Vaccines

A Clinical Overview and Practical Guide

Joseph Domachowske
Manika Suryadevara
Editors

Springer

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Preface

Vaccines—A Clinical Overview and Practical Guide is organized into 3 parts. *Part 1* begins with a review of the human response to infection including key definitions and general concepts important in the field of vaccinology. Next, detailed chapters on currently available strategies that provide passive and active immune protection against infectious diseases are presented, including descriptions for how these biologic products are produced. Given the complexity of the manufacturing processes used in vaccine production and the frequency with which questions arise regarding the presence of various additives and excipients found in vaccines, a full chapter has been dedicated to the topic. Part 1 concludes with a chapter outlining the regulatory processes and timelines needed for the development and testing of new vaccine candidates.

Part 2 of the book includes separate chapters on each of the 35 infections that are currently vaccine preventable. The chapters are presented in alphabetical order according to disease. The reader will find that certain terms and concepts important to the study of vaccines appear in many or even all of the chapters. Familiarity with the definition of several of these terms as they are used in vaccinology and in human clinical vaccine trials is key to developing an authoritative understanding of the field so they are introduced first here.

Adverse Events

During clinical vaccine trials, potential vaccine side effects are monitored by collecting all reported adverse events (AEs) from all study subjects for a period of time, typically for 1 or 2 weeks following each dose of the study vaccine. If the vaccine is approved for use, these rates are included in the vaccine's package insert. The adverse effects reported are therefore temporally related to receiving vaccine, but may not be causally related to it. For example, one day after receiving a dose of an investigational vaccine, a child breaks his arm while playing football with his friends. For the purposes of the clinical trial, the fracture is recorded as an adverse event. The study investigator at the site is then responsible for determining whether the adverse

event is likely related to the study vaccine. Since phase III efficacy trials include a control group of individuals that receive either the standard of care vaccine or a placebo, it is important to compare the rates of AEs between the 2 groups to determine whether the rates of reported side effects are different between the 2 groups.

Side Effects

Side effects of vaccines, like any medication, are the adverse events that are CAUSED BY the vaccine. Injection site redness or pain can be a side effect of any injected vaccine. All side effects are adverse events, but not all adverse events are side effects. Clinical vaccine trial data and experience with using the vaccine in the "real world" are usually necessary to clearly delineate the true side effect (cause and effect) profile of a vaccine.

Contraindications to Vaccine

A vaccine that is contraindicated under certain circumstances means that the vaccine should not be administered under any circumstances. Contraindications usually indicate that the vaccine would likely cause a serious safety problem for the recipient, and any perceived benefits of the vaccine will not outweigh the risk of doing harm.

Warnings and Precautions

Warnings and precautions are much longer lists of conditions. This category is used when the safety and efficacy of the vaccine are not known in a certain context because the vaccine has not been studied in that context. Here, the precaution indicates that the provider should carefully weigh the potential risks and potential benefits of a vaccine for a specific individual. Such decisions may differ, for example, during a community outbreak of a vaccine-preventable infection to which a recipient is not yet vaccinated. Under such circumstances, the potential benefits of the vaccine may outweigh the risks of the vaccine.

Vaccine Information Sheets

Vaccine Information Sheets (VIS) are official CDC single-page documents (sheets) that provide concise descriptions of the benefits and risks associated with the vaccine and include a statement of the availability of the National Vaccine Injury

Compensation Program. In the USA, the current version of the official VIS must be provided, by Federal Statute of the United States National Childhood Vaccine Injury Act, to patients prior to administering the vaccine.

WHO Prequalified Vaccine

UNICEF and other stakeholder agencies of the United Nations purchase vaccines for distribution to eligible nations. The World Health Organization provides a service to identify vaccine formulations from the many available sources that meet standards for quality and safety. Prequalified vaccines are those that have been vetted by the WHO and that continue to meet the necessary standards.

Finally, Part 3 of the book includes chapters dedicated to describing various successes and ongoing challenges with immunization programs. Rationale, risks, and benefits for promoting vaccine mandates are presented. Following the chapter dedicated to describing strategies to maintain vaccine confidence and reduce vaccine hesitancy, the book concludes with a chapter on communication techniques that can be used to help educate patients and their families about vaccines.

The 2020 United States Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommended immunization schedules for children and adults, according to age and underlying medical conditions, are detailed in Figs. 1 and 2, and provided here in the preface as a resource that readers may refer to as they progress through the book's content. Vaccine-preventable disease topics that are presented in Part 2 but that are not represented as vaccines on these schedules are, by definition, vaccines that are not routinely recommended. Instead, those vaccines serve the important role of being available to and recommended for individuals at risk for an unusual infection based on their occupation (e.g., adenovirus, plague, smallpox), travel plans (e.g., Japanese encephalitis, tick-borne encephalitis, cholera, dengue, typhoid, yellow fever), or known/suspected direct exposure (e.g., anthrax, rabies, Ebola).

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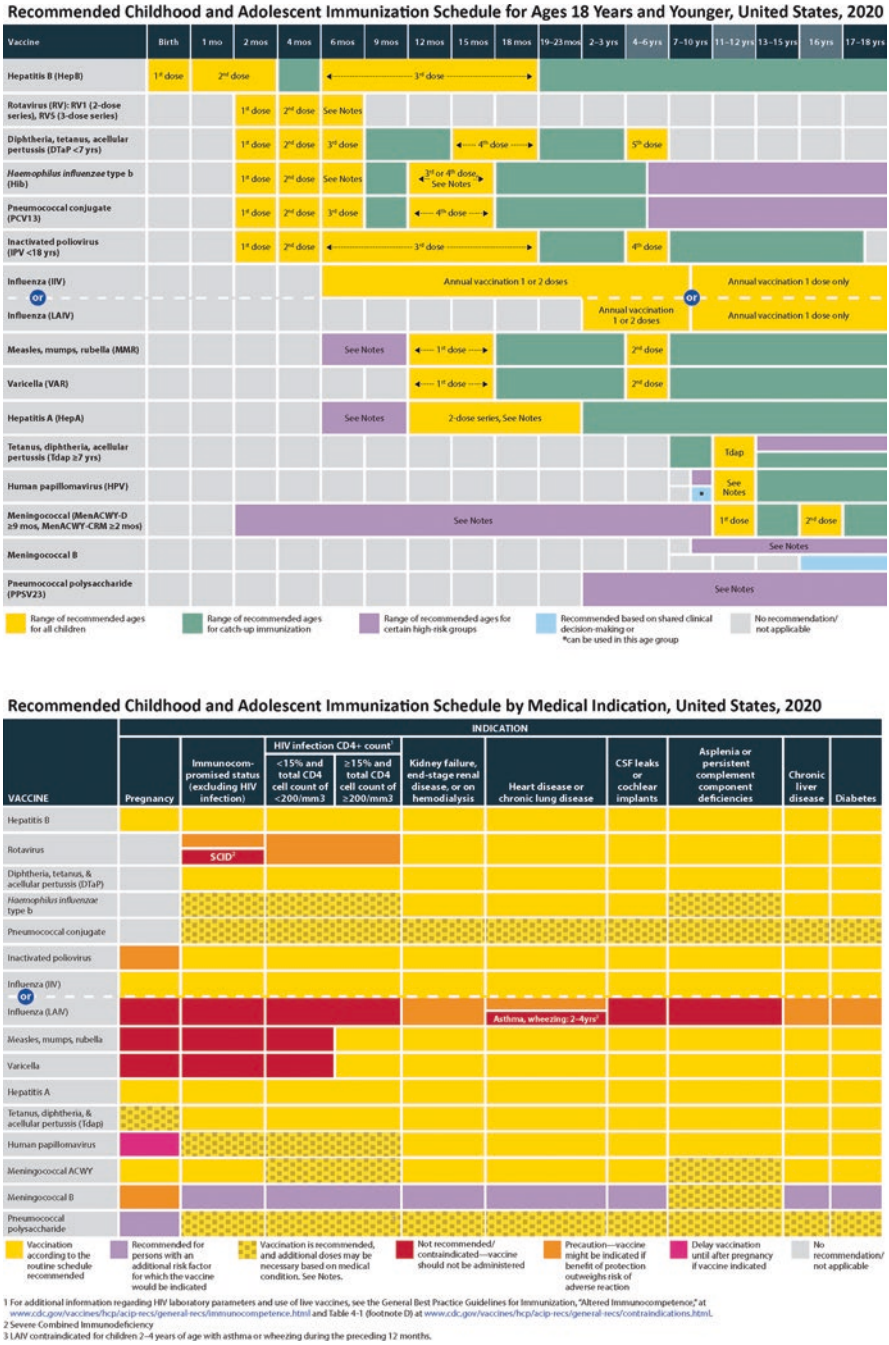

