TABLE 28.5 — Persons Eligible for Vaccination Against Mpox During the 2022 Outbreak[a]

- Known or suspected exposure to someone with mpox
- Having a sex partner in the past 2 wk who was diagnosed with mpox
- Gay, bisexual, and other men who have sex with men, and transgender or nonbinary people (including adolescents), who have had ≥2 sex partners or a new diagnosis of a sexually transmitted disease in the past 6 mo
- Having had, in the past 6 mo, sex at a commercial sex venue, sex in association with a large public event in an area where mpox transmission is occurring, or sex in exchange for money or other items
- Sexual partners of persons with the above risk factors
- Persons who anticipate experiencing any of the above scenarios
- Persons with HIV infection or other causes of immunosuppression who have had recent or anticipate potential mpox exposure
- Persons who work in settings where they may be exposed to mpox, including health care personnel response teams and those who work with orthopoxviruses in a laboratory

[a] Vaccination should be offered to persons at risk of exposure to mpox and may also be used for postexposure prophylaxis, in which case it should be given as soon as possible, ideally within 4 d of exposure (administration 4-14 d after exposure may still provide some protection). Individuals can self-attest to eligibility. Routine immunization of the general public is not recommended.

Adapted from Vaccination basics for healthcare professionals. CDC Web site. https://www.cdc.gov/poxvirus/mpox/clinicians/vaccines/vaccine-basics-healthcare.html. Accessed August 21, 2023.

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TABLE 28.6 — Vaccination to Prevent Mpox in Specific Populations

Population	ACAM2000[a]	Jynneos[a]
Persons <18 y	Do not administer to persons <12 mo	0.5 mL subcutaneously
History of developing keloid scars	Do not administer	0.5 mL subcutaneously
Eligible persons ≥18 y (see **Table 28.5**)[b]	Percutaneously (scarification)	0.1 mL intradermally or 0.5 mL subcutaneously
Pregnant or breastfeeding	Do not administer	0.1 mL intradermally or 0.5 mL subcutaneously
Three or more cardiac risk factors[c]	Do not administer	0.1 mL intradermally or 0.5 mL subcutaneously
Atopic dermatitis, eczema, other exfoliative skin conditions	Do not administer	0.1 mL intradermally or 0.5 mL subcutaneously
History of mpox	Do not administer	*Footnote d*
Immune deficiency disorder, immunosuppressive medication, HIV infection (regardless of immune status)	Do not administer	0.1 mL intradermally or 0.5 mL subcutaneously

EUA, Emergency Use Authorization

[a] ACAM2000 is given as one dose percutaneously (scarification). Jynneos is given as 2 doses separated by 4 wk. The labeled dose and route of administration is 0.5 mL subcutaneously for persons ≥18 y. Jynneos is also approved under EUA for administration to persons <18 y as 0.5 mL subcutaneously (contact jurisdictional health department before administering to persons <6 mo) and for persons ≥18 y as 0.1 mL intradermally.

[b] People with a history of smallpox vaccination should be vaccinated.

[c] Risk factors: hypertension, diabetes, hypercholesterolemia, heart disease at ≤50 y in a first-degree relative, or smoking. People with underlying heart disease (eg, previous myocardial infarction, angina, congestive heart failure, cardiomyopathy, stroke or transient ischemic attack) or ≥3 risk factors should be counseled about the theoretical risk for myopericarditis following vaccination with Jynneos.

[d] Vaccination is not recommended for persons who were diagnosed with mpox on or after May 17, 2022. Immunocompetent persons who develop mpox after Dose 1 of Jynneos do not need Dose 2. Immunocompromised persons who develop mpox after Dose 1 of Jynneos may receive Dose 2 on a case-by-case basis.

Adapted from Vaccination administration considerations for specific populations. CDC Web site. https://www.cdc.gov/poxvirus/mpox/interim-considerations/special-populations.html. Accessed August 21, 2023.

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Streptococcus pneumoniae

The Pathogen

S pneumoniae is a facultatively anaerobic, catalase-negative gram-positive bacterium that looks like lancet-shaped diplococci on Gram stain.[1] The organism produces a polysaccharide capsule that is the basis for serotyping; there are >90 known serotypes, although most invasive disease is caused by <20 of these. The capsule contributes to virulence by inhibiting phagocytosis by neutrophils, and antibodies to the capsular polysaccharide are protective. Other virulence factors include pneumolysin and pneumococcal surface protein A. *S pneumoniae* often colonizes the nasopharynx—disease results from contiguous spread to respiratory tract structures such as the middle ear space or lungs, hematogenous seeding of distant sites such as the meninges, or from bacteremia without focal infection. Resistance to penicillin and other antibiotics has increased dramatically since the early 1990s.

Clinical Features

Before the conjugate vaccine era, *bacteremia* without focal infection accounted for 70% of invasive disease in those <2 years of age; *bacteremic pneumonia* accounted for another 12% to 16%.[2] With the disappearance of invasive *H influenzae* type b disease from the US in the 1990s, *S pneumoniae* became the leading cause of bacterial meningitis among young children (collectively, bacteremia, meningitis, and infection of other normally sterile body sites is referred to as *invasive pneumococcal disease* or IPD). *S pneumoniae* was also a common cause of noninvasive respiratory syndromes including *acute otitis media* (AOM), where it accounted for 28% to 55% of cases. By 12 months of age, 62% of children had at least one episode of AOM, making this one of the more common reasons for sick visits to pediatric offices. Complications of otitis media include mastoiditis and suppurative intracranial infection.

Pneumonia is the most common presentation in adults. Classically, there is abrupt onset of fever and an episode of rigors. Other symptoms include pleuritic chest pain, productive cough yielding mucopurulent sputum, dyspnea, tachypnea, hypoxia, tachycardia, malaise, and weakness. Nausea, vomiting, and headaches occur less frequently. Complications include

empyema, pericarditis, and abscess. Pneumococcal meningitis also occurs in adults. Symptoms include headache, lethargy, vomiting, irritability, fever, nuchal rigidity, cranial nerve signs, seizures, and coma. The spinal fluid profile and neurologic complications are similar to those seen in other forms of bacterial meningitis.

Mortality is highest in patients with bacteremia or meningitis, in patients with underlying medical conditions, and in the very young and the very old. In some high-risk groups, mortality from bacteremia is as high as 40% despite antibiotic therapy.

Epidemiology and Transmission

Humans are the only natural hosts and transmission occurs by direct person-to-person contact or via respiratory droplets. Spread within the household is facilitated by crowding and occurs more often in the late winter and early spring when respiratory viral disease is more prevalent. In general, higher rates of nasopharyngeal carriage lead to higher rates of disease.

It is estimated that 1 million children worldwide die from IPD each year. Before the introduction of PCV7 in the US, the incidence of IPD was as high as 205 per 100,000 in children 1 year of age and 62 per 100,000 in adults ≥65 years of age, with a total of 64,400 cases and 7300 deaths every year.[3] In addition, an estimated 5 million cases of AOM due to pneumococcus occurred each year in children <5 years of age. Children with asplenia and HIV infection had IPD rates >50 times those in age-equivalent children without these conditions. Alaska Native, American Indian, and African American children were also at increased risk. Day care attendance was associated with a 2- to 3-fold increased risk of IPD and AOM among children <5 years of age.

IPD and community-acquired pneumonia (CAP) caused by *S pneumoniae* exact a significant toll among older adults. In the 1980s and 1990s the incidence of pneumococcal bacteremia among adults ≥65 years of age was 50 to 83 per 100,000. As of the early 2010s, despite herd effects from the childhood immunization program and longstanding recommendations for use of PPSV23, the annual incidence of IPD in this age group was still 31 per 100,000[4]; somewhere between 1500 and 4000 per 100,000 were hospitalized for CAP[5] and about 10% of them had evidence of *S pneumoniae* infection.[6,7] The persistent burden of IPD and pneumonia prompted incremental changes in the adult recommendations (*see below*).

Immunization Program

Current pneumococcal vaccine recommendations in the US derive from a succession of new products and incremental guidance over the decades rather than a contemporary comprehensive document (**Figure 29.1**). Dramatic declines in pneumococcal disease

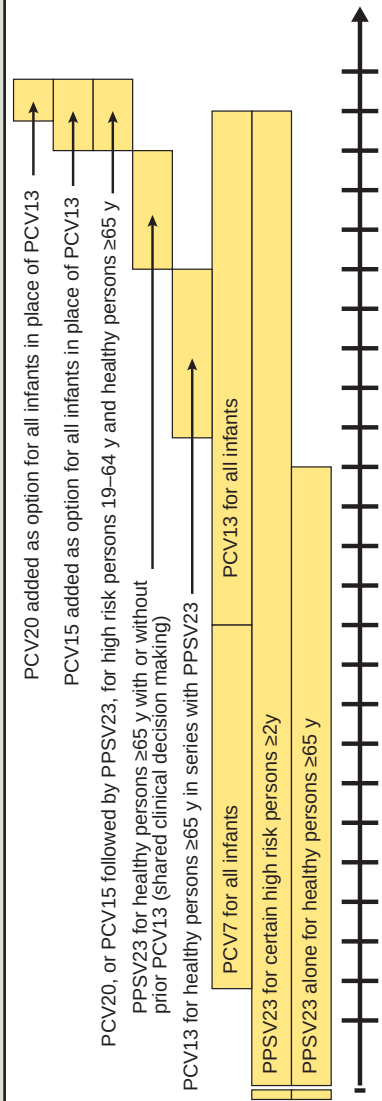

FIGURE 29.1 — Pneumococcal Immunization Recommendations Over Time

The figure shows major steps in the evolution of pneumococcal immunization recommendations in the US. PPSV23 was licensed in 1983. PCV7 was introduced for children in 2000 and PCV13 in 2010. The age indications for PCV13 expanded over time, and this allowed for incremental use in certain circumstances, with an accompanying rapid succession of new recommendations (not shown). PCV15 and PCV20 were introduced for adults in 2021, and by 2023 the age indication for both included young children.

Adapted from Pneumococcal ACIP vaccine recommendations. CDC Web site. https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html. Accessed June 15, 2023.

were seen within a few years of the introduction of PCV7 (*see below*). However, nasopharyngeal carriage of nonvaccine serotypes increased,[8,9] and there was an accompanying relative increase in IPD due to those serotypes, especially serotype 19A (this is referred to as *replacement disease*)[10]; this underscored the continuing need for higher valency vaccines. Considering both direct and indirect effects in all age groups, the PCV7 program was estimated to be cost saving, in the amount of $503 per child vaccinated (2006 dollars).[11] It was estimated that the switch to PCV13 would prevent 106,000 incremental IPD cases, 2.9 million cases of pneumonia, and save $11.6 billion over a 10-year period (2008 dollars).[12]

Universal use of PCV13 in series with PPSV23 was recommended for adults ≥65 years of age in 2014; at that time, the estimated cost per quality-adjusted life year (QALY) gained was $65,000 (2013 dollars).[13] Over time, however, profound herd effects from the childhood pneumococcal immunization program decreased the cost-effectiveness of the adult PCV13 program, such that the incremental cost per QALY gained was estimated to be $562,000 (2017 dollars, base case).[14] Accordingly, in 2019 the recommendation for PCV13 in persons ≥65 years of age changed from routine to one based on shared clinical decision-making (see *Chapter 2: Vaccine Infrastructure in the United States—Policy and Recommendations*).[15] PCV20 was licensed for adults in June 2021 and PCV15 in July 2021; these vaccines cover the PCV13 serotypes plus incremental serotypes still causing disease at the population level. New recommendations were published in 2022 for routine use of PCV20, or PCV15 followed by PPSV23, in adults ≥65 years of age, as well as recommendations for use of these vaccines in high-risk adults.[16] Incremental cost-effectiveness estimates for PCV20 alone ranged from cost-saving to $39,000 per QALY gained, and for PCV15 followed by PPSV23 from cost-saving to $282,000 per QALY gained (2021 dollars). In 2022 and 2023, the age indication for PCV15 and PCV20, respectively, was expanded to include children, and recommendations for use of these vaccines in children were made shortly thereafter.[17,18]

Vaccines

Characteristics of pneumococcal vaccines licensed in the US are given in **Tables 29.1** and **29.2**. **Figure 29.2** shows the serotypes covered by each vaccine. PPSV23 is a 23-valent polysaccharide vaccine. PCV13, PCV15, and PCV20 are protein-polysaccharide conjugate vaccines, analogous to Hib and MenACWY. Biologic differences between conjugate and polysaccharide vaccines are discussed in *Chapter 1: Introduction to Vaccinology—The Germinal Center Reaction* and are summarized in **Table 1.4**.

TABLE 29.1 — *S pneumoniae* Polysaccharide Vaccine

Trade name	Pneumovax 23
Abbreviation	PPSV23
Manufacturer/distributor	Merck
Type of vaccine	Non-live, subunit, purified
Composition[a]	Capsular polysaccharides (25 mcg each) from *S pneumoniae* serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F
Adjuvant	None
Preservative	Phenol (0.25%)
Excipients and contaminants	Isotonic saline
Latex	None
Labeled indications	Prevention of pneumococcal disease caused by vaccine serotypes
Labeled ages	≥2 y
Dose	0.5 mL
Route of administration	Intramuscular or subcutaneous
Labeled schedule	1 dose
Recommended schedule (age)	See **Figure 6.1**
How supplied (number in package)	1-dose vial (10)
	Prefilled syringe (10)
Cost per dose (USD, 2023)	
Public	65.80 (pediatric) 75.63 (adult)
Private	117.08
Reference package insert	April 2023

[a] See **Figure 29.2** for comparison of serotypes covered by the available vaccines.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

In a prelicensure trial involving nearly 40,000 children, PCV7 reduced IPD caused by vaccine serotypes by 97% and X-ray–confirmed pneumonia by 73%.[19] In a 2009 meta-analysis of clinical trials in young children, efficacy against IPD due to vaccine serotypes was approximately 90% and efficacy against otitis media due to vaccine serotypes was just over 50%; efficacy against radiographically confirmed pneumonia (serotypes largely unknown) was about

TABLE 29.2 — *S pneumoniae* Protein-Polysaccharide Conjugate Vaccines

Trade name	Prevnar 13	Prevnar 20	Vaxneuvance
Abbreviation	PCV13	PCV20	PCV15
Manufacturer/distributor	Pfizer	Pfizer	Merck
Type of vaccine	Non-live, subunit, engineered	Non-live, subunit, engineered	Non-live, subunit, engineered
Composition[a]	Capsular polysaccharides from *S pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F (2.2 mcg each) and 6B (4.4 mcg), conjugated to CRM_{197}, a nontoxic mutant diphtheria toxin (34 mcg)	Capsular polysaccharides from *S pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F (2.2 mcg each) and 6B (4.4 mcg), conjugated to CRM_{197}, a nontoxic mutant diphtheria toxin (51 mcg)	Capsular polysaccharides from *S pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F (2 mcg each) and 6B (4 mcg), conjugated to CRM_{197}, a nontoxic mutant diphtheria toxin (30 mcg)
Adjuvant	Aluminum phosphate (0.125 mg aluminum)	Aluminum phosphate (0.125 mg aluminum)	Aluminum phosphate (0.125 mg aluminum)
Preservative	None	None	None
Excipients and contaminants	Polysorbate 80 (100 mcg)	Polysorbate 80 (100 mcg)	L-histidine (1.55 mg)
	Succinate buffer (295 mcg)	Succinate buffer (295 mcg)	Polysorbate 20 (1 mg)
	Yeast[b]	Sodium chloride (4.4 mg)	Sodium chloride (4.5 mg)
		Yeast[b]	Yeast[b]
Latex	None	None	None
Labeled indications (age)	6 wk-5 y: prevention of invasive disease caused by all 13 vaccine serotypes and prevention of otitis media caused by the PCV7 serotypes	≥6 wk: prevention of pneumonia and invasive disease caused by all 20 serotypes[c]	Prevention of invasive disease caused by all 15 serotypes
	6-17 y: prevention of invasive disease caused by all 13 vaccine serotypes	6 wk-5 y: prevention of otitis media caused by serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F	
	≥18 y: prevention of pneumonia and invasive disease caused by all 13 serotypes		
Labeled ages	≥6 wk	≥6 wk	≥6 wk
Dose	0.5 mL	0.5 mL	0.5 mL
Route of administration	Intramuscular	Intramuscular	Intramuscular
Labeled ages			
Young children	2, 4, 6, and 12-15 mo	2, 4, 6, and 12-15 mo	2, 4, 6, and 12-15 mo
Older children and/or adults	≥6 y: 1 dose	≥18 y: 1 dose	≥18 y: 1 dose

Continued

TABLE 29.2 — *Continued*

Trade name	Prevnar 13	Prevnar 20	Vaxneuvance
Recommended schedule (age)			
Children	2, 4, 6, and 12-15 mo	2, 4, 6, and 12-15 mo	2, 4, 6, and 12-15 mo
Adults	—	≥65 y: 1 dose	≥65 y: 1 dose, followed by 1 dose of PPSV23 ≥1 y later
High-risk	See **Figure 6.1**	See **Figure 6.1**	See **Figure 6.1**
How supplied (number in package)	Prefilled syringe (1, 10)	Prefilled syringe (1, 10)	Prefilled syringe (1, 10)
Cost per dose (USD, 2023)			
Public	158.18 (pediatric)	173.00 (adult)	162.27 (pediatric) 149.90 (adult)
Private	226.43 (pediatric)	253.96 (adult)	216.09
Reference package insert	July 2019	April 2023	June 2022

[a] See **Figure 29.2** for comparison of serotypes covered by the available vaccines.
[b] Yeast extract-based medium is used in the production of pneumococcal polysaccharides (PCV15) or CRM (PCV13, PCV20), but the respective package inserts do not list yeast as a contaminant in the final products.
[c] The pneumonia indication is based on immune responses and was granted under accelerated approval. Continued approval may be contingent upon results of confirmatory trials.