Fig. 1 Shown are the 2020 US recommended childhood immunization schedules by age (top panel) and by medical indication (bottom panel). (Source: Centers for Disease Control and Prevention. The figures are available on the agency website at no charge: https://www.cdc.gov/vaccines/schedules/index.html. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the U.S. Government, Department of Health and Human Services, or Centers for Disease Control and Prevention.)

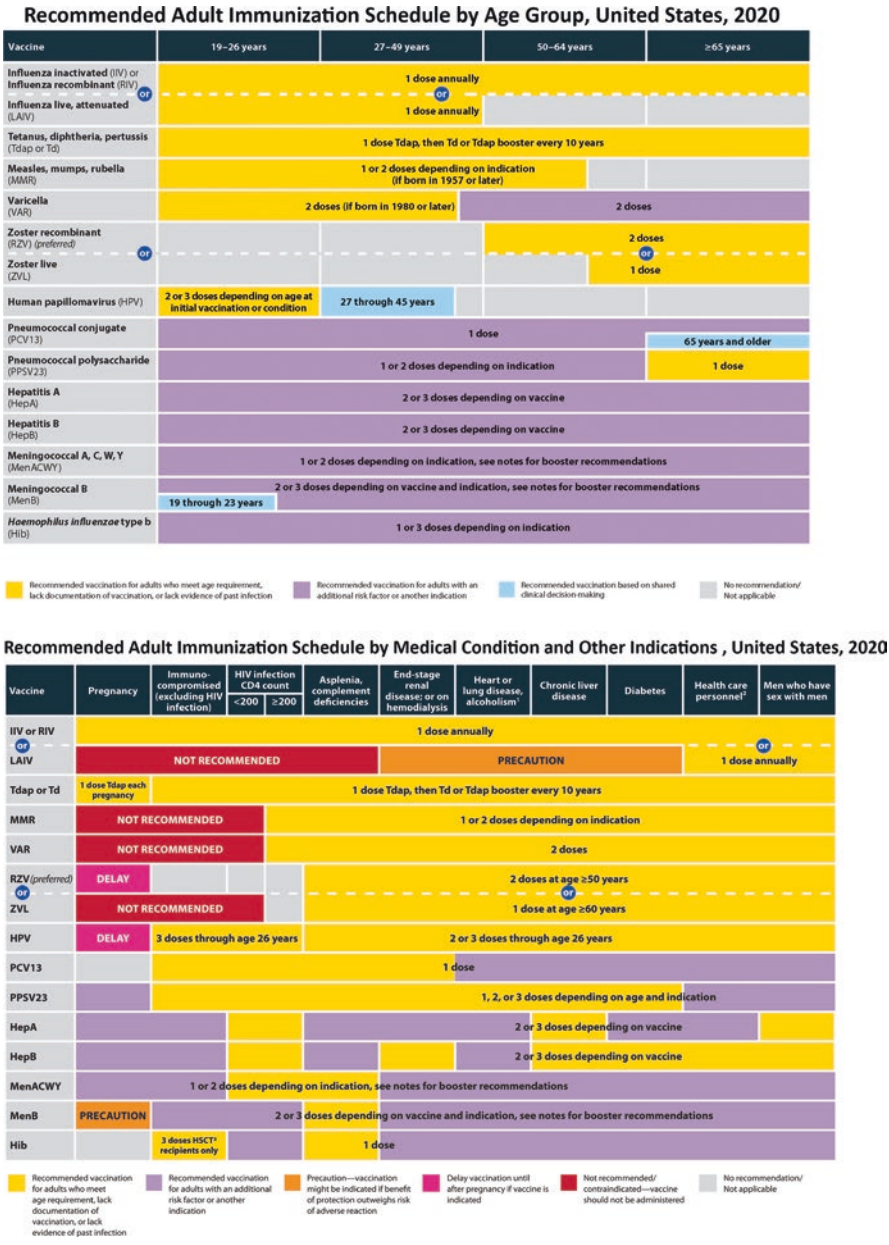

Fig. 2 Shown are the 2020 US recommended adult immunization schedules by age (top panel) and by medical condition and other indications (bottom panel)

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Part I
The Basics of Preventing Infection Through Immunization

Chapter 1
The Immune Response to Infection

Joseph Domachowske

Introduction

The terms "vaccination" and "immunization" are often used interchangeably, but there is an important difference in their formal definitions. The term immunization refers to the act of administering a medical product to an individual with the goal of providing or enhancing the recipient's protection against an infectious agent. Vaccination, on the other hand, refers to the act of administering a medical product to an individual with the goal of eliciting a protective response against an infectious agent. As such, vaccines function by inducing the recipient's immune system to generate protective responses. The similarity between the two definitions explains why the terms are commonly used as synonyms for one another. It is accurate to state that all vaccinations are a form of immunization. It is also accurate to state that most, but not all, immunizations are vaccinations because some medical products provide protection to the recipient without eliciting an immune response. The following definitions are helpful in circumstances when the subtle differences between the terms vaccination and immunization require a higher level of precision:

Passive immunization The administration of a medical product to an individual that provides or enhances protection against a foreign substance without inducing an immune response.

Active immunization The administration of a medical product to an individual that elicits a protective immune response against an infectious agent; synonymous with vaccination.

Vaccination A synonym for active immunization.

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Vaccinology A biomedical discipline encompassing all aspects of active and passive immunization

Using the term "vaccinology" to describe the discipline encompassing all aspects of active and passive immunization may seem counterintuitive because the formal definitions for vaccine and vaccination specifically exclude passive immunization. While "immunizationology" might convey the more precise definition, the term has never been used. Just as the terms vaccination and immunization are widely used interchangeably, "vaccinology" is widely used and accepted to include all aspects of active and passive immunization.

The current US recommended immunization schedules show the age at which each vaccine series should begin and the ideal range for the time interval between each dose (Fig. 1.1). An appreciation for the rationale behind these recommendations can be achieved through the careful study and understanding of key concepts from the disciplines of biochemistry, immunology, microbiology, and infectious disease epidemiology. To begin, it is first important to gain a general understanding of the immune response to infection, because the same principles apply to the protective immune responses that can be achieved with vaccination.

Overview of the Human Immune Response

When the human immune system encounters substances that are not recognized as self, a series of events are triggered to ward off the perceived invasion. Collectively, these events are referred to as the immune response. Innate immune responses encompass protective pathways that are elicited immediately, but are short-lived and not specific. In contrast, the adaptive immune response involves triggering pathways to recognize, clear, and remember a specific target. The immune response during and following a first infection or exposure leads to the formation of immune memory, thus allowing for more rapid and more efficient responses to subsequent challenges from the same agent. Vaccines are designed to trigger the precise adaptive immune responses necessary to confer durable protection from infections caused by specific pathogens. Adaptive immunity has two major components. The humoral immune response refers to the pathways necessary for the production of antibodies, while the cellular immune response refers to the development of cytotoxic and helper T lymphocytes.

The Humoral Immune Response

Globular proteins known as antibodies are the key component of the humoral immune system. These "immune globulins" comprise four polypeptide chains joined together to form a Y-shaped molecule. The part of each antibody that forms the arms of the Y is referred to as the Fab fraction; the stem of the Y is referred to as

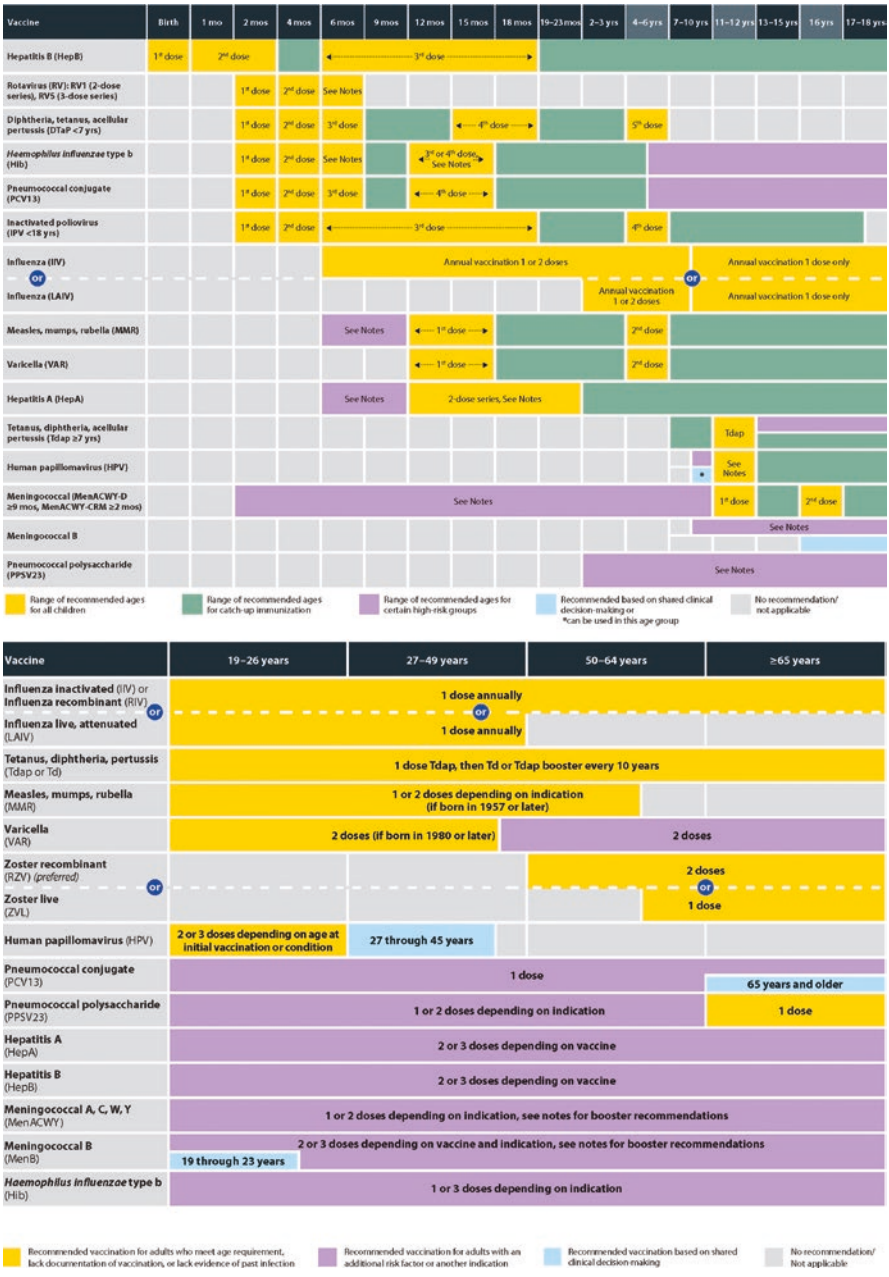

Fig. 1.1 2020 Recommended immunization schedules for children and adolescents (top panel) and for adults (bottom panel). (Source: Centers for Disease Control and Prevention. This material is available on the agency website at no charge: https://www.cdc.gov/vaccines/schedules/index.html. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the US Government, Department of Health and Human Services, or Centers for Disease Control and Prevention)

the Fc portion. By design, the amino-acid sequence at the top of the Y varies from one antibody to the next. This variability gives each antibody a unique tertiary conformation in that region, allowing it to recognize and bind to a highly specific target. Foreign substances capable of triggering an immune response are known as antigens. The target moieties of each antigen that are recognized by the variable regions of specific antibodies are termed epitopes. Each antibody binds best to a single epitope. The process of antibody binding to the surface epitope of a virus or a toxin may lead to neutralization by blocking the ability of the offending agent to enter its target cell. Antibodies can also recognize epitopes expressed by bacterial cells. The process whereby antibodies bind to and coat bacterial cells is called opsonization. The Fab portions of the antibodies bind epitopes on the surface of the bacterium, while the Fc portions of the antibodies remain free to bind to Fc receptors. Fc receptors are present on monocytes, macrophages, and neutrophils, among others. The Fc portions of antibodies coating the bacterial cell are recognized by recruited phagocytes, thereby facilitating phagocytosis. Once ingested, phagocytes kill most types of bacteria quite efficiently. Some bacteria are killed extracellularly, via antibody-dependent cell-mediated cytotoxicity, a process that does not require phagocytosis.