FIGURE 29.2 — Serotypes Covered by Pneumococcal Vaccines

Vaccine	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A	22F	33F	8	10A	11A	12F	15B	2	9N	17F	20
PCV7[a]	■	■	■	■	■	■	■																	
PCV13[b]	■	■	■	■	■	■	■	■	■	■	■	■	■											
PCV15[c]	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■									
PCV20[d]	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■				
PPSV23[e]	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■

The chart shows the pneumococcal serotypes that are covered by each vaccine. The Danish nomenclature for serotypes is given. The corresponding American nomenclature is as follows: 1=1; 2=2; 3=3; 4=4; 5=5; 6B=26; 7F=51; 8=8; 9N=9; 9V=68; 10A=34; 11A=43; 12F=12; 14=14; 15B=54; 17F=17; 18C=56; 19A=57; 19F=19; 20=20; 22F=22; 23F=23; 33F=70.

[a] Prevnar (Pfizer), licensed in 2000 but not available after 2010
[b] Prevnar 13 (Pfizer), licensed in 2010
[c] Vaxneuvance (Merck), licensed in 2021
[d] Prevnar 20 (Pfizer), licensed in 2021
[e] Pneumovax 23 (Merck), licensed in 1983. Pnu-Imune 23 (Wyeth) was licensed in 1983 but was not available after 2002.

Adapted from Kobayashi M, et al. *MMWR* 2022;71:109-117.

30%.[20] Within 5 years of implementation, the universal infant PCV7 program had resulted in a 77% reduction in IPD among children <5 years of age.[21] During 2001-2005, 62,000 children <5 years of age were spared IPD—59% through direct effects of the vaccine and the remainder through herd immunity.[22] Rates of hospitalization for pneumococcal meningitis in children <2 years of age declined from 7.7 per 100,000 in the prevaccine era to 2.6 per 100,000 in 2001-2004 (there was also a 33% decrease among adults ≥65 years of age, indicative of herd immunity).[23] Within a decade, there were an estimated 168,000 fewer annual hospitalizations for pneumonia, including 47,000 among children <2 years of age and 73,000 among adults ≥85 years of age.[24] There was also a 20% decrease in outpatient visits for AOM. Rates of infection due to drug-resistant strains declined[25]—possible mechanisms for this include direct effects on vaccine serotypes, which are disproportionately resistant, as well as global decreases in antibiotic use.[26]

PCV13 was compared with PCV7 in a clinical trial involving over 600 infants.[27] Seroprotection rates were noninferior for all shared serotypes except for 6B and 9V, but noninferiority was demonstrated for geometric mean concentrations (GMCs) of antibody and opsonophagocytic activity (OPA) for all serotypes. A robust response to the 6 unique serotypes also was demonstrated. After the replacement of PCV7 with PCV13 for infant immunization in the US, there was a 93% decline in IPD among children <5 years of age caused by the incremental serotypes; declines of 58% to 72% were seen in adults as well, depending on age group.[28] It was estimated that over 30,000 cases of IPD and 3000 deaths were averted in the first 3 years after PCV13 was introduced. From the pre-PCV era to the post-PCV13 era, there was a 95% reduction in pneumococcal bacteremia among children 3 to 36 months of age.[29] Some evidence suggests, however, minimal overall impact on pneumococcal meningitis in children, due, in part, to increases in meningitis caused by non-PCV13 serotypes.[30]

A randomized controlled trial in vaccine-naïve adults showed that among those 60 to 64 years of age, PCV13 induced significantly higher OPA than PPSV23 for 8 of the 12 shared serotypes and was comparable for the other 4.[31] Responses to serotype 6A, which is not shared between the vaccines, were robust. Responses to PCV13 among those 50 to 59 years of age were higher for 9 serotypes than they were in the older subjects. Results from the landmark CAPITA (Community Acquired Pneumonia Immunization Trial in Adults) study, a randomized, placebo-controlled trial of PCV13 conducted in the Netherlands in 84,000 adults ≥65 years of age, found about 45% fewer first episodes of noninvasive vaccine-type pneumonia and 75% fewer first episodes of vaccine-type IPD among vaccinated subjects[32]; secondary endpoints showed approximately 50% efficacy against all episodes of culture-confirmed pneumococcal CAP and all episodes of IPD (regardless of serotype).[33] Postlicensure studies have shown effectiveness against PCV13-type IPD to be in the range of 47% to 59%, noninvasive PCV13-type pneumonia 38% to 70%, and all-cause pneumonia 6% to 11%.[34]

In a Phase 3 study, 3009 adults ≥60 years of age were randomized to receive PCV20 or PCV13, followed 1 month later by placebo or PPSV23, respectively.[35] Noninferiority criteria were met for serotypes in common with PCV13 and for 6 additional serotypes in common with PPSV23. Robust antibody responses were also demonstrated in another Phase 3 study among 1710 adults 18 to 49 years of age.[36] Noninferior immunogenicity for the serotypes shared between PCV15 and PCV13 was demonstrated in a Phase 3 study of 1202 adults ≥50 years of age; superiority was demonstrated for serotype 3, and there were robust responses to the unique serotypes.[37] In another Phase 3 study, PCV15 or PCV13 was given to 652 adults ≥50 years of age followed 1 year later by PPSV23.[38] Robust immune responses were seen to all 15 serotypes after PCV15; the response to serotype 3 was higher than for PCV13 and the response to serotype 4 was lower. Antibody persistence was noted at 12 months and increases in antibody level were seen after PPSV23 administration. Other studies have confirmed the immunogenicity and safety of PCV15 in healthy[39] and high-risk persons.[40]

In a randomized controlled trial, 860 children received PCV15 and 860 received PCV13 at 2, 4, 6, and 12 to 15 months of age, along with other routine childhood vaccines.[41] After Dose 3, the serological response rate among PCV15 recipients was noninferior to PCV13 recipients for the shared serotypes, as well as for the unique serotypes when compared to the shared serotype with the lowest response rate. Noninferiority criteria for geometric mean antibody concentrations were missed for only one serotype (6A) after Dose 3; however, all noninferiority criteria were met after Dose 4, and in fact the response to serotype 3 was higher for PCV15 than for PCV13.

A randomized, controlled study involving 460 infants demonstrated that PCV20 caused local reactions and (mostly mild to moderate) systemic events that were similar to PCV13 when given at 2, 4, 6, and 12 months of age.[42] After Dose 3, antibody concentrations against the shared serotypes were modestly lower in PCV20 recipients, but the proportion with prespecified antibody concentrations was similar for all serotypes except for serotype 3; responses to the 7 incremental serotypes were robust. Strong boosting was observed for all serotypes after Dose 4, and OPA responses were confirmed. The pivotal Phase 3 study involved 1997 infants randomized 1:1 to receive PCV13 or PCV20 at 2, 4, 6, and 12 to 15 months of age.[43] Noninferiority criteria for IgG concentration and geometric mean ratio were met after Dose 3 for all serotypes, and OPA antibody concentrations for the shared serotypes were similar between the 2 groups. Noninferiority criteria were also met after Dose 4, and anamnestic responses were demonstrated.

Postlicensure case-control studies estimate the efficacy of PPSV23 in preventing serious pneumococcal disease in immunocompetent persons to be 56% to 81%, and a meta-analysis suggested efficacy against bacteremic pneumococcal pneumonia in low-risk, but not high-risk, adults.[44] A surveillance study demonstrated 57% overall effectiveness against IPD caused by vaccine serotypes; effectiveness was 65% to 84% in persons with underlying high-risk conditions and 75% in immunocompetent adults ≥65 years of age.[45] A 2013 Cochrane Review estimated the efficacy of PPSV23 against IPD to be 74% and against all-cause pneumonia to be 28%, but there was no evidence of an effect on all-cause or pneumococcal-related mortality.[46] More recent meta-analyses place the efficacy of PPSV23 against IPD at around 50% and show only a weak effect in preventing pneumonia.[47,48] Studies show the effectiveness of PPSV23 against vaccine serotype CAP to be 20% to 34%.[49,50]

Safety

The safety of PCV13 was evaluated in over 4700 vaccinees across 13 clinical trials. Serious adverse events were rare. Solicited local reactions in infants included redness (24% to 42%), swelling (20% to 32%), and tenderness (60%); very few reactions were considered severe. Fever occurred in 24% to 32% but was generally mild. Serious adverse events were also rarely reported among over 6000 adults who received PCV13 in clinical trials. Solicited local reactogenicity included redness (16% to 20%), swelling (20%), and pain (80%); very few reactions were considered severe. Fever ≥100.4°F (≥38°C) occurred in <5% of subjects. The prelicensure safety database for PCV15 included approximately 3800 children and 5600 adults, and for PCV20 included 3000 children and 4600 adults. Side effects were similar to those seen with PCV13.

For persons ≥65 years of age receiving PPSV23, overall injection-site adverse experiences occur in about 50% after primary vaccination; moderate-severe pain and/or significant induration occur in 10%. Systemic adverse experiences such as fatigue, myalgia, and headache, are reported in 22%. Reaction rates are higher after revaccination. From 1990 to 2013, just over 25,000 adverse events were reported to the Vaccine Adverse Events Reporting System; 8% were considered serious, and most of those were fever.[51] There were 62 deaths in adults and 4 in children, none of which were considered related to the vaccine. Overall, there was no disproportional reporting of unexpected adverse events.

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction). For PCV13, PCV15, and PCV20 this may include yeast (see *Footnote b* in **Table 29.1**) and any diphtheria toxoid-containing vaccine, since these vaccines contain CRM, a mutant diphtheria toxin.

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)

Recommendations

All children should be vaccinated against *S pneumoniae*. The primary series consists of doses of PCV15 or PCV20 at 2, 4, and 6 months of age, with a booster dose given at 12 to 15 months of age (PCV13 may be used if it is the only available vaccine). For previously unimmunized infants and children, the number of doses depends on the age at which the series is initiated (**Figure 8.2**). A single dose of PCV15 or PCV20 is recommended for healthy children 24 months to 4 years of age with any incomplete schedule, including those who have never been immunized.

All adults ≥65 years of age should be vaccinated against *S pneumoniae*. Options include a single dose of PCV20 or a single dose of PCV15 followed ≥1 year later by a single dose of PPSV23 (the minimum interval for the dose of PPSV23 is 8 weeks for persons with immunocompromising conditions, cochlear implants, or cerebrospinal fluid leaks). Adults ≥65 years of age who have only received PPSV23 in the past may receive PCV15 or PCV20 ≥1 year after the last dose of PPSV23. Those who have already received PCV13 as per previous recommendations (**Figure 29.1**) should receive a dose of PPSV23 ≥1 year later (PCV20 may be used if PPSV23 is not available).

Recommendations for high-risk persons are given in *Chapter 6: Special Circumstances* and **Figure 6.1**. It should be noted that PPSV23 is often used to assess the adequacy of polysaccharide antibody responses in persons ≥2 years of age who are suspected of having immune deficiency.[52]

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Tick-Borne Encephalitis

The Pathogen

Tick-borne encephalitis virus (TBEV) is an enveloped, single-stranded RNA virus in the Flaviviridae family, related to the viruses that cause dengue, yellow fever, and Japanese encephalitis.[1] There are 3 subtypes: European, Far Eastern, and Siberian. The virus is transmitted rapidly from the saliva of infected ticks, as evidenced by the fact that early tick removal does not prevent disease. Infected dendritic cells and macrophages traffic to regional lymph nodes, where amplification takes place and from which dissemination occurs, leading to flu-like symptoms. The virus has a distinct tropism for neuronal tissue, which leads to a second phase of illness characterized by direct infection of neurons, indirect damage caused by infiltrating immune cells, and clinical features of encephalitis.[2]

Clinical Features

Most human infections are asymptomatic. In those who do become ill, symptoms begin 1 to 2 weeks after a tick bite. The illness is biphasic in most patients. The first stage, characterized by fever, fatigue, malaise, headache, and body pain, lasts about 5 days. The clinical spectrum of the second stage, which begins about a week after acute symptoms resolve, ranges from mild meningitis to severe encephalitis, and flaccid polio-like paralysis can occur due to involvement of the anterior horn cells of the spinal cord. The case fatality rate is 1% to 2% for the European subtype, 6% to 8% for the Siberian subtype, and as high as 20% for the Far Eastern subtype.[3] Residual paralysis occurs in up to 7% of patients. About a third of survivors have persistently impaired quality of life, and while the severity of TBE generally increases with age, recent attention has focused on acute and chronic morbidity in children.[4]

Epidemiology and Transmission

Ticks appear to transmit the virus from one to another through feeding on the same animal at the same time, with the animal—usually a small rodent—acting as a "transient bridge".[5] The virus also can be transmitted trans-ovarially (from a female to her eggs) and trans-stadially (from one metamorphosis

stage to another). Ticks therefore are both vectors and reservoirs for TBEV; the role of persistent infection of vertebrate hosts in the ecology of TBEV is not clear. The principal tick species involved are *Ixodes ricinus* in Europe and *Ixodes persulcatus* from eastern Europe to Japan. The disease tends to be focally distributed within endemic areas; in some parts of Europe and Russia, up to 30% of ticks may be carrying the virus. Cases occur during warm weather months when ticks are active and as people engage in outdoor activities. Increases in incidence have been linked to global warming, which creates favorable conditions for tick populations to proliferate and for animal hosts to migrate. Transmission from infected livestock via unpasteurized dairy products has been reported.

Approximately 3800 cases were reported in Europe in 2020,[6] although this likely underestimates the true number of cases. The highest reporting rate was in Lithuania with 24.3 cases per 100,000, followed by Slovenia (8.9), Czechia (7.9) and Latvia (7.8). Cases among US travelers are rare.[7]

Immunization Program

TBE vaccines have been available in Europe since the 1970s.[8] In 2011, the World Health Organization recommended vaccination for all age groups in areas where the annual incidence of clinical disease is ≥5 per 100,000, as well as targeted vaccination of high-risk groups in lower incidence areas.[9] TBE vaccine was first licensed in the US in 2021 and recommendations were drafted at the Advisory Committee on Immunization Practices (ACIP) meeting in February 2022 (publication was pending as of August 2023).[10]

Vaccines

Characteristics of the TBE vaccine licensed in the US are given in **Table 30.1**. This is a non-live, whole-virus vaccine, made much the same way as the Salk polio vaccine.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Clinical trials involving approximately 370 children and 300 adolescents and adults demonstrated that 99% were positive for neutralizing antibody after Dose 3. Field effectiveness of TBE vaccination in Austria between 2000 and 2011, when about 85% of the population was immunized and ≥90% of the vaccine used was a European version of Ticovac, was estimated to be 96% to 99%.[11] Effectiveness against severe disease is somewhat lower, especially in children.[12]

Safety

Across 10 prelicensure clinical trials, approximately 7600 people received at least 1 dose of TBE vaccine. Common reactions among children were local tenderness (18%), local pain (11%), headache (11%); fever and restlessness occurred in <10%. Common reactions among adults were local tenderness (30%) and pain (13%); fatigue, headache, and muscle pain occurred in <10%.