Antibodies are divided into five isotypes: immunoglobulin (Ig) M, Ig G, Ig A, Ig D, and Ig E. Each isotype has a different primary function. The IgG isotype is further divided into four subclasses: IgG subclass 1, 2, 3, and 4. The immune function of each of the IgG subclasses overlaps substantially; however, there are key differences important to understanding concepts in vaccinology that will be presented later in this chapter. During the humoral immune response to infection, pathogen-specific IgM is the first immunoglobulin isotype to be produced.

While production and release of IgM begins almost immediately upon recognition of the offending pathogen, antibody of this isotype is of low affinity. Effective and efficient high-affinity recognition of an offending pathogen requires the IgM-producing cells to undergo an antibody isotype switch to produce IgG. Most often, the isotype class switch is then followed by a complex series of cellular events essentially designed to "fine-tune" the neutralizing quality of the IgG. This process, known as antibody affinity maturation, is described in more detail below. Effective humoral immune responses to subsequent challenges by the same pathogen occur much more quickly, since immune memory allows for rapid production of high-affinity IgG antibody without the need to go through the more time-consuming steps of isotype switching and affinity maturation. This immune memory explains, in part, why humans with healthy immune systems are unlikely to develop infections with the same pathogen more than once.

Production of Antibodies That Bind a Specific Target

Plasma cells, derived from B lymphocytes (B cells), are the cellular factories that produce all isotypes of antibodies. During B cell development, the genes that encode the most variable segments of the antibody Fab fragments undergo a series of genetic rearrangement events. This process leads to the formation of a vast repertoire of B cell clones, each with their own unique antibody specificity. When a B cell

clone encounters its antigenic match, it becomes activated. One of two major pathways ensue depending on the nature of the antigen recognized by that B cell.

Upon encountering its antigenic match, most B cell clones migrate to the germinal centers of the spleen or lymph nodes. There, under the direction of T lymphocytes (T cells), the B cells undergo differentiation into either memory B cells or plasma cells. Those that transform into plasma cells begin to produce large amounts of antibody. At first, the antibody produced is all of the low-affinity (germline) IgM isotype. Cell-to-cell contact with a T cell signals the B cell to switch from producing IgM to producing IgG. As the B cells continue to proliferate under these conditions, they undergo a process called somatic hypermutation, randomly producing a series of antibodies with varying affinities for the original target. Those expressing the highest-affinity antibodies are selected for clonal proliferation. The result of the added affinity maturation step is the production of a B cell population capable of producing antibodies with higher affinity for the epitope than the original germline B cell. Future exposures to a pathogen that expresses an identical epitope lead to a rapid and robust memory response. The price paid for the higher-affinity antibody and the development of immune memory is the time necessary for the sequence of steps to be completed: typically about 3–4 weeks.

Some B cell activation and differentiation take place outside of the germinal centers of the spleen or lymph nodes, a process referred to as an extrafollicular type response. Extrafollicular responses proceed in the absence of T cell help. Germline B cell clones that recognize polysaccharide epitopes are the most important example. When such a B cell encounters its antigenic match to a polysaccharide antigen, the cell undergoes an extrafollicular type response, which, by definition, occurs in the absence of T cell involvement. The B cell clone proliferates and rapidly transforms into a plasma cell to begin producing germline (low-affinity) antibody, predominantly of the IgM isotype. In the absence of T cell help, affinity maturation does not occur, so the antibody produced is identical to the low-affinity germline antibody. Moreover, without T cell involvement, immune memory fails to develop. Over a period of months to years, plasma cells that were generated as a result of this process slowly die off. Subsequent rechallenge with an identical polysaccharide epitope in the future, at best, results in the same short-lived, low-affinity response. Frequent, repeated challenges with the same polysaccharide epitopes can result in complete or near-complete depletion of the germline B cell clones that are capable of recognizing the antigen. In their absence, a complete failure to respond to future challenges with those antigens is seen. In vaccinology, the phenomenon of observing a paradoxical reduction in serum antibody concentrations following repeated doses of a polysaccharide vaccine is referred to as vaccine hyporesponsiveness.

The Cellular Immune Response: The Role of T Helper Cells

Antigen-presenting cells (APCs) participate in the innate immune response by migrating through tissues searching for molecules that have conformational patterns or sequences only found on pathogens and other nonself substances. When an agent expressing a pathogen-specific molecular pattern is encountered, the APC engulfs

and digests it. Small peptides are taken from the digestion products and loaded strategically on the surface of the cell into the groove of the cell's major histocompatibility complex class II (MHC-II) molecule. The APC migrates to a local or regional lymph node via the lymphatic vessels to "present" the encountered peptide to a T helper cell. Each T helper cell recognizes a specific MHC-II/peptide moiety via interactions of its unique T cell receptor and CD4 coreceptor. The vast diversity of unique TCR-binding affinities is generated during fetal development through a random process similar to the generation of B cell germline clones with unique and specific antibody-binding affinities. When a T helper cell encounters and recognizes it "matching" unique MHC-II/peptide moiety of an APC, it becomes activated and matures into one of two antigen-specific cell subtypes: T helper type 1 (Th1) or T helper type 2 (Th2). Both Th1 and Th2 cells have direct antimicrobial activity. In addition, Th1 cells seek out cytotoxic T cells (discussed below) and "help" them kill the target that they both now recognize, such as a virus. In parallel, Th2 cells migrate to the spleen or lymph nodes, seeking out their B cell counterparts. Once they encounter their B cell match, Th2 cells "help" some of them undergo immunoglobulin isotype class switching and affinity maturation, and others to undergo transition into memory B cells. Memory B cells reside in the spleen and lymph nodes, remaining quiescent for very long periods. If or when the memory B cell encounters its specific antigen again, it immediately proliferates. The clones differentiate into plasma cells that rapidly produce large quantities of high-affinity IgG antibody. This rapid and highly efficient memory B cell activity is called an anamnestic response.

The Cellular Immune Response: The Role of Cytotoxic T Cells

Cytotoxic T cells, like T helper cells, are lymphocytes that express a T cell receptor (TCR) on their surface. As previously described, each TCR has unique specificity for a specific antigen that is encoded during germline development. The coreceptor expressed on the surface of cytotoxic T cells is the CD8 molecule. The CD8 coreceptor directs the cytotoxic T cell's unique TCR to engage a matching peptide-loaded MHC class I molecule. Like MHC-II, MHC-I loads pathogen-derived peptides into its groove, and then presents the MHC-I/peptide moiety on its surface. The peptides loaded onto MHC-I molecules are not derived from digestion products of engulfed proteins, but instead are produced inside the infected cell. All viruses are obligate intracellular pathogens, and several bacterial pathogens have evolved to survive intracellularly for prolonged periods of time. MHC-I molecules are expressed on the surface of all cell types; therefore, all cell types are capable of expressing peptide loaded MHC-I on their surface should they become infected with an intracellular pathogen, such as a virus. Cytotoxic T cell clones that express the unique TCR capable of recognizing the specific MHC-1/peptide complex on the surface of the infected will find, bind to, and engage the infected cell. The cell-to-cell contact activates the cytotoxic T cell. In order for activated cytotoxic T cells to kill a cell recognized to be infected, it must also receive "help" from activated Th1