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)

Recommendations

TBE vaccine is recommended for laboratory workers who may be exposed to TBEV and for persons who are moving or traveling to a TBE-endemic area and will be exposed to ticks. TBE vaccine may also be considered for persons traveling or moving to a TBE-endemic area who might engage in outdoor activities in areas where ticks are likely to be found; factors involved in the decision to vaccinate include a person's planned activities and itinerary, risk factors for a poorer medical outcome, and personal perception and tolerance of risk.

TABLE 30.1 — Tick-borne Encephalitis Vaccine

Trade name	Ticovac[a]
Abbreviation	TBE vaccine
Manufacturer/distributor	Pfizer
Type of vaccine	Non-live, whole agent
Composition	
Virus strain and amount	TBEV (European strain Neudörfl), inactivated (2.4 mcg)
Propagation	Chick embryo fibroblast cells
Inactivation	Formaldehyde
Adjuvant	Aluminum hydroxide (0.35 mg/0.5 mL)
Preservative	None
Excipients and contaminants (per 0.5 mL)	Human serum albumin (0.5 mg)
	Sodium chloride (3.45 mg)
	Dibasic sodium phosphate (0.22 mg)
	Monobasic potassium phosphate (0.045 mg)
	Formaldehyde (≤5 mcg)
	Sucrose (≤15 mg)
	Protamine sulfate (≤0.5 mcg)
	Chick protein and DNA (trace)
	Neomycin (trace)
	Gentamicin (trace)
Latex	None
Labeled indications	Prevention of tick-borne encephalitis
Labeled ages	≥1 y
Dose	
Pediatric (1-15 y)	0.25 mL
Adult (≥16 y)	0.5 mL
Route of administration	Intramuscular
Labeled schedule	
Pediatric (1-15 y)	Doses at 0, 1-3 mo and 5-12 mo after Dose 2
Adult (≥16 y)	Doses at 0, 2 wk-3 mo, and 5-12 mo after Dose 2
Recommended schedule	Same
How supplied (number in package)	
Pediatric formulation	Prefilled syringe (1,10)
Adult formulation	Prefilled syringe (1,10)
Cost per dose (USD, 2023)	
Public	—
Private	297.74
Reference package insert	August 2021

[a] Versions of this vaccine have been licensed in Europe since 1976.

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Typhoid Fever

The Pathogen

Salmonella typhi (also known as *Salmonella enterica* serotype Typhi) is a motile, non-lactose fermenting, gram-negative bacillus. Infection begins in the gut, where the organism invades Peyer's patches, multiplies in macrophages, and disseminates to the mesenteric lymph nodes, reticuloendothelial organs, and ultimately the bloodstream. The Vi capsular antigen enhances virulence. *S typhi* produces a cholera-like toxin that causes efflux of electrolytes and water into the intestinal lumen.

Clinical Features

Typhoid fever refers to enteric fever caused by *S typhi* (enteric fever can also be caused by *Salmonella enterica* serotype Paratyphi).[1] The incubation period is 5 to 21 days, depending on inoculum size and health of the host. The onset is insidious, with fever and abdominal pain accompanied by malaise and anorexia. Fever climbs each day, reaching 104°F (40°C) by the end of the first week; adults display relative bradycardia for the level of fever. Early on, up to 50% of patients have constipation and 30% have diarrhea. Diarrhea is more common in infants and is typically of small volume and pea soup-like, containing red blood cells and leukocytes but not gross blood. During the first week of illness, children complain of headache and often are irritable, drowsy, or delirious. Adults may display psychosis or delirium, and arthralgia and back pain are common. Patients may appear toxic, have meningismus, a coated tongue with musty odor, and a tender doughy abdomen with guarding. During the second week of illness, a rash may appear on the abdomen or chest consisting of crops of salmon-colored, blanching, slightly raised lesions measuring 2 to 4 mm, referred to as *rose spots.* The spleen may be palpable and tender and respiratory symptoms may develop. Untreated, the illness lasts 4 to 6 weeks.

Complications generally occur during the third or fourth week and may include intestinal hemorrhage or perforation, coma, hepatitis, cholecystitis, arthritis, osteomyelitis, parotitis, endocarditis, myocarditis, pericarditis, pneumonia, meningitis, pyelonephritis, pancreatitis, and orchitis. Laboratory abnormalities include anemia, leukopenia or leukocytosis, thrombocyto-

penia, and elevated hepatic and muscle enzymes. Relapses occur in 5% to 20% of cases even after appropriate therapy, although they are usually milder than the initial illness. Infants are more likely than adults to develop massive hepatosplenomegaly and thrombocytopenia, and they have a higher mortality rate. Young children may have *S typhi* bacteremia with mild disease manifestations. Up to 4% of patients who recover from typhoid fever become chronic carriers of *S typhi* and are potential sources of infection for others.

S typhi can also cause nontyphoidal gastroenteritis, bacteremia, and extraintestinal focal infection.

Epidemiology and Transmission

In 2019, there were an estimated 9.2 million cases of typhoid fever worldwide, with 110,000 deaths; the highest incidence was in the South-east Asian, Eastern Mediterranean, and African regions.[2] Incidence rates are highest among school-aged children, and the global case-fatality rate is around 1%.[3] Just over 350 cases are reported in the US each year, 85% of which occur in people who traveled or lived outside the country in the previous 30 days.[4]

Humans are the only reservoir of *S typhi* and transmission is by the fecal-oral route; the infectious dose is about 10^7 organisms. Patients with cholecystitis or gallstones are especially vulnerable to chronic carriage and may excrete up to 10^9 organisms per gram of stool. Direct person-to-person transmission is unusual; rather, disease spreads through feces-contaminated food or water. For this reason, countries with inadequate sanitation systems, overcrowded living conditions, and limited potable water have the highest rates of disease. Laboratory workers have acquired infection through accidents and health care personnel have acquired infection from patients because of poor handwashing. Occasionally, transplacental transmission occurs from a bacteremic mother to her fetus, and infants may be infected at the time of birth through exposure to bacteria shed in the mother's stool.

Immunization Program

Interest in vaccination is highest in endemic areas where antibiotic treatment is not readily available and where antibiotic-resistant strains have increased in prevalence. Outbreaks of multidrug-resistant *S typhi* infection have occurred in the Indian subcontinent, Southeast Asia, and Africa and have been associated with high rates of complications and death. Vaccination might be beneficial for persons at high risk for disease, including children, international travelers, and military personnel. Persons who travel from low risk to high-risk areas are particularly susceptible because they have not developed immunity through repeated exposure to low doses of *S typhi* over time.

Updated recommendations for use of typhoid vaccine in the US were published in 2015.[5] In 2018, the World Health Organization recommended programmatic use of typhoid vaccines to control typhoid fever in countries with a high burden of disease or a high prevalence of antimicrobial resistance; preference was given to protein-polysaccharide conjugate vaccines, which are not licensed in the US.[6]

Vaccines

Characteristics of the typhoid fever vaccines licensed in the US are given in **Table 31.1**. One of these is a parenterally administered polysaccharide vaccine, analogous to PPSV23. The other is an orally administered live attenuated bacterium.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

In a clinical trial of TViPSV conducted in Nepal, 3454 subjects received a liquid formulation of the vaccine, and 3454 controls received a pneumococcal polysaccharide vaccine.[7] Efficacy against blood culture-confirmed typhoid fever was 74% during the 20-month follow-up period. In a subsequent trial conducted in South Africa, a lyophilized formulation was evaluated in approximately 11,000 school children who received either the vaccine or a placebo.[8] Efficacy was 55% against blood culture-confirmed typhoid fever during a 3-year follow-up period.

A large-scale effectiveness trial was conducted in Kolkata, India from 2004 to 2006 using TViPSV manufactured by GSK (Typherix).[9] Nearly 40,000 slum-dwelling residents ≥2 years of age were randomized by geographic cluster to receive TViPSV or a control vaccine. Effectiveness was 61% in general but as high as 80% among children 2 to 5 years of age. Effectiveness was 44% among unvaccinated persons living in TViPSV clusters, an indication of herd immunity that was achieved with only 60% vaccine coverage. However, a cluster-randomized study in Karachi, Pakistan involving >27,000 subjects demonstrated 57% effectiveness in children 5 to 16 years of age but no effectiveness in younger children.[10]

The efficacy of Ty21a was first evaluated in Egypt, where >16,000 children 6 to 7 years of age were given 3 doses of a liquid formulation on alternate days and an almost equal number were given placebo. Efficacy was 95% during a 3-year surveillance period.[11] A series of field trials was then performed in Santiago, Chile. The first one, which compared 1 or 2 doses given 1 week apart, involved approximately 82,500 school-aged children. Efficacy at 24 months was 29% and 59%, respectively.[12] Another trial, which compared 3 doses on alternate days to 3 doses given 21 days apart, involved about 110,000 school-aged children.[13] Efficacy was best in the group that

TABLE 31.1 — Typhoid Vaccines[a]

Trade name	Typhim Vi	Vivotif
Abbreviation	TViPSV	Ty21a
Manufacturer/ distributor	Sanofi	Emergent Travel Health[b]
Type of vaccine	Non-live, subunit, purified	Live, attenuated, engineered
Composition	Capsular polysaccharide Vi extracted from strain *Salmonella enterica* serovar *Typhi*, *S typhi* Ty2 (25 mcg)	Strain *Salmonella typhi* Ty21a mutagenized and selected for attenuation ($2 - 10 \times 10^9$ colony-forming units)
Adjuvant	None	None
Preservative	Phenol (0.25%)	None
Excipients and contaminants	Polydimethylsiloxane or fatty-acid ester-based antifoam (residual)	Sucrose (3.3-34.2 mg)
	Isotonic phosphate buffered saline	Ascorbic acid (0.2-2.4 mg)
	Sodium chloride (4.15 mg)	Amino acid mixture (0.3-3.0 mg)
	Disodium phosphate (0.065 mg)	Lactose (≤180-200 mg)
	Monosodium phosphate (0.023 mg)	Magnesium stearate (3.6-4.0 mg)
	Formaldehyde (≤100 mcg)	Non-viable *S typhi* Ty21a ($5 – 50 \times 10^9$ bacterial cells)
Latex	None	None
Labeled indications	Prevention of typhoid fever[c]	Prevention of typhoid fever[c]
Labeled ages	≥2 y	≥7 y[d]
Dose	0.5 mL	1 capsule
Route of administration	Intramuscular	Oral (swallow 1 hour before meal with a cold or lukewarm drink)
Labeled schedule	1 dose	Doses at 0, 2, 4 and 6 d[e]
	Booster doses every 2 y (for persons with continued exposure)	Booster series of 4 doses every 5 y (for persons with continued exposure)
Recommended schedule	Same	Same
How supplied (number in package)	20-dose vial (1)	4 capsules in a single foil blister package
	Prefilled syringe (1)	
Cost per dose (USD, 2023)		
Public	—	—
Private	146.99	116.44
Reference package insert	March 2020	September 2020

[a] Typhoid Vaccine USP (Wyeth), a phenol-inactivated, whole-cell vaccine for parenteral administration, is no longer produced.
[b] Previously manufactured by PaxVax Berna GmbH. Manufacture was suspended from January 2021 to June 2022 due to decreased demand during the COVID-19 pandemic.
[c] Typhoid vaccines are not licensed for prevention of enteric fever caused by *S paratyphi*.
[d] The Advisory Committee on Immunization Practices recommends use at ≥6 y.
[e] Some experts recommend repeating the series if all 4 doses are not given within 3 wk.

received the shorter schedule, reaching 69% over 4 years and with persistent efficacy demonstrated at 5 years. Subsequent studies established that efficacy was best using a 4-dose, alternate-day regimen.

Safety

TViPSV causes local tenderness in 97% to 98% of vaccinees, pain in 27% to 41%, induration in 5% to 15%, and erythema in 4% to 5%. Systemic signs and symptoms include malaise (4% to 24%), headache (16% to 20%), myalgia (3% to 7%), and nausea (2% to 8%). Fever ≥100°F occurs in <2% of vaccinees. Reactogenicity is similar after repeat immunization but is less pronounced in children. Postmarketing surveillance in countries where >14 million doses were distributed demonstrated some systemic reactions but very few serious adverse events. From 1995 to 2002, the Vaccine Adverse Event Reporting System (VAERS) reporting rate was 4.5 per 100,000 doses distributed, and for serious adverse events, it was 0.34 per 100,000 doses distributed.

Symptoms reported during clinical studies of Ty21a included abdominal pain (6%), nausea (6%), headache (5%), fever (3%), diarrhea (3%), vomiting (2%), and rash (1%), but only nausea occurred more frequently than in placebo recipients. There were no serious adverse reactions in field trials involving >500,000 school children. Postmarketing surveillance in the early 1990s, during which time 60 million doses were distributed, revealed only a handful of adverse events and only one serious allergic reaction.[14] From 1991 to 2002, the reporting rate to VAERS was 9.7 per 100,000 doses distributed for adverse events and 0.59 per 100,000 doses distributed for serious adverse events.

Contraindications

- Both vaccines: severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)
- Ty21a: immune impairment (risk of disease caused by live bacterium)

Precautions

- Both vaccines: moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- Ty21a: concomitant antibiotic or proguanil therapy (inactivation of live bacterial vaccine). Mefloquine and chloroquine may be given.

Recommendations

Routine immunization is not recommended in the US, not even for sewage sanitation workers, persons attending rural summer camps, or people living in areas in which natural disasters such as floods have occurred. Also, there is no evidence that typhoid vaccine is useful in controlling common-source outbreaks.

Vaccination is, however, recommended for the following groups:

- Travelers to endemic areas (see *Chapter 6: Vaccination in Special Circumstances—Travel*)
- Persons with intimate exposure (eg, household contact) to a documented carrier of *S typhi* (the vaccine cannot be used to treat chronic carriers)
- Microbiology laboratory workers who have frequent contact with *S typhi.*

There are no data on interchangeability of typhoid vaccines. However, if a booster series is necessary in a person who previously received the non-live whole-cell vaccine, it is reasonable to give 4 doses of Ty21a or 1 dose of TViPSV. There is no evidence that concomitant administration of either typhoid vaccine with other live oral or live or non-live parenteral vaccines impairs immune responses.

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Varicella

The Pathogen

Varicella-zoster virus (VZV) is a large, enveloped virus in the Herpesviridae family, a hallmark feature of which is the ability to establish *latency* and to undergo *reactivation.*[1] After inoculation at mucosal surfaces, replication occurs in the regional lymph nodes, resulting in a primary viremia that seeds the liver and other reticuloendothelial organs. A secondary mononuclear cell-associated viremia then ensues, which distributes virus to the skin, resulting in the vesicular lesions of *chickenpox*, as well as to the respiratory mucosa, facilitating contagion through respiratory droplets. Latent infection is invariably established in the dorsal root ganglia, where the linear, double-stranded DNA genome takes on a closed circular configuration. With reactivation, the genome linearizes, viral proteins are made, and virions are assembled; these are transported along sensory nerves to the skin, where replication causes *herpes zoster* (HZ), also known as *shingles.*

Cellular immunity is critical to limiting primary infection and preventing reactivation. Periodic re-exposure to exogenous natural varicella and/or subclinical reactivation of endogenous VZV may boost immunity.

Clinical Features

The incubation period ranges from 10 to 21 days. In children, *rash* is often the first sign of disease, but adults may have a 1- to 2-day prodrome of fever and malaise. The rash is pruritic, usually beginning on the scalp or hairline, moving to the trunk and extremities. Lesions are 1 to 4 mm in diameter and appear in successive crops over several days; at any given time, these crops are in different stages of development. Lesions characteristically evolve from macules to papules and then to superficial, delicate vesicles containing clear fluid on an erythematous base, so-called "dew drops on rose petals." They rapidly become pustules that crust and fall off, leaving shallow ulcers. Lesions can occur on mucous membranes and the cornea. The average patient with primary varicella has malaise and fever for 2 to 3 days and develops 200 to 500 lesions, some of which may form scars.[2] Varicella in vaccinated persons, termed *breakthrough* or

vaccine-modified varicella, is characterized by a shorter duration of illness and the absence of systemic symptoms and complications.[3] There are usually <50 lesions, and these are often maculopapular rather than vesicular and are difficult to recognize as chickenpox.

In the prevaccine era, 5% to 10% of otherwise healthy children experienced complications. Half of these were secondary bacterial infections, usually caused by *Staphylococcus aureus* or group A beta-hemolytic streptococcus (GABHS). Varicella increased the risk of severe GABHS infection 40- to 60-fold. Otitis media occurred in up to 5% of cases. Serious secondary infections, such as pneumonia, bacteremia, osteomyelitis, septic arthritis, endocarditis, necrotizing fasciitis, and toxic shock syndrome occurred much less frequently. Other complications included cerebellar ataxia, encephalitis, and Reye syndrome (associated with aspirin use during the illness). Although the case-fatality rate in children was very low, so many children got chickenpox that the annual number of childhood deaths was appreciable.[4] Ninety percent of children who died had no identifiable risk factors for severe disease. Adults have more severe disease, with a case-fatality rate 25 times higher than in children.

Immunocompromised persons may develop *progressive varicella*, characterized by high fever, an extensive vesicular eruption, and a high complication rate. *Hemorrhagic varicella* is characterized by thrombocytopenia and extensive purpuric lesions. Although rare, *congenital varicella syndrome*, characterized by birth defects and neurologic devastation, occurs in 1% of pregnancies complicated by varicella in the first or second trimester. Maternal varicella in the peripartum period can lead to severe *neonatal varicella* because of the high inoculum and absence of transplacental maternal antibodies. Recent attention has focused on vasculopathies induced by reactivation of VZV.[5,6]

When immunity wanes, as it does with aging, reactivation of latent VZV can result in HZ (see *Chapter 34: Zoster*).

Epidemiology and Transmission

Humans are the only natural hosts. Transmission occurs via respiratory droplets or by direct contact with, or aerosolization of virus from, vesicular skin lesions. Natural chickenpox is highly contagious, with attack rates among susceptible household contacts approaching 90%; contagiousness begins 1 to 2 days before onset of rash and lasts until the last lesion has crusted. Vaccine-modified varicella is less contagious than primary chickenpox, unless the number of lesions is >50.[7] Varicella is less common in tropical than in temperate areas. In the US, the incidence is highest between March and May and lowest between September and November.

Immunization Program

VAR was licensed in the US in 1995 and was recommended for routine use in children 12 to 18 months of age, with catch-up for children 19 months to 12 years of age and vaccination of certain high-risk persons ≥13 years of age.[8,9] Despite the successes of this program (*see below*), outbreaks of varicella continued to occur, likely due to the failure of some children to seroconvert after 1 dose (so called *primary vaccine failure*),[10] as well as waning immunity in vaccinated children.[11] It became clear that a 1-dose strategy would not eliminate indigenous transmission, something that is especially critical to protecting those who cannot be vaccinated; this led to adoption of a routine 2-dose strategy in comprehensive recommendations published in 2007.[12] For the 2006 birth cohort (4.1 million children) followed over 40 years, it was estimated that a 1-dose program would prevent 3.6 million cases and result in a net savings of $1.1 billion (2006 dollars); a 2-dose program would prevent 375,000 additional cases at an incremental cost of $104 million, with a cost per quality-adjusted life year saved of $109,000.[13]

Recommendations for health care personnel (HCP), including the definition of evidence of immunity, were updated in 2011.[14]

Vaccines

Characteristics of the VAR licensed in the US are given in **Table 32.1**. This is a single human varicella strain (originally isolated from a child in Japan) that was attenuated by serial passage in tissue culture, much the same way as the Sabin polio vaccine. VAR is the only herpesvirus vaccine to be licensed and is the first live vaccine that can establish latency.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

In prelicensure trials, efficacy of 1 dose was 70% to 90% against any disease and 95% against severe disease. Severe varicella, characterized by >500 lesions, hospitalization, and complications, is extremely rare in vaccinees. A randomized trial in children showed 94% efficacy of 1 dose over 10 years, compared with 98% efficacy of 2 doses given 3 months apart; in this study, the breakthrough rate was reduced 3.3-fold by the second dose.[15] Case-control studies estimate the effectiveness of VAR at 76% to 86% for 1 dose and 94% to 98% for 2 doses.[16,17] In a study involving >7000 children followed for 14 years (38% of whom had received 2 doses), overall vaccine effectiveness was 90%; no increase in breakthrough disease was seen over time, and breakthrough cases that did occur were mild.[18]

TABLE 32.1 — Varicella Vaccine[a]

Trade name	Varivax
Abbreviation	VAR
Manufacturer/distributor	Merck
Type of vaccine	Live, attenuated, classical
Composition	Oka/Merck strain
	Propagated in human diploid (MRC-5) cells
	At least 1350 plaque-forming units
Adjuvant	None
Preservative	None
Excipients and contaminants	Sucrose (24 mg)
	Hydrolyzed gelatin (12.0 mg)
	Sodium chloride (3.1 mg)
	Monosodium L-glutamate (0.5 mg)
	Sodium phosphate dibasic (0.44 mg)
	Potassium phosphate monobasic (0.08 mg)
	Potassium chloride (0.08 mg)
	Residual components of MRC-5 cells, including DNA and protein
	Sodium phosphate monobasic (trace)
	Ethylenediaminetetraacetic acid (trace)
	Neomycin (trace)
	Fetal bovine serum (trace)
Latex	None
Labeled indications	Prevention of varicella
Labeled ages	≥12 mo
Dose	0.5 mL
Route of administration	Subcutaneous or intramuscular
Labeled schedule (age)	12 mo-12 y: 1 dose and revaccination ≥3 mo later
	≥13 y: 1 dose and revaccination ≥4 wk later
Recommended schedule (age)	12-15 mo and 4-6 y
	Catch-up
How supplied (number in package)	1-dose vial (10), lyophilized, with diluent
Cost per dose (USD, 2023)	
Public	96.65
Private	159.99
Reference package insert	March 2023

[a] VAR is also available in combination with MMR (ProQuad; Merck). See *Chapter 35: Combination Vaccines*.

Before universal immunization began in 1995, essentially every young child in the US got chickenpox; every year there were 4 million cases, 11,000 hospitalizations, and 100 deaths.[19] Between 1997 and 2005, disease incidence declined 90% and the most affected age shifted from 3 to 6 years up to 9 to 11 years. Overall varicella-related hospitalizations declined from 2.54 per 100,000 to 0.62 per 100,000; this included a 77% decrease among persons <20 years of age and 60% decrease among those ≥20.[20] From 2000 to 2006, an estimated 50,000 varicella-related hospitalizations were prevented.[21] The rate of varicella-related ambulatory visits decreased 66% in the 8 years after licensure,[22] and by 2007 deaths from chickenpox had been nearly eliminated.[23] The 2-dose strategy adopted in 2007 quickly resulted in incremental declines in varicella incidence.[24,25] Data from the National Notifiable Diseases Surveillance System showed an 89% reduction in varicella incidence by 2019, and significant decreases were seen in all age groups (**Figure 32.1**).[26] An 80% reduction in varicella outbreaks also has been reported in the 2-dose era,[27] as have incremental reductions in outpatient visits and hospitalizations.[28]

There's been an added benefit of the varicella immunization program—a marked decline in the incidence of HZ among children.[29,30] Vaccine virus establishes latency but reactivates much less frequently than wild-type virus; thus, the more people that are latently infected with vaccine virus and the fewer with wild-type virus, the less HZ there will be. Some studies show that there was an increase in HZ incidence among adults early on in the varicella vaccine era[31]; this could have been due, in part, to less natural boosting from circulating wild-type virus, which protects against HZ.[32] More recent data suggest that any increases have begun to level off and even decline.[33]

In three controlled trials involving a total of 110 healthy susceptible children with household varicella exposure, the attack rate among children receiving postexposure vaccination was 18%

compared with 78% among controls.[34] In a study involving 77 household contacts vaccinated within 5 days of exposure, effectiveness of VAR in preventing any disease was estimated at 62% and in preventing moderate-to-severe disease at 79%.[35] None of the breakthrough cases were severe.

Safety

Injection-site reactions are reported in about 20% of vaccinees, and 15% may have low-grade fever. About 3% of children and 1% of adults get a few vesicles at the injection site, and up to 5% may experience a generalized varicella-like rash, with a median of 5 lesions, mostly maculopapular. Transmission of the vaccine virus from healthy vaccinees to others is extremely rare (only 13 cases were identified in a systematic review of the literature through 2018[36]). Whereas transmission is thought to only occur when the vaccinee develops a rash, the Varivax package insert (March 2023) mentions the possibility of transmission from vaccinees without rash. When transmission does occur, disease is mild and there is no evidence of reversion to virulence.

Safety surveillance data from the postmarketing pharmacovigilance program were reviewed in 2019, encompassing the first 22 years of vaccine availability.[37] By that time, >212 million vaccine doses had been distributed worldwide, and 46,855 reports of adverse events had been received. No new safety concerns were identified. Only 357 reports of potential secondary transmission were received, representing 0.0001% of doses distributed. Of the 68 cases in which the virus strains were analyzed, 38 were actually the wild-type virus (ie, these were cases of natural VZV transmission, not transmission of the vaccine virus). A total of 13 deaths associated with varicella or herpes zoster were reported. Twelve of those were in immunocompromised patients, in whom the vaccine is contraindicated; the 1 death in an immunocompetent person was confirmed to be due to the wild-type virus, not the vaccine strain.

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction; this includes reactions to gelatin and neomycin)
- Severe immunodeficiency or immunosuppression (risk of disease caused by live virus); providers should pay special attention to this possibility in children who have first-degree relatives with primary immune deficiency
- Pregnancy (theoretical risk to the fetus of live-virus vaccine or attribution of birth defects to vaccination). The Advisory Committee on Immunization Practices (ACIP) recommends that vaccinated women avoid pregnancy for 1 month; the package insert says 3 months (ACIP recommendations are usually followed in practice).

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction). The package insert specifically includes active, untreated tuberculosis (risk of exacerbation of tuberculosis).
- Recent receipt of antibody-containing blood product (risk of impaired response to vaccine)
- Aspirin and other salicylate-containing therapy in children and adolescents (theoretical risk of Reye syndrome). Given the association between natural varicella infection, aspirin use and Reye syndrome, there is a theoretical risk of Reye syndrome in children who are taking aspirin (or other salicylates) and who receive VAR. As of 2015, there were no reports of Reye syndrome after receipt of VAR, despite 140 million doses distributed in the US (it is not known how many children received the vaccine while taking aspirin). The manufacturer recommends withholding salicylates at least 6 weeks after vaccine administration, although the ACIP says that vaccination with subsequent close monitoring should be considered for children requiring aspirin for anti-inflammatory therapy. However, if the patient can be switched to an alternative anti-inflammatory or anti-platelet drug (only salicylates are associated with Reye syndrome), it would seem reasonable to stop aspirin, switch therapy, and give VAR after a "washout" period of ≥24 hours (enough time for aspirin to be cleared from the blood).
- VAR replication can theoretically suppress the response to a tuberculin skin test (TST) and may cause false negative results in an interferon-gamma release assay (IGRA). If testing for tuberculosis is warranted, the preferred option is to place the TST or perform the IGRA before or on the same day as vaccination (any immunosuppression would occur later, at the peak of viral replication). Otherwise, the tuberculosis test should be delayed ≥4 weeks.
- Receipt of specific antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination (avoid use of these antiviral drugs for 14 days after vaccination)

Recommendations

All people without evidence of immunity to varicella (**Table 32.2**) should be vaccinated. For children, Dose 1 is usually given at 12 to 15 months of age and Dose 2 at 4 to 6 years of age, although Dose 2 may be given any time ≥3 months following Dose 1. For

TABLE 32.2 — Evidence of Immunity to Varicella

Any one of the following criteria constitutes evidence of immunity:

1. Documentation of age-appropriate vaccination[a,b]:
   - Preschool-aged children: 1 dose[c]
   - School-aged children, adolescents, and adults: 2 doses
2. Laboratory evidence of immunity[d]
3. Laboratory confirmation of disease
4. Birth in the US before 1980 (exception: health care personnel, pregnant women, and immunocompromised persons)
5. History of typical varicella: diagnosis or verification of history by any health care professional (eg, school or occupational clinic nurse, nurse practitioner, physician assistant, physician)[e]
6. History of atypical or mild varicella: diagnosis or verification of history by a physician or physician's designee, utilizing the following information:
   - Epidemiologic link to a typical or laboratory-confirmed case
   - Laboratory confirmation performed at the time of acute disease
7. Herpes zoster: diagnosis or verification of history by any health care professional[e]

[a] Appropriately vaccinated persons who become immunosuppressed later in life are considered immune, except for hematopoietic cell transplant recipients.

[b] Documented receipt of any zoster vaccine in the absence of other criteria is not proof of immunity to varicella.

[c] Young children being considered for solid organ transplantation should have had 2 doses to be considered immune.

[d] Serologic testing of adults who have no documentation of vaccination and no verified history of varicella may be cost-effective, since approximately 80% will be seropositive. Those who test negative should receive 2 doses of VAR separated by ≥4 wk, even if they are ≥50 y and would routinely (without serologic testing) be given RZV. Once a person has demonstrable antibody, he or she is considered immune for life ("once immune, always immune"). Receipt of blood products can cause false-positive serologic test results because of passive transfer of antibodies.

[e] In general, immunocompromised individuals with a verified history of varicella are considered immune. The exception is hematopoietic cell transplant recipients, who are considered susceptible, regardless of their own personal history of varicella or a history of varicella in the donor. Transplant recipients who develop HZ are subsequently considered immune.

Adapted from Marin M, et al. *MMWR*. 2007;56(RR-4):1-40; Shefer A, et al. *MMWR*. 2011;60(RR-7):1-45.

persons ≥13 years of age, 2 doses are given 4 to 8 weeks apart. Anyone who received 1 dose in the past should receive a second dose. Evidence of immunity should be assessed in all individuals, with special attention paid to school-aged children, students in college and other postsecondary educational institutions, HCP, household contacts of immunosuppressed persons, teachers, day care employees, residents and staff in institutional settings, inmates and staff of correctional facilities, military personnel, nonpregnant women of childbearing age, persons living in homes with children, and international travelers.

Infants who had chickenpox before 6 months of age, and possibly before 9 months, should probably be vaccinated when they reach 12 months. This is because the immunity imparted by natural disease in infants who still have maternal antibodies may be suboptimal. Pregnant women without evidence of immunity should be vaccinated beginning in the postpartum period. HIV-infected persons without evidence of *severe* immunosuppression should be vaccinated (**Table 6.1**). Susceptible household and other close contacts of immunocompromised persons also should be vaccinated; if the vaccinee develops a rash, contact with the immunocompromised person should be avoided until the rash resolves.

Vaccination can be used as postexposure prophylaxis for healthy, susceptible persons if given within 3 to 5 days of exposure (off-label recommendation). Exposed persons who lack evidence of immunity, have contraindications to vaccination, and are at high risk for complications of varicella should receive passive immunoprophylaxis with varicella zoster immune globulin (VariZIG) as soon as possible but within 10 days of exposure.[38] Exposure is constituted by living in the same household as an infectious person with either chickenpox or HZ; direct, indoor, face-to-face contact with an infectious person for >5 minutes (some experts say 1 hour); or sharing the same hospital room. The following persons should receive VariZIG if susceptible and exposed:

- Immunocompromised patients, including those with primary and acquired immunodeficiencies, those receiving immunosuppressive medications, and those with cancer
- Pregnant women (VariZIG is given to protect the mother from complications of varicella; whether it will protect the fetus is not known).