Table 1.1 Key characteristics of T helper and T cytotoxic lymphocytes

T cell subset	Unique antigen-specific TCR	Coreceptor used to engage MHC	Class of MHC engaged when loaded with peptide	Source of peptide bound by the MHC
T helper cell	Yes	CD4	MHC-II	Digestion products of engulfed extracellular proteins
Cytotoxic T cell	Yes	CD8	MHC-I	Produced inside the cell

Table 1.2 Examples of the size and complexity of four human pathogens

Infectious disease	Pathogen	Genome type	Genome size	Encoded proteins	Surface
Paralytic polio	Poliovirus	ssRNA	7.5 kb	~10	Protein capsid of repeating trimers of VP1, 2, and 3
Smallpox	Variola virus	dsDNA	186 kbp	~200	Complex 3-layered envelope
Meningitis	*H. influenzae* type b	DNA	1985 kbp	~1900	Polysaccharide capsule of polyribosylribitol phosphate
Streptococcal pharyngitis	*Streptococcus pyogenes*	DNA	1841 kbp	~1850	>70 surface proteins

cells in the form of cell signaling molecules called cytokines. Key characteristics of T helper and T cytotoxic lymphocytes are summarized in Table 1.1.

Protective Immune Responses Following Infection: Surrogates of Immunity

The humoral and cellular immune responses to infection are directed against antigens expressed by that pathogen. Infectious agents vary in size and complexity (Table 1.2). Viruses, for example, have smaller genomes and express fewer proteins than bacteria. A number of pathogens in both groups have evolved to express virulence factors as effective strategies to evade host defenses. Bacterial genomes encode thousands of proteins. During infection, an individual's immune system responds to exposed antigenic sites on the surface of the bacteria and on the proteins that are secreted by the organism. Immune responses to the epitopes on each of antigenic sites vary in magnitude. Those associated with the most robust responses are referred to as *immunodominant epitopes*. Antibodies generated against immunodominant epitopes are not always neutralizing, explaining why individuals who are seropositive (antibody positive) for a particular agent are not necessarily immune to reinfection.

Example 1: Poliovirus

Poliovirus is a 30-nanometer nonenveloped icosahedral protein capsid that surrounds a single strand of RNA 7500 nucleotides in length. The RNA genome is translated as a single polypeptide that undergoes posttranslational cleavage into 10 viral proteins. The capsid surface is composed of repeating VP 1, VP 2, and VP 3 trimers. The structural conformation formed by adjacent VP 1 moieties in the capsid binds to the poliovirus receptor (CD155) on the surface of target cells to initiate infection. Antibodies generated in response to vaccine or infection that bind to and sterically block this interaction prevent subsequent infection. Such antibodies are said to be *neutralizing*. Neutralizing antibodies are generally protective.

Example 2: Haemophilus influenzae *Type b*

H. influenzae type b is a good example of a bacterial pathogen that evolved to express a virulence factor to evade host defenses. The organism produces and secretes a polysaccharide capsule comprised of polyribosylribitol phosphate. The capsule surrounds the bacterial cell protecting it from effective opsonization and phagocytosis. Polysaccharides like polyribosylribitol phosphate are weak immunogens in older children and adults, and are not immunogenic in children less than 2 years of age. In the prevaccine era, invasive *H. influenzae* type b caused ~20,000 cases of invasive infection in young children in the USA alone. Half of these infections were associated with bacterial meningitis. Advances in biotechnology during the late 1980s led to the development of *H. influenzae* type b vaccines that are safe and effective to use in infants starting at 6 weeks of life. The key development leading to the success was to link the polyribosylribitol phosphate capsular polysaccharide to a simple peptide (tetanus toxoid). The immune system processes the protein-conjugated polysaccharide in a T-cell-dependent manner, thereby allowing a robust response, even during infancy, that includes IgG affinity maturation and the development of immune memory against an antigen that would otherwise be processed in the usual extragerminal manner. Invasive infections caused by *H. influenzae* type b are now very uncommon across every region of the world where vaccine programs have been introduced. The vast majority of the fewer than 100 cases now seen annually in the USA occur in children who are underimmunized, too young to be fully immunized, or subsequently found to have an inherited immunodeficiency.

Example 3: Streptococcus pyogenes

S. pyogenes, or group A β-hemolytic *Streptococcus*, remains a common cause of bacterial pharyngitis especially in school-age children that can lead to development of infectious and noninfectious complications. Infection is associated with the development of pathogen-specific antibodies, but the response does not confer

immunity to reinfection. *S. pyogenes* expresses more than 70 surface and secreted proteins. The ease at which immunodominant responses are detected serologically is well known, because antibody testing is commonly used as diagnostic proof of recent infection (antistreptolysin O or ASO, anti-DNase B, and/or anti-hyaluronidase titers). Unfortunately, even robust antibody responses to these and other group A β-hemolytic streptococcal antigens have not been found to be reliable surrogates of protective immunity. A better understanding of the correlates for protective immunity is necessary for the successful future development of a vaccine.

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Chapter 2
Passive Immunization

Joseph Domachowske

Introduction

Following certain high-risk exposures, coadministration of both passive and active immunization is required to optimize protection. Under these circumstances, the passive immunization (antibody) and the first (or missing) dose of active immunization needed for the primary series are given as soon as the exposure is recognized. Additional doses of active immunization are then scheduled to complete the primary series according to recommended dosing intervals.

Short-term protection against certain infections can be achieved by passive immunization by the administration of antibodies. The antibodies present in the injection or infusion bind to and neutralize the pathogen, thereby preventing infection, or neutralize a toxin, thereby treating an ongoing toxin-mediated process. The main benefit of using this strategy to prevent infection is that the protection conferred is immediate. Passive immunization, therefore, is ideal for individuals who are exposed to a preventable infection, but have not been previously vaccinated. Despite the benefit of providing immediate protection, passive immunization suffers from two major shortcomings. First, the protection afforded is brief. Most antibodies have a circulating half-life of ~20 days. As the concentration of the antibody provided by the injection declines over time, the protective effect wanes. Ongoing, or re-exposure to the same pathogen would require repeated dosing to maintain protection if active immunization is not or cannot be provided. Second, when passive immunization is successful in preventing infection, the individual's immune system does not engage, so adaptive immunity does not develop.

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Passive Immunity and Newborns

During the 3rd trimester of pregnancy, maternal immunoglobulin G (IgG) is actively transported across the placenta from the mother to the fetus. The process begins at approximately 28 weeks gestational age (GA), slowly becoming more efficient as the pregnancy progresses. By 36 weeks GA, fetal IgG levels approximate those of the mother. Transplacental active transport of IgG continues until birth explaining why term infants, born at 40 weeks GA, typically have umbilical cord blood IgG concentrations that exceed maternal IgG levels by 20%.

Healthy adults have a mean total serum IgG concentration of ~1000 mg/dL. Mean cord blood IgG levels are dependent on the newborn's GA. Premature infants born at or before 28 weeks are endowed with little or no maternal IgG, those born between 29 and 35 weeks GA have mean cord blood IgG concentrations well below maternal levels, and those born at 36 weeks GA or later have cord blood IgG concentrations that meet or exceed maternal levels.

Maternal IgG contains high-quality (affinity-matured) antibodies directed against a repertoire of pathogens and vaccines to which the mother has been exposed. Maternally derived, transplacental antibodies provide term infants with a broad range of passive humoral immune protection during the first several months of life as they begin to mount their own active immune responses to the vaccines and pathogens they encounter.

Passive Immunity Administered Therapeutically

Beyond the newborn period, passive humoral immunity can be provided medically, when necessary, using various antibody preparations. Passive immunization formulations are available for the prevention of an array of infections and for the treatment of envenomation following certain bites and stings. Available products can be grouped into three main categories:(1) pooled human immunoglobulin (IgG), (2) hyperimmune globulin, and (3) monoclonal antibodies. Indications for their use depend on the specific target for neutralization, the timing of or potential for an exposure, and a variety of host specific details such as immune competence, age, prior active immunization history, and underlying risk factors for severe illness, among others.

Pooled Human Immunoglobulin (IgG)

Pooled human IgG, derived from plasma, was first used in the early 1950s as an intramuscular injection for the treatment of X-linked agammaglobulinemia (Bruton disease). Patients with this condition lack B lymphocytes, so they do not produce

immunoglobulins. The deficiency in circulating antibody places these individuals at high risk for the development of severe sinopulmonary and gastrointestinal infections. Infections caused by encapsulated bacteria (e.g., *Streptococcus pneumoniae, Haemophilus influenzae, Salmonella spp.*) are especially problematic. Other inherited humoral (antibody) immune deficiencies that are associated with hypogammaglobulinemia (low serum IgG) or the production of normal amounts, but poor-quality, IgG share clinical characteristics with Bruton disease. Immunoglobulin treatment for this group of primary immunodeficiencies is now administered by intravenous or subcutaneous infusion. Regular treatment with replacement IgG infusions reduces the frequency and severity of bacterial infections in these patients by conferring transient passive immunity reflective of the infection and active immunization status of the general population (or more accurately, of the donor group). Since the half-life of human IgG is less than 3 weeks, the protective effect of each infusion wanes quickly. Ongoing protection requires life-long replacement at monthly (or more frequent) intervals.

Intramuscular, intravenous, and subcutaneous immunoglobulin products all contain IgG that is collected, purified, and pooled from blood donated by thousands of individuals. The final products are >90% IgG, with trace amounts of immunoglobulin A (IgA) and/or immunoglobulin M (IgM). Several different intramuscular, intravenous, and subcutaneous preparations are approved by the Food and Drug Administration (FDA) for the prevention of infections in patients with primary humoral immunodeficiencies. Immunoglobulin intravenous (IgIV) infusions can also be considered for HIV-infected children who are experiencing recurrent bacterial infections. Excellent reviews on the medical indications for immunoglobulin infusions other than for passive protection from infectious diseases can be found in the suggested readings.

Adverse Reactions to IgIV

As many as 25% of individuals will experience one or more adverse reactions during an infusion with IgIV. Patients may develop fever, headache, chills, cough, or muscle aches. Most reactions are mild, transient, and self-limiting. Slowing the infusion rate helps in most situations. Relief can also be achieved by administering diphenhydramine and acetaminophen or ibuprofen. Some patients respond better to the use of glucocorticoids. Premedication with one or more of these drugs may help to reduce or eliminate reactions during subsequent infusions. Rarely, an anaphylactic reaction occurs. In such instances, the infusion should be stopped. Appropriate resuscitative measures should be implemented immediately including the administration of epinephrine, isotonic fluid support, diphenhydramine, and glucocorticoids.

Some patients experience adverse reactions 1–2 days following the infusions. Headache is common, resulting from IgIV-associated aseptic meningitis. This chemical irritation can usually be managed easily with nonsteroidal

anti-inflammatory drugs (NSAIDs) such as ibuprofen. Some patients respond best to migraine rescue medications in the triptan group (e.g., sumatriptan). Others benefit from treatment with glucocorticoids. Systemic complaints of malaise with or without myalgia are also reported fairly regularly. NSAIDs are generally effective. Since many of these infusion and postinfusion adverse reactions are product-specific, switching to an alternate for subsequent dosing may offer relief. Trial and error are typically necessary to determine which product(s) and which premedication regimens work best for individuals.

Immunoglobulin Subcutaneous (IgSC)

Pooled immunoglobulin products have also been formulated to be administered via subcutaneous infusion. Rates of systemic adverse reactions are generally much lower than seen with IgIV preparations. Patients do not require placement of an intravenous catheter. Subcutaneous placement of the small gauge catheters is not technically difficult, so most patients self-administer the infusions at home. The volume administered per site is limited, so multiple sites on the abdomen and legs are used, and rotated with subsequent doses. Dosing intervals vary from daily to once every 2 weeks.

Immunoglobulin Intramuscular (IgIM)

Immunoglobulin intramuscular (IgIM) preparations are no longer used as a treatment for primary humoral immune deficiency because the volume that can be injected into the muscle limits dosing. The current role for the use of IgIM is limited to specific circumstances where passive prophylaxis is desired for susceptible individuals following exposure to hepatitis A, measles, or rubella (Table 2.1).

Table 2.1 Recommendations for the use of pooled human immunoglobulin intramuscular (IgIM)

Exposed to	Timing	Indication	Comments
Hepatitis A	Within 14 days of exposure	Immunocompromised Chronic liver disease Less than 12 months or more than 40 years of age	Healthy individuals 12 months through 40 years of age who are not previously immunized should receive hepatitis A vaccine, not IgIM
Measles	Within 6 days of exposure	Not previously immunized Immunocompromised	Vaccine eligible individuals 12 months and older should receive MMR vaccine, not IgIM if within 72 hours of initial exposure
Rubella	ASAP[a]	Rubella-susceptible pregnant women	Should only be offered for those who decline a therapeutic abortion

[a]Congenital rubella syndrome has occurred even when IgIM is administered soon after exposure

Adverse Reactions to IgIM

Injection site discomfort is expected, and can be reduced by administering the dose at room temperature. Some recipients experience transient flushing, headache, or nausea. Allergic reactions are uncommon. Anaphylaxis is rare. Those who have received IgIM doses for other reasons in the past are more likely to experience fever and chills. IgIM should not be administered to individuals known to have selective IgA deficiency because of the risk for developing anti-IgA antibodies. Such individuals are at risk for developing an anaphylaxis reaction from subsequent infusions of blood products containing IgA.

Hyperimmune Globulins

Hyperimmune globulins are pooled immunoglobulin products prepared from the plasma of donors known to have high concentrations of antibody directed against a specific target. These products are administered to susceptible individuals following a suspected or known exposure to a specific pathogen or toxin. Administration of hyperimmune globulin delivers short-term, but immediate, neutralizing antibody. The more commonly used, and most familiar, hyperimmune globulins are used to target tetanus toxin and hepatitis B, rabies, and varicella viruses. These products are derived from pooled plasma collected from human donors and are easily recognized by their product descriptions, tetanus immune globulin (TIG), hepatitis B immune globulin (HBIG), rabies immune globulin (RIG), and varicella zoster immune globulin (VariZIG).