A special case of exposure that carries high risk is the neonate whose mother develops chickenpox in the peripartum period. The following should receive VariZIG:

- Neonates whose mothers have signs and symptoms of varicella from 5 days before to 2 days after delivery
- Preterm neonates who are exposed postnatally at any time during their hospitalization for prematurity:

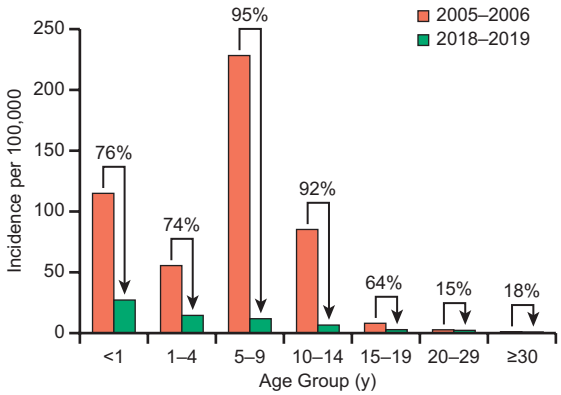
– ≥28 weeks' gestation whose mothers lack evidence of immunity
– <28 weeks' gestation or birth weight ≤1000 g, regardless of maternal immunity.

Patients who receive regular immune globulin infusions do not need prophylaxis if the last dose was ≤3 weeks before exposure. Persons with immunity who later become immunosuppressed are considered immune. Susceptible HIV-infected persons without evidence of immunosuppression do not need immunoprophylaxis.

VariZIG (Saol) is used for postexposure prophylaxis. It consists of IgG derived from pooled plasma of human donors who have high titers of antibody to VZV; VariZIG is therefore polyclonal (contains a variety of antibodies, including antibodies to other organisms). Various procedures are used to purify the immune globulin and reduce the potential for transmission of blood-borne pathogens, and the product is formulated for intramuscular administration. It is available from several distributors (https://varizig.com/liquid-ordering_info.html. Accessed July 6, 2023). Patients with selective IgA deficiency may be at increased risk for anaphylactic reactions to VariZIG because it may contain minute amounts of IgA. VariZIG is supplied in 125-IU vials; the dose is 62.5 IU (0.5 vial) for patients weighing ≤2 kg, 125 IU for those weighing 2.1 to 10 kg, 250 IU for 10.1-20 kg, 375 IU for 20.1-30 kg, 500 IU for 30.1-40 kg, and 625 IU for ≥40.1 kg. For those who become eligible for VAR, administration should be delayed ≥5 months after receipt of VariZIG (prior to that time point, the antibodies in VariZIG could inactivate the vaccine virus). If VariZIG is not available, intravenous immune globulin can be used for postexposure prophylaxis.

High-risk patients with additional exposures should receive another dose of VariZIG if ≥3 weeks have elapsed since the last dose. Receipt of VariZIG may extend the incubation period of varicella to 28 days. If the patient develops varicella, antiviral therapy should be instituted. Acyclovir (20 mg/kg/dose given 4 times per day, maximum dose 800 mg) can also be used to prevent chickenpox. It is usually given for 7 days beginning about a week after exposure, with the intent to limit the primary viremia.

FIGURE 32.1 — Effectiveness of Varicella Immunization in the United States



The figure shows the incidence of reported varicella by age group in 2005-2006 (data from 24-29 states and the District of Columbia), a decade after the immunization program began, and in 2018-2019 (38 states and the District of Columbia). Note the dramatic decrease (arrows) in incidence in all age groups.

Adapted from Marin M, et al. *J Infect Dis*. 2022;226(S4):S392-399.

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Yellow Fever

The Pathogen

Yellow fever virus, a member of the Flaviviridae family, consists of a single-stranded RNA genome surrounded by a protein nucleocapsid and a lipid envelope.[1] After inoculation by the bite of an infected mosquito, the virus spreads through lymphatics to the viscera, and viremia ensues. The liver is particularly affected, with the appearance of necrotic masses (Councilman's bodies) in hepatocytes; the resulting bleeding diathesis that can occur is the basis for classifying yellow fever as a *hemorrhagic fever*. Cytokine storm contributes to the pathogenesis of life-threatening disease.

Clinical Features

Infection may be asymptomatic or present as a viral syndrome of varying severity.[2] The classic triad of *jaundice, hemorrhage*, and *albuminuria* occurs in 10% to 20% of patients, and the associated case fatality rate is 20% to 50%. The onset of symptoms is abrupt, with fever, headache, backache, malaise, myalgia, nausea, vomiting, prostration, photophobia, restlessness, irritability, and dizziness; epistaxis and bleeding from the gums may also occur. Children may experience febrile seizures. Examination reveals congestion of the skin, conjunctivae, and mucous membranes. Leukopenia, albuminuria, and elevated serum transaminase levels may be present. After about 3 days of illness, most patients experience a remission of symptoms, but up to 20% of patients relapse with prostration, marked venous congestion, extreme bradycardia, severe nausea, vomiting, epigastric pain, jaundice, marked albuminuria, anuria, hematemesis (referred to as *vomito negro*), and melena. The hemorrhagic manifestations may be so severe as to cause hypotension, shock, acidosis, myocardial dysfunction, arrhythmias, and death, usually after 7 to 10 days. Central nervous system signs include delirium, agitation, seizures, stupor, and coma; complications include pneumonia, parotitis, skin infections, and renal abscesses. Late-onset relapsing hepatitis due to yellow fever virus has been described.[3]

Epidemiology and Transmission

Transmission of *jungle* (sylvatic) yellow fever involves tree hole-breeding mosquitoes and nonhuman primates in the rain forests of Africa and South America. Humans exposed to the mosquitoes in this environment, such as forestry workers, soldiers, and settlers, may acquire the infection and travel to urban areas where *Aedes aegypti* mosquitoes become infected after feeding on them. These mosquitoes may in turn infect other persons, leading to epidemics of *urban* yellow fever ("jungle" and "urban" describe the epidemiology—the clinical manifestations are identical). *A aegypti* breeds in and around houses and thereby sustains human-to-human transmission. Yellow fever virus is also transmitted vertically from infected female mosquitoes to their offspring. This mode of transmission is important to survival of the virus during prolonged dry periods.

Yellow fever occurs throughout sub-Saharan Africa, where epidemics have been common, as well as in tropical South America. In 2013, there were an estimated 84,000 to 170,000 severe cases of yellow fever and 29,000 to 60,000 deaths in Africa and Central and South America.[4] Under a 2006 global initiative, tens of millions of people in endemic areas have been vaccinated; as a result, there were no outbreaks of yellow fever in West Africa in 2015. As other arboviruses—dengue, West Nile, chikungunya, and Zika—have re-emerged in the Americas, so has yellow fever[5]; in Brazil alone from 2016 to 2018, there were >2000 cases and >500 deaths, and the virus was seen to move from north to south at over 2.5 miles per day.[6] Mass vaccination campaigns and mosquito-control programs have been instituted there to prevent urban outbreaks. Interestingly, yellow fever has never been reported in Asia.

Immunization Program

As with Japanese encephalitis, control of mosquito populations can reduce the risk of transmission. Mosquito bites can be minimized with insect repellent, permethrin-impregnated clothing, and staying in screened-in or air-conditioned rooms. Immunization is recommended, however, because these measures provide no guarantee against exposure. One of the most important rationales for vaccination is to prevent re-emergence of yellow fever carried by *A aegypti* mosquitoes in urban areas of the Americas. This is a possibility because *A aegypti* infests many areas that are currently free of yellow fever, including coastal regions of South America, the Caribbean, North America, the Middle East, coastal eastern Africa, the Indian subcontinent, Asia, and Australia.

Comprehensive yellow fever vaccination recommendations were published in 2010[7] and updated in 2015.[8]

Vaccines

Characteristics of the YFV licensed in the US are given in **Table 33.1**. This is a live vaccine that was attenuated by serial passage in vitro, much the same way as the Sabin polio vaccine. Because continued serial passage can result in strains with higher rates of adverse events, vaccine lots are prepared from a large pool of secondary seed lots. It should be noted that YFV was used as the backbone for development of the live, tetravalent dengue vaccine (see *Chapter 13: Dengue*).

Immunogenicity, Efficacy, Effectiveness, and/or Impact

While the efficacy of YFV has never been tested in a controlled clinical trial, numerous observations suggest efficacy. For example, neutralizing antibodies can be demonstrated in 90% of vaccinees after 10 days and in 99% by 30 days.[9] Infection of laboratory workers disappeared after vaccination became routine, and in Brazil and other South American countries, yellow fever only occurs in people who have not been immunized. In fact, only 18 vaccine failures were documented beyond the immediate postvaccination period after >540 million doses of YFV were given.[10] Immunization during outbreaks results in rapid disappearance of new cases, and high rates of coverage in endemic areas are followed by marked reductions in disease incidence. During an epidemic in Nigeria in 1986, vaccine efficacy was estimated at 85%. Immunity following vaccination persists for at least 30 to 35 years and probably for life.[11]

Safety

Reactions to YFV are typically mild—less than 5% of vaccinees experience erythema and pain at the infection site, headaches, and fever, typically 5 to 7 days after immunization. A study among 715 adults demonstrated mild systemic reactions such as headache, myalgia, malaise, and asthenia in 10% to 30% of subjects. The rate of systemic adverse events appears to be higher in older vaccinees.

Two important serious adverse events have been described[12]:

- *Vaccine-associated viscerotropic disease*: Formerly known as *febrile multiple organ-system failure*, this begins within 10 days of vaccination and is characterized by fever, nausea, vomiting, malaise, diarrhea, myalgia, or dyspnea along with evidence of end-organ damage, including jaundice, hepatic dysfunction, renal impairment, myocarditis, rhabdomyolysis, and thrombocytopenia. Progression to cardiorespiratory failure and death may occur. The liver pathology resembles that seen with wild-type yellow fever, but the disease appears to be related to host factors rather than reversion to virulence of the vaccine virus. The overall

TABLE 33.1 — Yellow Fever Vaccine[a]

Trade name	YF-Vax
Abbreviation	YFV
Manufacturer/distributor	Sanofi
Type of vaccine	Live, attenuated, classical
Composition	Yellow fever virus strain 17D-204
	Propagated in chick embryos
	≥4.74 $\log_{10}$ plaque-forming units
Adjuvant	None
Preservative	None
Excipients and contaminants	Sorbitol
	Gelatin
	Sodium chloride
Latex	None
Labeled indications	Prevention of yellow fever
Labeled ages	≥9 mo
Dose	0.5 mL
Route of administration	Subcutaneous
Labeled schedule	1 dose
	Booster dose every 10 y (for persons with continued exposure)
Recommended schedule	1 dose
	See text regarding boosters and vaccination of infants 6-8 mo
How supplied (number in package)[b]	1-dose vial (5), lyophilized, with diluent
Cost per dose (USD, 2023)	
Public	—
Private	213.99
Reference package insert	March 2020

[a] In 2015, many doses of YF-Vax were lost while the manufacturer was transitioning production to a new plant, and by July 2017, existing stocks were totally depleted. In October 2016, the US Food and Drug Administration approved an expanded access investigational new drug application for importation and use of Stamaril, which has comparable efficacy and safety to YF-Vax and is made by the same manufacturer. YF-Vax availability was restored in April 2021.

[b] Caution should be exercised not to reconstitute the 5-dose vial (which requires 3 mL of diluent) using the diluent (0.6 mL) intended for use with the 1-dose vial (McNeil MM, et al. *MMWR*. 2018;76:109-110).

incidence of this adverse event in the US is estimated at 1 in 250,000 doses administered.[13] Risk groups include men ≥56 years of age, young women, people with autoimmune disease, and persons thymectomized for treatment of thymoma.[14]

- *Vaccine-associated neurotropic disease*: Formerly known as *postvaccination encephalitis*, symptoms begin within 30 days of vaccination and include fever, headache, and focal or global neurological dysfunction. Signs of inflammation or encephalopathy are seen on cerebrospinal fluid examination, electroencephalogram, or imaging studies. The overall incidence of this adverse event in the US is estimated at 1 in 125,000 doses administered, but the rate is higher in persons ≥60 years of age.

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component, including eggs (risk of recurrent allergic reaction). Being able to eat lightly cooked (eg, scrambled) eggs without a reaction is reasonable evidence of a very low risk of anaphylaxis. Being able to eat eggs in baked products is not a reliable predictor because heat can denature egg proteins. Mild or local manifestations of allergy to eggs or feathers are not a contraindication. Skin testing can be done, and desensitization may be possible (the procedure is described in the package insert).
- Age <6 months (risk of disease caused by live virus)
- Immune impairment (risk of disease caused by live virus). This includes symptomatic HIV infection or CD4 count <15% (<6 years if age) or <200 cells/mcL (≥6 years of age); thymic disorder including thymoma; primary immunodeficiencies; malignant neoplasms; transplantation; and immunosuppressive or immunomodulatory therapies, including radiation. Corticosteroid use is not a contraindication in the following situations: administration of <20 mg prednisone or equivalent (<2 mg/kg for persons ≤10 kg) per day; short-term (<2 weeks) therapy; long-term, alternate-day administration of short-acting preparations; physiologic replacement; topical or inhaled preparations; intra-articular, bursal, or tendon injection.

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- Age 6 to 8 months or ≥60 years (risk of disease caused by live virus)
- Asymptomatic HIV infection and CD4 count 15% to 24% (<6 years of age) or 200 to 499 cells/mcL (≥6 years of age) (risk of disease caused by live virus)

- Pregnancy (theoretical risk to the fetus of live-virus vaccine or attribution of birth defects to vaccination). Woman should wait 4 weeks after receiving YFV before conceiving.
- Breast-feeding (risk of disease caused by live virus[15]). Some experts recommend that women should temporarily suspend breastfeeding, pump, and discard pumped milk for at least 2 weeks after receiving YFV.
- Yellow fever vaccine virus replication can suppress the response to a tuberculin skin test (TST) and may cause false negative results in an interferon-gamma release assay (IGRA). If testing for tuberculosis is warranted, the preferred option is to place the TST or perform the IGRA before or on the same day as vaccination (any immunosuppression would occur later, at the peak of viral replication). Otherwise, the tuberculosis test should be delayed ≥4 weeks.

Recommendations

Vaccination is recommended for persons ≥9 months of age who are traveling to or living in areas of South America and Africa where yellow fever transmission is possible (see *Chapter 6: Vaccination in Special Circumstances—Travel*). Vaccination should be limited to situations where exposure to yellow fever is likely or where vaccination is required for entry into the country. If international travel requirements are the only reason for vaccination of an individual at high risk for vaccine complications, consideration should be given to writing a waiver letter. Most travelers need only 1 lifetime dose; exceptions include the following: 1) women who were pregnant at the time of their initial dose (they should receive 1 additional dose before their next high-risk travel); 2) hematopoietic cell transplant patients who were vaccinated before transplant (they should receive a dose of YFV before high-risk travel, if they are sufficiently immunocompetent to receive a live attenuated vaccine); 3) persons who were infected with HIV when they received their last dose (they should be revaccinated every 10 years if they remain at risk); and 4) otherwise healthy persons who will be in very high risk situations (they should receive a booster dose ≥10 years after their last dose). Laboratory personnel who might be exposed to virulent yellow fever virus or to concentrated preparations of vaccine strains should be vaccinated; neutralizing antibody titers should be measured every 10 years to determine if booster doses are needed (booster doses should be given every 10 years if antibody titers cannot be obtained).

YFV can only be administered at a site approved by the World Health Organization (WHO). The Division of Global Migration and Quarantine at the Centers for Disease Control and Prevention (CDC), as well as state and territorial health departments, can designate nonfederal vaccination centers. Vaccinees must receive an *International Certificate of Vaccination or Prophylaxis* ("Yellow Card") that has been completed, signed, and validated with the center's stamp. New certificates have been produced since December 15, 2007 in response to a revision of the International Health Regulations (IHRs); persons vaccinated before that date may use the old certificate until it expires.[16] The IHRs were amended in 2016 to specify that a completed Yellow Card is valid for the lifetime of the vaccinee, and countries cannot require proof of revaccination as a condition of entry.