Unlike IgIV, IgIM, and IgSC, not all hyperimmune globulin products are derived from human blood donors. The origins and targets for available hyperimmune globulins are summarized in Table 2.2. For example, hyperimmune globulins used for the treatment of foodborne and wound botulism, and those used for the treatment of diphtheria, are derived from horses that have been hyperimmunized (i.e., given multiple doses of diphtheria toxoid) for the purpose of harvesting and purifying the

Table 2.2 Source and targets of available hyperimmune globulins

	Human origin		Animal origin: commonly called antitoxins
Target of the high-titer antibody	Hepatitis B surface antigen	Botulinum toxins A + B	Diphtheria toxin
	rabies virus	cytomegalovirus	botulinum toxins A thru G
	tetanus toxin	vaccinia virus	toxins associated with various envenomations[a]
	varicella virus		

[a]Bites from black widow spiders, rattlesnakes, coral snakes, and stings from scorpions; most administered intravenously. Black widow antitoxin is given intramuscularly

desired product. Similarly, the "antivenins" and "antitoxins" used for the treatment of some poisonous snake and spider bites and scorpion stings are hyperimmune globulins derived from horses or sheep.

As noted, some hyperimmune globulins are used therapeutically, while others are used for prevention of illness following a known or suspected exposure. Products that are specifically designed to bind to and neutralize toxin, such as botulism antitoxin, work best when administered early in the toxin-mediated disease process. Most, but not all, hyperimmune globulins that are administered to prevent transmission of an infection, following an exposure, are used in combination with active vaccination (Table 2.3). The hyperimmune globulin provides immediate, passive, and transient protection for the 2–3 week period needed for the active vaccination to initiate durable immunity.

Table 2.3 Use of hyperimmune globulins for the prevention and treatment of infectious diseases

Product	Nickname	Route[a]	Indications	Co-administer active vaccine?
Botulinum antitoxin bivalent A + B	Baby-BIG, BIG-IV	IV	Infant botulism	N/A, no vaccine available
Botulinum antitoxin heptavalent A − G	BAT	IV	Foodborne, wound, and other noninfant forms of botulism	N/A, no vaccine available
Cytomegalovirus immune globulin	CMV-Ig	IV	Prevention of CMV in seronegative organ transplant recipients from a seropositive donor	N/A, no vaccine available
Diphtheria antitoxin	none	IV	Treatment for diphtheria, in combination with antibiotics	YES, but later during convalescence
Hepatitis B immune globulin	HBIG	IM	Prevention of hepatitis B transmission following exposure, if not previously immunized	YES
Rabies immune globulin	RIG	IM[b]	Prevention of rabies transmission following exposure, if not previously immunized	YES
Tetanus immune globulin	TIG	IM	Prevention of tetanus following a tetanus-prone injury for anyone who has received fewer than 3 doses of tetanus vaccine	YES
Vaccinia immune globulin	VIG	IV	Complications following smallpox vaccination	NO
Varicella zoster immune globulin	VariZIG	IV	Prevention of varicella in susceptible, high-risk individuals within 10 days of exposure	NO

[a]*IV* intravenous, *IM* intramuscular

[b]As much of the dose as possible should be infiltrated directly into the wound. Any remaining volume should be given IM

Monoclonal Antibodies

When the immune system is challenged with an antigen, such as a vaccine, a number of different B-cell clones are activated. Each of the activated B-cell clones produces antibodies directed against different epitopes of the antigen. This results in a polyclonal antibody response, defined as the collection of different antibodies that recognize different binding sites on the same antigen. In the laboratory, it is possible to identify and isolate each of those B-cell clones. Each individual B-cell clone produces antibody with a single affinity directed against a specific epitope of the antigen. Antibodies produced by a single B-cell clone are referred to as monoclonal. A B-cell clone that is found to produce an antibody with desired characteristics can be immortalized using special laboratory techniques, and then used as a cellular "factory" to produce large quantities of the monoclonal antibody for therapeutic indications.

More than 80 different therapeutic monoclonal antibodies have been approved for use by the US FDA for use in humans, with hundreds of others currently under evaluation in various phases of human clinical trials. The vast majority of these specialized products are used or being developed to treat malignancies, autoimmune diseases, and metabolic disorders. At the time of this writing, only ~6% of approved monoclonal antibody products target the prevention or treatment of infectious diseases (Table 2.4). Of those listed, palivizumab is the only one that is widely used.

Respiratory Syncytial Virus: RSV

Palivizumab was the first monoclonal antibody to gain FDA licensure (1998) for the prevention of an infection. Infections caused by its target pathogen, respiratory syncytial virus (RSV), are severe enough to require hospitalization in 1–2% of the US birth cohort each winter. Hospitalization rates among some high-risk infant populations exceed 12%. Like other antibody-based prophylaxis, the protection conferred by palivizumab is passive and short-lived. As such, high-risk infants, such as those born prematurely, are recommended to receive monthly intramuscular dosing of palivizumab during "RSV season" (see http://bit.ly/2kwhSpF). This strategy reduces RSV-associated hospitalizations by ~54%. A safe and effective active vaccine for the prevention of infant RSV infection has remained elusive; therefore, monthly intramuscular injections of palivizumab have remained the standard of care for high-risk infants for more than 20 years. In an effort to improve on the modest success of palivizumab, new-generation, investigational monoclonal RSV antibodies have been developed. Nirsevimab is a fully human monoclonal RSV antibody that was strategically modified during development to offer several advantages. First, amino acids were modified in the Fab region to optimize its capacity to neutralize RSV. Next, 3 amino acids were modified in the Fc region to extend its half-life such that one dose could offer protection for an entire season. Phase 2b clinical

Table 2.4 Monoclonal antibodies used for the prevention of infectious diseases

	Palivizumab	Nirsevimab	Raxibacumab	Obiltoxaximab	Bezlotoxumab	Ibalizumab
Year approved	1998	BTD	2012	2016	2016	2018
Source	Humanized	Human with strategic modifications[a]	Human	Chimeric Mouse/ human	Human	humanized
Route of administration	IM	IM	IV	IV	IV	IV
Target	RSV F protein	RSV F protein	Anthrax toxin	Anthrax toxin	*Clostridioides difficile* toxin B	HIV-1
Indication	Prevents severe RSV disease	Prevents severe RSV disease	Treatment of inhalation anthrax[b]	Treatment of inhalation anthrax[b]	Prevents recurrence of *C. difficile* diarrhea	Treatment of HIV-1 infection[b]

BTD Breakthrough therapy designation by the US FDA, *IM* intramuscular, *IV* intravenous, *RSV* respiratory syncytial virus, *HIV* human immunodeficiency virus

[a]Modifications made to Fab fragment to enhance and broaden neutralizing activity; modifications of Fc fragment prolong serum half-life. Ongoing phase 3 trials due to complete enrollment in 2021

[b]In combination with anti-infective medications

trial results showing an 80% reduction in severe RSV infection and an excellent safety profile following a single intramuscular injection just prior to the start of RSV season have earned the product "breakthrough therapy designation" status by the US FDA. The designation expedites investigational drug development under Section 902 of the Food and Drug Administration Safety and Innovation Act when early clinical trial data suggest a substantial therapeutic advantage over existing options for serious or life-threatening diseases.