Certain countries in Africa require evidence of vaccination from all entering travelers. Some countries waive the requirements for travelers who will be staying <2 weeks and come from areas with little risk of yellow fever transmission. Other countries require persons, even if only in transit, to have a valid certificate if they have been in countries either known or thought to have yellow fever, or even where yellow fever does not exist but where *A aegypti* mosquitoes are found. The CDC[17] and WHO[18] web sites contain information on yellow fever endemic areas and countries that require certificates.

The minimum interval between YFV and other live vaccines not given on the same day is 30 days, and travel should be postponed if this minimal interval cannot be established.

Because of the risk of vaccine-associated encephalitis, infants <6 months of age should not be vaccinated under any circumstances. Travel of infants 6 to 8 months of age to endemic areas should be deferred; if travel is unavoidable, vaccination is acceptable (off-label recommendation), but the risk of adverse events may be higher than in infants ≥9 months of age. Pregnant women may be vaccinated if travel cannot be postponed and if exposure is very likely; while there is no definitive evidence of fetal harm from maternal vaccination, there is the possibility of decreased immune response, and testing for seroconversion should be considered.

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Zoster

The Pathogen

The biology of varicella-zoster virus (VZV) is described in *Chapter 32: Varicella. Herpes zoster* (HZ), or *shingles*, is caused by reactivation of latent VZV from sensory dorsal root or cranial nerve ganglia.[1] The virus initially reaches these ganglia by retrograde axonal transport from the skin during an episode of chickenpox. In latency, which may last for many decades, there is restricted gene transcription and limited protein expression, and intact virions are not produced. What triggers release from latency into active, lytic infection is not clear, but it is known that reduced VZV-specific T-cell responder cell frequency characterizes all conditions associated with reactivation.

Normally there is enough ongoing immune surveillance such that when active replication begins, infected cells are destroyed, or replication is otherwise shut down. When immune surveillance wanes, lytic infection in neuronal cell bodies can progress, and virions are transported back along sensory nerves to the skin, where lesions much like those of chickenpox emerge. Unlike with chickenpox, however, the lesions are restricted to a single dermatome (more than one dermatome may be involved in immunocompromised individuals). Moreover, they are associated with significant pain, the result of cell destruction and inflammation in the sensory ganglion. Pain often persists after regression of the lesions, a condition termed *postherpetic neuralgia* (PHN).[2] This is associated with degeneration of primary afferent neuronal cell bodies and axons, scarring in the dorsal root ganglion, and *central sensitization*, which refers to changes in the dorsal horn of the spinal cord that generalize and perpetuate pain impulses.

HZ is a re-immunizing event—immunity to VZV is boosted, and for this reason most people only have one lifetime episode.

Clinical Features

A prodrome of headache, photophobia, and malaise without fever may occur.[3] Pain (often described as burning, shooting, stabbing, or throbbing), itching, or tingling precede skin lesions by 1 to 5 days. Lesions form over 3 to 5 days, beginning

as clusters of erythematous macules in one dermatome that rapidly become papules with superimposed clear vesicles, and—much like chickenpox—evolve to pustules and shallow ulcers with crusts that fall off in 2 to 4 weeks, often leaving scars and permanent changes in pigmentation. Thoracic, cervical, and ophthalmic dermatomes are most often involved, and the lesions do not cross the midline. Motor nerve involvement with associated paresis may be seen in 5% to 15% of patients (the mechanism for this is not clear). Involvement of the geniculate ganglion can lead to facial nerve paralysis (sensory and motor nerves are joined in nerve VII); the combination of lesions on the ear, hard palate, or tongue and facial paralysis is termed *Ramsay Hunt syndrome* and is associated with vertigo, hearing loss, tinnitus, and loss of taste. Occasionally, pain occurs without skin lesions—this is called *zoster sine herpete*.

HZ tends to be more severe with advanced age. Subclinical involvement of the central nervous system is common in immunocompetent individuals; half of patients have cerebrospinal fluid (CSF) pleocytosis and a third may have detectable VZV in the CSF. Immunocompromised patients may experience severe localized HZ or disseminated HZ due to hematogenous spread of the infection beyond the original dermatome. The spectrum of illness ranges from generalized rash to life-threatening pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy.

PHN lasting ≥1 month occurs in 20% to 30% of patients, and about 10% have pain lasting ≥3 months. Pain may be constant, intermittent, or triggered by trivial stimuli; half of patients describe it as excruciating. Quality of life and work productivity may be dramatically affected, leading to social withdrawal, depression, and even suicide.[4] The severity of PHN correlates with advanced age, and PHN is rare in children.

Other complications of HZ include secondary bacterial infection, eye involvement with keratitis or retinitis, and myelitis. VZV reactivation and spread to nerves that project into cerebral arteries can cause vasculopathy and stroke.[5,6] Controversy exists over the role of VZV reactivation in the pathogenesis of temporal arteritis.[7,8]

Epidemiology and Transmission

HZ only occurs in people who have had been infected with VZV—this includes >99.5% of the US population ≥40 years of age. It is contagious in the sense that VZV from the lesions can cause chickenpox in a susceptible individual; however, HZ cannot directly cause HZ in another person, nor can chickenpox, because latency must first be established. The risk of contagion from HZ is less than that from chickenpox because there is less virus that can aerosolize from the lesions and there is no transmission from respiratory secretions before the lesions erupt.

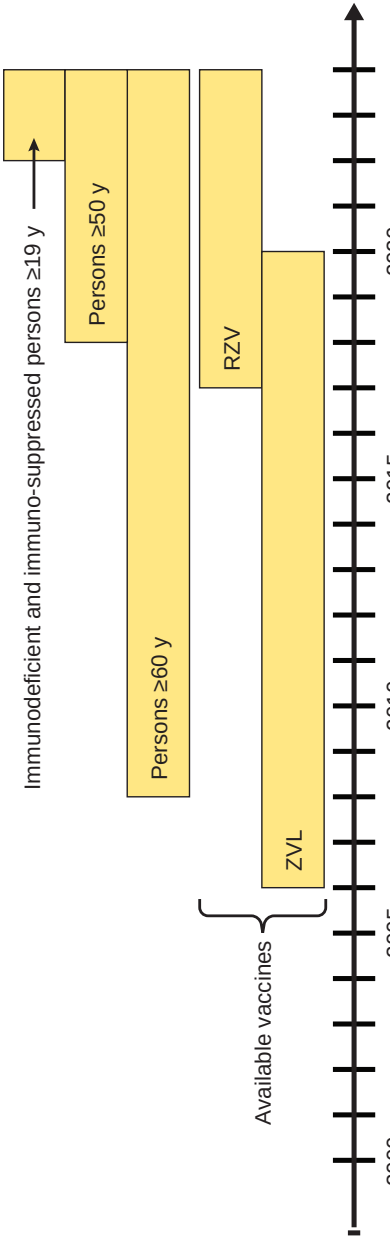
Estimates of age-adjusted incidence rates in the US vary from 3.2 to 4.2 per 1000 population, translating into 1 million cases annually.[9] The rate is much higher—about 10 per 1000—in persons ≥60 years of age. About one third of people will experience an episode of HZ in their lifetime. The most important risk factors are increasing age and conditions or medications that impair cell-mediated immunity; other risk factors include psychological stress, female gender, white race, mechanical trauma, and genetic susceptibility. Varicella vaccination protects against HZ (see *Chapter 32: Varicella*); when HZ due to wild-type virus does occur in children, a history of maternal varicella during pregnancy or chickenpox in the first year of life is often elicited (these are situations that can lead to immune tolerance, ie, blunting of immune memory to VZV).

The incidence of HZ in children has decreased markedly since 1995, the year that universal varicella vaccination began[10]; vaccinated children are likely to be latently infected with vaccine, rather than wild-type, virus, which reactivates much less commonly. Several studies show increases in HZ among adults, consistent with the fact that there is less circulating wild-type virus to boost immunity and prevent reactivation of endogenous wild-type virus[11,12] (there are, however, studies that do not show increased risk among older persons[13]). A meta-analysis published in 2019 suggested that any increase in HZ after implementation of varicella vaccination programs is confined to one age group (10 to 49 years of age) and is of the order of 2 additional cases per 100,000 persons.[14]

Immunization Program

Figure 34.1 shows the evolution of zoster immunization recommendations in the US. In the prevaccine era, each case of HZ resulted in up to three outpatient visits and from one to five medication prescriptions. Up to 4% of episodes resulted in hospitalization, with a mean duration of 5 days and average cost of $3221 to $7206 (2006 dollars). Annualized health care costs for PHN were as high as $5000 per episode. ZVL was licensed in 2006 and shortly thereafter recommended for routine use in persons ≥60 years of age. The cost-effectiveness of the program was estimated to be between $27,000 and $112,000 (2005-2006 dollars) per quality-adjusted life year (QALY) gained. RZV was licensed in 2017 for persons ≥50 years of age, and recommendations for use were published in early 2018.[15] Based on studies showing greater efficacy than ZVL, the possibility of longer duration of protection, and models predicting greater cost-effectiveness, RZV was given preference over ZVL, and the age for routine vaccination was lowered to 50 years. Under base assumptions, RZV was expected to cost <$50,000 (2016 dollars) per QALY gained at all ages, and under certain conditions it would be cost saving.[16] In 2021, the label for RZV was expanded to include persons ≥18 years of age at increased risk due to immunodeficiency

FIGURE 34.1 — Zoster Immunization Recommendations Over Time



The figure shows major steps in the evolution of zoster immunization recommendations in the US. Note the transition from ZVL to RZV, lowering of the recommended age for routine immunization, and recent recommendations for use in immunocompromised adults.

Adapted from Zoster (Shingles) ACIP vaccine recommendations. CDC Web site. https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/shingles.html. Accessed August 24, 2023.

or immunosuppression, and in 2022 RZV was recommended for immunocompromised persons ≥19 years of age (19 rather than 18 years of age was chosen to align with the adult immunization schedule).[17]

Vaccines

Characteristics of the HZ vaccine licensed and used in the US are given in **Table 34.1**. RZV consists of a recombinantly-expressed surface glycoprotein from the viral envelope combined with a novel adjuvant (see **Table 1.3**). ZVL (Zostavax; Merck), a classical live attenuated vaccine, is no longer available.

Immunogenicity, Efficacy, Effectiveness, and/or Impact

Large studies of ZVL in older adults established the paradigm that shingles is vaccine-preventable.[18-21] In general, efficacy against HZ was about 50% (70% in middle-aged adults); efficacy against PHN was about 70%. Among subjects who developed HZ, the risk of PHN was reduced by about 40%. However, protection against HZ waned considerably with time. The efficacy of RZV was established in the Zoster Efficacy Study in Adults 50 Years of Age or Older (ZOE-50), in which 7698 subjects received the vaccine and 7713 received a placebo.[22] After a mean follow-up period of 3.2 years, efficacy against HZ was 97% and was similar in all age groups. In a separate study conducted at the same sites among 13,900 persons ≥70 years of age (ZOE-70), efficacy against HZ was 90%. In pooled analyses from ZOE-50 and ZOE-70, efficacy against postherpetic neuralgia was 91% among persons ≥50 years of age and 89% among those ≥70 years of age,[23] and efficacy against other complications of HZ was >90% in both age groups.[24] Robust protection against HZ has been shown to persist as long as 10 years in an ongoing follow-up study.[25] Early data show that real-world effectiveness during the first year or so after vaccination with RZV is about 86%.[26]

Safety

In the pivotal clinical trials, injection site reactions occurred in approximately 80% of RZV recipients; over half of subjects experienced systemic symptoms, but severe symptoms (those preventing everyday activity) occurred in only 6% to 11%. A similar safety and reactogenicity profile was seen after vaccination of subjects who had received placebo in the original trials.[27] No increase in immune-mediated diseases (a theoretical concern with adjuvanted vaccines) has been observed in vaccinees. During the first 8 months of use in the US, after approximately 3.2 million doses had been distributed,

TABLE 34.1 — Zoster Vaccine[a]

Trade name	Shingrix
Abbreviation	RZV (recombinant zoster vaccine)
Manufacturer/distributor	GSK
Type of vaccine	Non-live, subunit, in vitro-expressed
Composition	Surface glycoprotein E (gE) (50 mcg)
	Expressed in Chinese Hamster Ovary cells
Adjuvant	$AS01_B$ (3-*O*-desacyl-4′-monophosphoryl lipid A from *Salmonella minnesota* [50 mcg] and QS-21, a saponin purified from plant extract *Quillaja saponaria* Molina [50 mcg]; liposomal formulation using dioleoyl phosphatidylcholine [1 mg] and cholesterol [0.25 mg])
Preservative	None
Excipients and contaminants	Sucrose (20 mg)
	Sodium chloride (4.385 mg)
	Potassium dihydrogen phosphate (0.54 mg)
	Cholesterol (0.25 mg)
	Sodium dihydrogen phosphate dihydrate (0.160 mg)
	Disodium phosphate anhydrous (0.15 mg)
	Dipotassium phosphate (0.116 mg)
	Polysorbate 80 (0.08 mg)
	Residual host cell proteins (≤3.0%)
	Residual host cell DNA (≤2.1 picograms)
Latex	None
Labeled indications	Prevention of herpes zoster (shingles)
Labeled ages	≥50 y Immunodeficiency or immunosuppression: ≥18 y
Dose	0.5 mL
Route of administration	Intramuscular
Labeled schedule	Doses at 0 and 2-6 mo[b]
Recommended schedule (age)	50 y Immunodeficiency or immunosuppression: ≥19 y
How supplied (number in package)	1-dose vial (1, 10), lyophilized, with adjuvant/diluent
Cost per dose (USD, 2023)	
Public	104.53
Private	183.41
Reference package insert	May 2023

[a] ZVL (Zostavax; Merck) was discontinued in the US in 2020.
[b] Immunocompromised or immunosuppressed persons who may benefit from a shorter vaccination schedule may receive doses at 0 and 1-2 mo.

there were no unexpected patterns of adverse events in the Vaccine Adverse Event Reporting System database.[28]

Contraindications

- Severe allergic reaction (eg, anaphylaxis) to previous dose of vaccine or any vaccine component (risk of recurrent allergic reaction)

Precautions

- Moderate or severe acute illness (difficulty distinguishing illness from vaccine reaction)
- There is no recommendation for use in pregnancy, so providers should consider delaying RZV until after pregnancy (theoretical risk to the fetus or attribution of birth defects to vaccination)

Recommendations

All persons ≥50 years of age, including those with chronic medical conditions, should be vaccinated against HZ. The usual schedule is 2 doses of RZV separated by 2 to 6 months. Catch-up vaccination is recommended for zoster vaccine-naïve persons, and revaccination using RZV is recommended for previous recipients of ZVL (beginning ≥2 months after the previous dose of ZVL). There is no upper age limit in either of these scenarios. Vaccination is recommended whether or not a person has a history of varicella (adults known to be non-immune to varicella should receive 2 doses of VAR separated by ≥4 weeks, rather than RZV—see **Table 32.2**). Because HZ can recur, patients who have had HZ should be vaccinated (there is no

minimum interval between an episode of HZ and vaccination, but vaccination should not occur *during* an episode).

See **Table 6.1** regarding vaccination of immunodeficient or immunosuppressed persons ≥19 years of age.

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Combination Vaccines

Background

Some of the first vaccines licensed in the US were combinations of antigens. For example, the influenza vaccine (first licensed in 1945) historically contained antigens from three different strains of influenza virus. Likewise, the 6-valent pneumococcal polysaccharide vaccine (1947), DTwP vaccine (1948), 3-valent IPV (1955), and 3-valent OPV (1963) were also combinations. Modern combination vaccines, whose development began in the 1990s, are made of components that could be given as separate products.

Producing safe and effective combination vaccines is more complex than simply mixing antigens together in a single vial.[1] Adjuvants, buffers, stabilizers, and excipients can have *physical* or *chemical interactions* with antigens that reduce immunogenicity, and many of these interactions cannot be predicted beforehand. *Antigenic competition* can occur as vaccine components vie for position in binding to major histocompatibility molecules on antigen-presenting cells. This may explain, in part, the decreased responses to *H influenzae* type b that were seen with initial attempts to combine Hib with DTaP.[2] *Carrier-induced epitopic suppression* may cause decreased antibody responses to protein-polysaccharide conjugates when there has been prior or simultaneous immunization with free (homologous) carrier protein.[3] Interference can be seen when different conjugates containing the same carrier protein are given at the same time, although the effects are unpredictable. When live viral vaccines are given together, *viral interference* may limit responses as the replication of one virus is inhibited by the replication of the other; thus, to overcome that inhibition MMRV contains higher amounts of mumps virus and VZV than what is present in MMR (Merck) and VAR. While these interactions are important considerations, they must be differentiated from "immune overload," a popular concept that has no scientific basis (see *Chapter 7: Addressing Concerns About Vaccines—Immune Overload and Alternative Schedules*).

US Food and Drug Administration (FDA) guidelines require that clinical trials compare candidate combination vaccines to their separately but simultaneously administered component vaccines. Reactogenicity is measured against the

most reactogenic of the individual components. For antigens that have an established serologic correlate of protection, it may be enough to demonstrate that the combination induces protective antibody responses. However, the FDA generally requires demonstration of *noninferiority* with component vaccines (see *Chapter 2: Vaccine Infrastructure in the United States—Vaccine Development and Licensure*). Efficacy against disease is inferred for most new combination vaccines rather than directly demonstrated.

Use of combination vaccines, by reducing the number of shots due, can lead to improvements in coverage and timeliness.[4-6] In the past, one barrier to the adoption of combination vaccines was that providers were reimbursed for each separate injection (fewer injections, less revenue).[7] Today, providers are reimbursed according to the antigens delivered—whether separate or in combination with other antigens (see *Chapter 4: Vaccine Practice—Coding, Billing and Costs*)—and combination vaccines have become the standard of care.

Vaccines

DTaP-based combination vaccines available in the US are listed in **Table 35.1**, and other modern combination vaccines are listed in **Table 35.2**. The following generalizations are offered:

- *Efficacy and/or immunogenicity*—Licensure by the FDA ensures that the immunogenicity (and it follows, protective efficacy) of a given combination vaccine is noninferior to that of the component vaccines given separately. Persistence of immunity from combination vaccines generally follows that of their components. For example, immunity to hepatitis A and hepatitis B has been demonstrated up to 15 years after receipt of HepA-HepB.[8]
- *Safety*—Similarly, licensure by the FDA ensures that, in all clinically meaningful respects, a given combination vaccine is as safe as the separately administered components. However, a few issues are noteworthy. For example, higher rates of fever can be seen after DTaP-HepB-IPV and DTaP-IPV-Hib-HepB administration, although most of these fevers are low-grade and do not result in medical attention.[9,10] DTaP-IPV/Hib is not associated with increased rates of fever,[11] and no safety signals were detected in a retrospective observational study involving over 14,000 infants who received at least one dose of vaccine.[12] Prelicensure clinical trials demonstrated higher rates of fever following the first dose of MMRV compared to MMR plus VAR, and postlicensure studies show that this can lead to febrile seizures in about 1 out of every 2300 to 2600 vaccinees (see *Chapter 7: Addressing Concerns About Vaccines—Febrile Seizures*).
- *Contraindications and precautions*—Contraindications and precautions for combination vaccines are the same as for the individual components. One exception is MMRV, where a personal or family (ie, sibling or parent) history of seizures is listed as an incremental precaution.[13]

Recommendations

In 1999, the Advisory Committee on Immunization Practices (ACIP), American Academy of Pediatrics (AAP), and American Academy of Family Physicians expressed a clear preference for combination vaccines over separate injections of the components.[14] In 2009, the preference was reworded to state that combination vaccines are "generally" preferred, giving providers some leeway in deciding whether or not to use them.[15] One exception to this general preference is that MMR plus VAR is recommended over MMRV for the first dose when given at 12 to 47 months of age, because of the risk of febrile seizures (it should be noted that the AAP views either option as acceptable, as long as the caregivers are fully informed about the risks and benefits of either approach[16]). MMRV is preferred for the first dose in children 4 through 12 years of age, as well as for second doses.

Use of combination vaccines may result in *overimmunization* because unnecessary doses of an antigen may be given. For example, an infant who receives the birth dose of HepB and then receives DTaP-HepB-IPV or DTaP-IPV-Hib-HepB at 2, 4, and 6 months of age will receive 4 total doses of HepB, when only 3 doses are required. As another example, a child who receives DTaP-IPV/Hib at 2, 4, 6, and 15 months of age will need DTaP and IPV at 4 to 6 years of age—a total of 5 doses of IPV will be given, when only 4 are required. These extra doses are not harmful and are an accepted consequence of using combination vaccines.

Tables 34.1 and **34.2** include published, product specific ACIP recommendations. Providers are warned not to combine vaccines in the same syringe unless the products are specifically labeled for this purpose.

TABLE 35.1 — DTaP-Based Combination Vaccines[a]

Trade name	Kinrix	Pediarix	Pentacel[b]	Quadracel[b]	Vaxelis
Abbreviation	DTaP-IPV	DTaP-HepB-IPV	DTaP-IPV/Hib	DTaP-IPV	DTaP-IPV-Hib-HepB
Manufacturer/distributor	GSK	GSK	Sanofi	Sanofi	Merck and Sanofi
Diseases prevented					
Diphtheria	✓	✓	✓	✓	✓
Tetanus	✓	✓	✓	✓	✓
Pertussis	✓	✓	✓	✓	✓
Hepatitis B	—	✓	—	—	✓
H influenzae type b	—	—	✓	—	✓
Polio	✓	✓	✓	✓	✓
Type of vaccine	See chapters for the respective component vaccines				
Component vaccines[c]					
DTaP	Infanrix	Infanrix	Daptacel	Daptacel	Daptacel
HepB	—	Engerix-B	—	—	Recombivax HB
Hib	—	—	ActHIB[d]	—	PedvaxHIB
IPV	IPV[e]	IPV[e]	IPOL	IPOL	IPOL
Composition					
Diphtheria toxoid	25 Lf units	25 Lf units	15 Lf units	15 Lf units	15 Lf units
Tetanus toxoid	10 Lf units	10 Lf units	5 Lf units	5 Lf units	5 Lf units
Inactivated pertussis toxin	25 mcg	25 mcg	20 mcg	20 mcg	20 mcg
Filamentous hemagglutinin	25 mcg	25 mcg	20 mcg	20 mcg	20 mcg
Pertactin	8 mcg	8 mcg	3 mcg	3 mcg	3 mcg
Fimbriae types 2 and 3	—	—	5 mcg	5 mcg	5 mcg
HBsAg	—	10 mcg	—	—	10 mcg
Polyribosylribitol phosphate	—	—	10 mcg conjugated to tetanus toxoid (24 mcg)	—	3 mcg conjugated to *N meningitidis* serogroup B (strain B11) outer membrane protein (50 mcg)
Poliovirus type 1 (Mahoney)	40 D antigen units	40 D antigen units	29 D antigen units	29 D antigen units	29 D antigen units

Continued

TABLE 35.1 — *Continued*

Trade name	Kinrix	Pediarix	Pentacel[b]	Quadracel[b]	Vaxelis
Composition (*continued*)					
Poliovirus type 2 (MEF-1)	8 D antigen units	8 D antigen units	7 D antigen units	7 D antigen units	7 D antigen units
Poliovirus type 3 (Saukett)	32 D antigen units	32 D antigen units	26 D antigen units	26 D antigen units	26 D antigen units
Poliovirus propagation	Vero (African green monkey kidney) cells	Vero (African green monkey kidney) cells	Vero (African green monkey kidney) cells	Vero (African green monkey kidney) cells	Vero (African green monkey kidney) cells
Poliovirus inactivation	Formaldehyde	Formaldehyde	Formaldehyde	Formaldehyde	Formaldehyde
Adjuvant	Aluminum hydroxide (≤0.5 mg aluminum)	Aluminum hydroxide and aluminum phosphate (≤0.7 mg aluminum)	Aluminum phosphate (0.33 mg aluminum)	Aluminum phosphate (0.33 mg aluminum)	Aluminum hydroxyphosphate sulfate and aluminum phosphate, (0.319 mg aluminum)
Preservative	None	None	None	None	None
Excipients and contaminants	Sodium chloride (≤ 4.4 mg)	Sodium chloride (≤ 4.4 mg)	Polysorbate 80 (<8.1 mcg)	Polysorbate 80 (<8.1 mcg)	Polysorbate 80 (<0.0056%)
	Formaldehyde (≤100 mcg)	Formaldehyde (≤100 mcg)	Formaldehyde (2-7 mcg)	Formaldehyde (2-7 mcg)	Formaldehyde (≤14 mcg)
	Polysorbate 80 (≤100 mcg)	Polysorbate 80 (≤100 mcg)	Glutaraldehyde (<50 ng)	Glutaraldehyde (<50 ng)	Glutaraldehyde (≤50 ng)
	Neomycin sulfate (≤0.05 ng)	Neomycin sulfate (≤0.05 ng)	Bovine serum albumin (≤10 ng)	Bovine serum albumin (≤10 ng)	Bovine serum albumin (≤50 ng)
	Polymyxin B (≤0.01 ng)	Polymyxin B (≤0.01 ng)	Neomycin (<0.01 pg)	Neomycin (<0.01 pg)	Neomycin (<5 ng)
		Yeast protein (≤5%)	Streptomycin sulfate (<0.0001 pg)	Streptomycin sulfate (<0.0001 pg)	Streptomycin sulfate (<200 ng)
			Polymyxin B sulfate (<0.000001 pg)	Polymyxin B sulfate (<0.000001 pg)	Polymyxin B sulfate (<25 ng)
			2-phenoxyethanol (3.3 mg)[f]	2-phenoxyethanol (3.3 mg)[f]	Ammonium thiocyanate (≤0.125 mcg)

Continued

TABLE 35.1 — *Continued*

Trade name	Kinrix	Pediarix	Pentacel[b]	Quadracel[b]	Vaxelis
Excipients and contaminants (*continued*)			Sucrose (42.5 mg)		Yeast protein (≤0.1 mcg)
Latex	Tip cap of prefilled syringe contains latex	Tip cap of prefilled syringe contains latex	None	None	None
Labeled ages	4-6 y	6 wk-6 y[g]	6 wk-4 y	4-6 y	6 wk-4 y[g]
Dose	0.5 mL	0.5 mL	0.5 mL	0.5 mL	0.5 mL
Route of administration	Intramuscular	Intramuscular	Intramuscular	Intramuscular	Intramuscular
Labeled schedule	Dose 5 of DTaP and Dose 4 of IPV in previous recipients of Pediarix and/or Infanrix	2, 4, and 6 mo[h]	2, 4, 6, and 15-18 mo[i]	Dose 5 of DTaP and Dose 4 or 5 of IPV in previous recipients of Pentacel and/ or Daptacel and/or Vaxelis	2, 4, and 6 mo[h]
Recommended schedule[j]	Same	Same	Same	Same	Same
How supplied (number in package)	1-dose vial (10)	Prefilled syringe (10)	1-dose vial (5) of ActHIB, lyophilized, with 1-dose vial (5) of DTaP-IPV as diluent	1-dose vial (10)	1-dose vial (10)
	Prefilled syringe (10)			Prefilled syringe (10)	Prefilled syringe (10)
Cost per dose (USD, 2023)					
Public	46.96	64.25	68.25	46.18	97.79
Private	59.39	92.63	111.30	61.13	146.59
Reference package insert	November 2022	November 2022	October 2022	July 2022	October 2022
Reference ACIP recommendation	CDC. *MMWR*. 2008; 57:1078-1079.	CDC. *MMWR*. 2003;52:203-204.	CDC. *MMWR*. 2008;57:1079-1080.	Liang J, et al. *MMWR*. 2015;64:948-949.	Oliver SE, et al. *MMWR*. 2020;69:136-139.

ACIP, Advisory Committee on Immunization Practices; HBsAg, hepatitis B surface antigen

[a] TriHIBit (DTaP/Hib-T; Sanofi) was discontinued in 2012.

[b] In 2021-2022, the polio component of Pentacel and Quadracel was transitioned from human diploid (MRC-5) cell-based (Poliovax) to Vero (African green monkey kidney) cell-based (IPOL). As of May 2022, the only MRC-5–based vaccine being distributed was Quadracel, and the last vials of that were shipped in March 2023.

[c] The combination vaccines may not be strict mixtures of the component vaccines. In some cases, the amount of antigen or the method of production may be different than the separate components. In addition, the methods used to measure antigen in the final product may differ from those used for the component products.

[d] The liquid DTaP-IPV combination is used to reconstitute the lyophilized ActHIB.

[e] Not licensed separately in the US.

[f] Not present as a preservative.

Continued

TABLE 35. 1 — *Continued*

[g] Pediarix and Vaxelis are labeled for the primary series (not booster doses) in infants of HBsAg-negative mothers. Either one may be used in infants of HBsAg-positive or -unknown mothers to complete a HepB series initiated at birth with single antigen vaccine (off-label recommendation). Vaxelis does not have a preferential recommendation for use in American Indian or Alaska Native infants, as does the component vaccine PedvaxHIB.

[h] With the birth dose of HepB, use of Pediarix or Vaxelis will result in four total doses of HepB. This does not increase reactogenicity or compromise immunogenicity. Patients who receive Pediarix or Vaxelis according to this schedule will need DTaP boosters at 15-18 mo and 4-6 y, as well as an IPV booster at 4-6 y.

[i] Patients who receive Pentacel according to this schedule do not need further doses of Hib, but they do need DTaP and IPV boosters at 4-6 y. Dose 4 may be given as early as 12 mo if the opportunity to vaccinate later may be missed and if ≥6 mo have elapsed since Dose 3.

[j] ACIP expresses a preference for the same DTaP product for the entire series, but vaccination should not be deferred if the same product is not immediately available or if the previous products are not known.

TABLE 35.2 — Other Combination Vaccines[a]

Trade name	ProQuad	Twinrix
Abbreviation	MMRV	HepA-HepB
Manufacturer/ distributor	Merck	GSK
Diseases prevented	Measles	Hepatitis A
	Mumps	Hepatitis B
	Rubella	
	Varicella	
Type of vaccine	See chapters for the respective component vaccines	
Component vaccines[b]	M-M-R_{II} (MMR)[c]	Havrix (HepA)
	Varivax (VAR)[d]	Engerix-B (HepB)
Composition	Measles virus, Moraten strain (derived from the Edmonston B strain), propagated in chick embryo cells, at least 1000 $TCID_{50}$	HAV, HM175 strain, propagated in human diploid (MRC-5) cells and inactivated with formalin (720 ELISA units)
	Mumps virus, Jeryl Lynn strain (consists of two distinct strains), propagated in chick embryo cells, at least 19,950 $TCID_{50}$	HBsAg expressed in yeast (*Saccharomyces cerevisiae*) (20 mcg)
	Rubella virus, RA 27/3 strain, propagated in human diploid lung fibroblast (WI-38) cells, at least 1000 $TCID_{50}$	
	Varicella virus, Oka/ Merck strain, propagated in human diploid (MRC-5) cells, at least 9770 plaque-forming units	

Continued

TABLE 35.2 — *Continued*

Trade name	ProQuad	Twinrix
Adjuvant	None	Aluminum phosphate, aluminum hydroxide (0.45 mg aluminum)
Preservative	None	None
Excipients and contaminants	Sucrose (21 mg)	Amino acids
	Hydrolyzed gelatin (11 mg)	Sodium chloride
	Sodium chloride (2.4 mg)	Phosphate buffer
	Sorbitol (1.8 mg)	Polysorbate 20
	Monosodium L-glutamate (0.40 mg)	Formalin (≤0.1 mg)
	Sodium phosphate dibasic (0.34 mg)	Residual MRC-5 proteins (≤2.5 mcg)
	Recombinant human albumin (0.31 mg)	Neomycin sulfate (≤20 ng)
	Sodium bicarbonate (0.17 mg)	Yeast protein (≤5%)
	Potassium phosphate monobasic (72 mcg)	
	Potassium chloride (60 mcg)	
	Potassium phosphate dibasic (36 mcg)	
	Residual components of MRC-5 cells, including DNA and protein	
	Neomycin (<16 mcg)	
	Bovine calf serum (≤0.5 mcg)	
	Other buffer and media ingredients	
Latex	None	Tip cap of prefilled syringe contains latex

Continued

TABLE 35.2 — *Continued*

Trade name	ProQuad	Twinrix
Labeled ages	12 mo-12 y	≥18 y
Dose	0.5 mL	1 mL
Route of administration	Subcutaneous	Intramuscular
Labeled schedule	12-15 mo	Doses at 0, 1, and 6 mo
	Revaccination at 4-6 y	Alternative: doses at 0, 7, and 21-30 d[e]; booster at 12 mo
Recommended schedule	Same[f]	Same
How supplied (number in package)	1-dose vial (10), lyophilized, with diluent	Prefilled syringe (10)
Cost per dose (USD, 2023)		
Public	165.09	70.33 (pediatric) 67.93 (adult
Private	262.37	121.40
Reference package insert	March 2023	December 2018
Reference ACIP recommendation	Marin M, et al. *MMWR*. 2010;59(RR-3):1-12.	CDC. *MMWR*. 2007;56:1057.

ACIP, Advisory Committee on Immunization Practices; HBsAg, hepatitis B surface antigen

[a] Comvax (HepB-Hib-OMP; Merck) was discontinued in 2014. MenHibrix (HibMenCY-T; GSK) was discontinued in 2016.

[b] The combination vaccines may not be strict mixtures of the component vaccines. In some cases, the amount of antigen or the method of production may be different than the separate components.

[c] The amount of mumps virus in MMRV is 1.6-times higher than in MMR (Merck).

[d] The amount of varicella virus in MMRV is 7-times higher than in VAR (Varivax; Merck).

[e] The 4-day grace period for minimum intervals (see *Chapter 3: Standards, Principles, and Regulations—Mandates and Exemptions*) does not apply to the first 3 doses of Twinrix

[f] Unless the parent or caregiver expresses a preference for MMRV, children in this age group being immunized for the first time should receive separate MMR and VAR (risk of febrile seizures with MMRV administered as the first dose).

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Appendix

Table 36.1 Internet Resources

Table 36.2 Books

Table 36.3 Vaccine Abbreviations

Table 36.4 Vaccine and Infectious Agent Nomenclature

TABLE 36.1 — Internet Resources

Agency or Organization	Web Site
US Government	
Centers for Medicare & Medicaid Services	www.cms.hhs.gov
National Institute of Allergy and Infectious Diseases	www.niaid.nih.gov
US Food and Drug Administration	www.fda.gov
Centers for Disease Control and Prevention	www.cdc.gov
Health Resources and Services Administration	www.hrsa.gov
National Vaccine Program Office	www.hhs.gov/nvpo
National Vaccine Advisory Committee	www.hhs.gov/nvpo/nvac
International	
Pan American Health Organization	www.paho.org/hq
World Health Organization	www.who.int
Professional	
American Academy of Family Physicians	www.aafp.org
American Academy of Pediatrics	www.aap.org
American College Health Association	www.acha.org
American College of Obstetricians and Gynecologists	www.acog.org/programs/immunization-for-women
American College of Physicians	www.acponline.org
American Medical Association	www.ama-assn.org
American Nurses Association	www.nursingworld.org
American Pharmacists Association	www.pharmacist.com
American Public Health Association	www.apha.org
Association for Prevention Teaching and Research	www.aptrweb.org
Association of State and Territorial Health Officials	www.astho.org
Infectious Diseases Society of America	www.idsociety.org
Pediatric Infectious Diseases Society	www.pids.org

Continued

TABLE 36.1 — *Continued*

Agency or Organization	Web Site
Advocacy, Implementation, Safety	
Allied Vaccine Group	www.vaccine.org
American Immunization Registry Association	www.immregistries.org
Bill & Melinda Gates Foundation	www.gatesfoundation.org
Brighton Collaboration	www.brightoncollaboration.org
Children's Hospital of Philadelphia Vaccine Education Center	www.chop.edu/centers-programs/vaccine-education-center
Children's Vaccine Program at PATH	www.path.org
Clinical Immunization Safety Assessment Network	www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html
Families Fighting Flu	www.familiesfightingflu.org
Generations United	www.bandageofhonor.org
Global Alliance for Vaccines and Immunization	www.devex.com/organizations/global-alliance-for-vaccines-and-immunisation-gavi-44118
Immunize.org (formerly the Immunization Action Coalition)	www.immunize.org and www.vaccineinformation.org
Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health	www.vaccinesafety.edu
National Foundation for Infectious Diseases	www.nfid.org
National Meningitis Association	www.nmaus.org
Parents of Kids with Infectious Diseases	www.worldhepatitisalliance.org/member/parents-of-kids-with-infectious-diseases-pkids/
Sabin Vaccine Institute	www.sabin.org
Society of Teachers of Family Medicine	www.stfm.org
Stronger	https://stronger.org/
Vaccinate Your Family (the next generation of Every Child by Two)	www.vaccinateyourfamily.org

Continued

TABLE 36.1 — *Continued*

Agency or Organization	Web Site
Advocacy, Implementation, Safety *(continued)*	
Vaccine Confidence Project (London School of Hygiene & Tropical Medicine)	www.vaccineconfidence.org
Vaccines.gov	www.vaccines.gov
Voices for Vaccines	www.voicesforvaccines.org
Coverage and Assessment	
Behavioral Risk Factor Surveillance System	www.cdc.gov/brfss
Comprehensive Clinic Assessment Software Application	www.cdc.gov/vaccines/programs/cocasa/index.html
Healthcare Effectiveness Data and Information Set	www.ncqa.org/hedis/measures/
National Health Interview Survey	www.cdc.gov/nchs/nhis.htm
National Immunization Survey	www.cdc.gov/vaccines/imz-managers/nis/index.html
National Notifiable Diseases Surveillance System	www.cdc.gov/nndss/index.html
Manufacturers and Distributors	
AstraZeneca	www.astrazeneca.com
Bavarian Nordic	www.bavarian-nordic.com
BioNTech	www.biontech.com
Dynavax	www.dynavax.com
Emergent Biosolutions	www.emergentbiosolutions.com
GSK (formerly GlaxoSmithKline)	www.gsk.com
Janssen/Johnson & Johnson	www.jnj.com
Merck	www.merck.com
Moderna	www.modernatx.com
Novavax	www.novavax.com
Pfizer	www.pfizer.com
Sanofi (formerly Sanofi Pasteur)	www.sanofi.com
CSL Seqirus	www.cslseqirus.us
Teva	www.tevapharm.com
Valneva	https://valneva.com/
VBI Vaccines	www.vbivaccines.com

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TABLE 36.2 — Books

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TABLE 36.3 — Vaccine Abbreviations

aIIV	adjuvanted inactivated influenza vaccine
AVA	anthrax vaccine adsorbed
BCG	Bacille Calmette-Guérin (tuberculosis vaccine)
ccIIV	cell culture-derived inactivated influenza vaccine
COV-Ad26	COVID-19 vaccine, replication-incompetent adenovirus type 26 vector
COV-aPS	COVID-19 vaccine, adjuvanted protein subunit
COV-mRNA	COVID-19 vaccine, mRNA lipid nanoparticle
DT	diphtheria, tetanus vaccine (infant/child formulation)
DTaP	diphtheria, tetanus, acellular pertussis vaccine (infant/child formulation)
DTwP	diphtheria, tetanus, whole-cell pertussis vaccine
hdIIV	high-dose inactivated influenza vaccine
HepA	hepatitis A vaccine
HepB	hepatitis B vaccine
HepB-CpG	hepatitis B vaccine, CpG-adjuvanted
HepB3	hepatitis B vaccine, 3-component
Hib	*H influenzae* type b conjugate vaccine
Hib-CRM	*H influenzae* type b vaccine, CRM_{197} conjugate
Hib-D	*H influenzae* type b vaccine, diphtheria toxoid conjugate
HibMenCY-T	*H influenzae* type b vaccine and *N meningitidis* serogroups C and Y, tetanus toxoid conjugate
Hib-OMP	*H influenzae* type b vaccine, (*N meningitidis*) outer membrane protein conjugate
Hib-T	*H influenzae* type b vaccine, tetanus toxoid conjugate
HPV	human papillomavirus vaccine
HPV2	human papillomavirus vaccine, 2-valent
HPV4	human papillomavirus vaccine, 4-valent
HPV9	human papillomavirus vaccine, 9-valent
idIIV	intradermal inactivated influenza vaccine
IIV	inactivated influenza vaccine
IPV	inactivated poliovirus vaccine
JEV	Japanese encephalitis vaccine
JEV-VC	Japanese encephalitis vaccine, Vero cell-derived
LAIV	live attenuated influenza vaccine

Continued

TABLE 36.3 — *Continued*

MenACWY	meningococcal conjugate vaccine, 4-valent
MenACWY-CRM	meningococcal vaccine, 4-valent, CRM_{197} conjugate
MenACWY-D	meningococcal vaccine, 4-valent, diphtheria toxoid conjugate
MenACWY-T	meningococcal vaccine, 4-valent, tetanus toxoid conjugate
MenB	meningococcal vaccine, serogroup B
MenB-4C	meningococcal vaccine, serogroup B, 4-component
MenB-FHbp	meningococcal vaccine, serogroup B, Factor H binding protein
MMR	measles, mumps, rubella vaccine
MMRV	measles, mumps, rubella, varicella vaccine
MPSV	meningococcal polysaccharide vaccine
MPSV4	meningococcal polysaccharide vaccine, 4-valent
OPV	oral polio vaccine
PCV	pneumococcal conjugate vaccine
PCV7	pneumococcal conjugate vaccine, 7-valent
PCV13	pneumococcal conjugate vaccine, 13-valent
PCV15	pneumococcal conjugate vaccine, 15-valent
PCV20	pneumococcal conjugate vaccine, 20-valent
PCV7-CRM	pneumococcal vaccine, 7-valent, CRM_{197} conjugate
PCV13-CRM	pneumococcal vaccine, 13-valent, CRM_{197} conjugate
PCV15-CRM	pneumococcal vaccine, 15-valent, CRM_{197} conjugate
PCV20-CRM	pneumococcal vaccine, 13-valent, CRM_{197} conjugate
PPSV	pneumococcal polysaccharide vaccine
PPSV23	pneumococcal polysaccharide vaccine, 23-valent
RAB	rabies vaccine
RAB-HDC	rabies vaccine, human diploid cell
RAB-PCEC	rabies vaccine, purified chick embryo cell
rIIV	recombinant-derived inactivated influenza vaccine
RRV-TV	rhesus-human reassortant rotavirus vaccine, tetravalent
RSV	respiratory syncytial virus
RV	rotavirus vaccine
RV1	rotavirus vaccine, monovalent (live attenuated human rotavirus vaccine)

Continued

TABLE 36.3 — *Continued*

RV5	rotavirus vaccine, 5-valent (pentavalent bovine rotavirus vaccine)
RZV	recombinant zoster vaccine
sIIV	standard inactivated influenza vaccine
Td	tetanus, diphtheria vaccine (adolescent/adult formulation)
Tdap	tetanus, diphtheria, acellular pertussis vaccine (adolescent/adult formulation)
TT	tetanus toxoid
TViPSV	typhoid Vi polysaccharide vaccine
Ty21a	(oral) typhoid vaccine
VAR	varicella vaccine
YFV	yellow fever vaccine
ZVL	zoster vaccine live

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TABLE 36.4 — Vaccine and Infectious Agent Nomenclature

Disease	Infectious Agent Name	Abbreviation	Vaccine Designation(s)[a]
Anthrax	*Bacillus anthracis*	*B anthracis*	AVA
Cholera	*Vibrio cholerae* serogroup O1	*V cholerae*	Cholera vaccine
COVID-19	Severe acute respiratory syndrome coronavirus 2	SARS-CoV-2	COV-mRNA, COV-aPS
Dengue	Dengue virus	DENV	Dengue vaccine[b]
Diphtheria, tetanus (lockjaw), pertussis (whooping cough)	*Corynebacterium diphtheriae*	*C diphtheriae*	DTwP, DTaP, Tdap, DT, Td, TT
	Clostridium tetani	*C tetani*	
	Bordetella pertussis	*B pertussis*	
Ebola	Ebola virus	EBOV[c]	Ebola vaccine[d]
H influenzae type b (invasive)	*Haemophilus influenzae* type b	*H influenzae* type b	Hib (Hib-OMP, Hib-T)
Hepatitis A	Hepatitis A virus	HAV	HepA
Hepatitis B	Hepatitis B virus	HBV	HepB, HepB-CpG, HepB3
Cervical and anal cancer, genital warts	Human papillomavirus	—	HPV (HPV2, HPV4, HPV9)
Influenza	Influenza virus	—	IIV, aIIV, ccIIV, hdIIV, idIIV, rIIV, LAIV
Japanese encephalitis	Japanese encephalitis virus	JE virus	JEV (JEV-VC)
Measles, mumps, rubella	Measles virus, mumps virus, rubella virus	—	MMR (Merck), MMR (GSK)
N meningitidis (invasive)	*Neisseria meningitidis*	*N meningitidis*	MenACWY (MenACWY-CRM, MenACWY-D, MenACWY-T), MPSV4, MenB (MenB-4C, MenB-FHbp)
Polio	Poliovirus	—	IPV
Rabies	Rabies virus	—	RAB (RAB-HDC, RAB-PCEC)
Respiratory syncytial virus (lower respiratory tract infection)	Respiratory syncytial virus	RSV	RSV (GSK), RSV (Pfizer)
Rotavirus gastroenteritis	Rotavirus	—	RV (RV1, RV5)
S pneumoniae (invasive, otitis media, pneumonia)	*Streptococcus pneumoniae*	*S pneumoniae*	PCV (PCV7-CRM, PCV13-CRM, PCV15-CRM, PCV20-CRM), PPSV23
Smallpox	Variola virus	—	Smallpox vaccine (vaccinia)
Tick-borne encephalitis	Tick-borne encephalitis virus	TBEV	TBE vaccine
Typhoid fever	*Salmonella typhi*	*S typhi*	TViPSV, Ty21a
Varicella (chickenpox)	Varicella zoster virus	VZV	VAR
Yellow fever	Yellow fever virus	Yellow fever virus	YFV
Zoster (shingles)	Varicella zoster virus	VZV	RZV, ZVL

Continued

TABLE 36.4 — *Continued*

Disease	Infectious Agent Name	Abbreviation	Vaccine Designation(s)[a]
Modern combination vaccines			DTaP-IPV
			DTaP-IPV/Hib
			DTaP-HepB-IPV
			DTaP-IPV-Hib-HepB
			MMRV
			HepA-HepB

[a] For conjugate vaccines, "-CRM," "-D," "-OMP," and "-T," indicate the protein carrier to which the polysaccharide is conjugated (respectively, CRM_{197} [a mutant diphtheria toxin]; diphtheria toxoid; *N meningitidis* outer membrane protein; and tetanus toxoid). Numbers following the abbreviations indicate the valency of the vaccine (eg, HPV4 contains four virus types whereas HPV9 contains nine types). For combination vaccines, dashes indicate that the components are premixed (eg, DTaP-HepB-IPV); slash marks indicate that the components must be combined prior to administration (eg, DTaP-IPV/Hib, where liquid DTaP-IPV is used to reconstitute the lyophilized Hib-T).

[b] Dengue vaccine may be referred to as CYF-TDV, for "chimeric yellow fever dengue-tetravalent dengue vaccine."

[c] Technically, the abbreviation EBOV refers to the species *Zaire ebolavirus*.

[d] Ebola vaccine may be referred to as rVSVΔG-ZEBOV-GP, for "recombinant vesicular stomatitis virus, (envelope) G-glycoprotein deleted-Zaire (strain) Ebola virus (envelope) GP-glycoprotein (expressing)."