Anthrax

In the fall of 2001, letters containing anthrax spores were mailed to news media offices and to 2 US Senators. As a result, at least 22 people were infected; 5 died. The nefarious nature of the bioterrorism, and the scientific expertise needed to produce the highly purified spores, led to speculation that the bacteria could also be genetically modified to be resistant to penicillin and other antibiotics. Interest in developing therapeutic interventions for use in combination with antibiotics ultimately led to the development of monoclonal antibodies targeting anthrax toxin. Two different products, raxibacumab (2012) and obiltoxaximab (2016), have now been approved for the treatment of inhalation anthrax, but only in combination with antibiotics.

Clostridioides difficile

Bezlotoxumab, a monoclonal antibody directed against toxin B of *Clostridioides difficile*, was approved in 2016 as an intravenous infusion to prevent recurrent *C. difficile* diarrhea. During clinical trials, the coadministration of a second investigational monoclonal antibody directed against *C. difficile* toxin A offered no added benefit compared with the administration of bezlotoxumab alone.

Human Immunodeficiency Virus, HIV

Highly effective, well-tolerated, combination antiretroviral treatment regimens are available for the majority of patients who are infected with human immunodeficiency virus (HIV). Drug-resistant HIV strains are unlikely to emerge in those patients with good adherence to an effective regimen. A number of factors can lead to intermittent or prolonged interruptions in medication adherence. Patients who struggle with consistency in their medication regimen are at risk for developing multidrug resistance. Despite the growing armamentarium of available medications, identifying effective drug combinations can become challenging for those patients

infected with multidrug resistant strains. Ibalizumab is a monoclonal antibody approved for the treatment of multidrug resistant HIV type-1 when used in combination with other antiretroviral drugs. The antibody functions as an entry inhibitor by binding to CD4, the primary HIV receptor, and blocking virus from access to the CCR5 and CXCR4 coreceptors.

Conclusions

Passive immunity is a state of temporary protection against infection that occurs among individuals who receive antibodies from another source. Full-term infants are born with passive immunity from maternal IgG that is actively transported across the placenta during the 3rd trimester of pregnancy. Available pharmaceutical products used to provide passive immune protection are formulated with antibodies derived from humans or animals. Indications for their use depend on the specific pathogen(s) being targeted, the timing of or potential for an exposure, and various host factors such as immune competence, age, prior active immunization history, and underlying risk factors for severe illness, among others. Passive immune protection occurs immediately upon receipt of the antibody, but is temporary, waning over time. Ongoing protection requires repeat dosing at regular intervals (usually monthly), or, if appropriate and available, the administration of an active immunization series.

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Chapter 3
Active Immunization

Joseph Domachowske

Introduction

The goal of active immunization is to provide protective immunity if or when the individual is exposed to a specific pathogen. While the concept is straightforward, the process requires that the disease-specific immunogen(s) be delivered to the patient's immune system in a manner that has been optimized to achieve that goal. The immunogen(s) must be carefully selected as those capable of stimulating a protective response. They must be formulated in a manner that optimizes the quality of the protective responses. They must remain stable and sterile during any period of storage between manufacturing and use. Vaccine immunogens that are administered by the oral route must withstand passage through the low pH of the stomach, and those administered intranasally need to be formulated using a volume and consistency easily tolerated by the vaccine. Vaccine immunogens that are delivered by injection (intradermal, subcutaneous, or intramuscular) need to be prepared using volumes and viscosity that can be administered using a needle and syringe. Some require the addition of a substance called an adjuvant to enhance and modulate the immune response to the immunogen. The biologic and chemical processes needed to manufacture and purify active vaccine components are complex. Each vaccine immunogen must be produced in a highly controlled and regulated manner to ensure safety and consistency from lot to lot of the final product, year after year. The system, known as *Good Manufacturing Practice*, relies heavily on adherence to a series of detailed standard operating procedures and quality control measures. Active immunization programs, with the consistent and appropriate delivery of vaccines in our current armamentarium, are among the safest and most effective medical interventions available. Rigorous public health immunization efforts have led to the

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elimination of polio and measles from the Western hemisphere, and the complete global eradication of smallpox and 2 of 3 poliovirus types that cause paralytic polio. Today, more than 30 infectious diseases are vaccine-preventable. This chapter offers a review of the basic concepts of active immunization followed by detailed descriptions for the active components included in each of the available, US-approved vaccines.

The World's First Vaccine

Smallpox was a highly contagious airborne infection once endemic to nearly all regions of the world. Outbreaks and epidemics, once impossible to control, were associated with 30% mortality. High rates of complications were seen among survivors including disfiguring facial scars, vision loss, neurologic sequelae, infertility, and pregnancy loss. Long before the discovery of vaccines, it was well recognized that survivors of smallpox would not become reinfected during subsequent community outbreaks or epidemics, even when occurring many years later. A related, but more subtle, observation was instrumental in driving the development of the smallpox vaccine. Milkmaids, especially those who had previously developed a relatively mild occupational infection from cowpox, were routinely unaffected during community outbreaks of smallpox. The British physician Edward Jenner was among those who suspected that infection with, or exposure to, the related cowpox virus was the key to this protection. In 1796, a local milkmaid named Sarah Nelmes sought treatment from Jenner for cowpox lesions that she developed on her hand. Jenner collected material from the cowpox lesions and used it to inoculate his gardener's 8-year-old son, James Phipps. James, as anticipated, developed a cowpox lesion at the inoculation site on his arm. The lesion and associated low-grade fever both resolved without treatment after a few days. Two months later, Jenner challenged James with material he had collected from the smallpox lesions of another patient. The boy remained completely healthy after the challenge. He was immune to smallpox. In describing his work, Jenner first coined the terms "vaccine" and "vaccination," from the Latin word *vacca*, meaning cow.

Beyond Smallpox Vaccine: The Jennerian Approach

The Jennerian approach of using a replication competent agent to induce protective immunity to a related pathogen has led to the development of at least 17 live and live attenuated viral and bacterial vaccines that remain in widespread use today. As such, more than half of the vaccines that are currently available in the USA were born from vaccine theory in alignment with the original and highly successful Jennerian approach.

An almost equal number of vaccines currently available are based on alternative, non-Jennerian approaches. Inactivated whole virus vaccines have proven to be a highly effective strategy for the prevention of polio, hepatitis A, influenza, rabies, tick borne encephalitis, and Japanese encephalitis. Inactivated whole cell pertussis vaccines were instrumental in reducing morbidity and mortality from whooping cough starting in the 1940s and are still used in much of the developing world. Acellular pertussis vaccines that include as many as five immunogens extracted and purified from whole bacteria have replaced whole cell vaccines in most developed countries. Several other vaccines use pathogen-specific proteins or polysaccharides that have been purified from cultures of the pathogen or generated using recombinant DNA technology as the active vaccine ingredient. In each case, the active ingredient can only perform its function as the vaccine immunogen if it is manufactured and formulated correctly.

Active Vaccine Components

This section includes descriptions for how the active ingredients in available vaccines are manufactured. Headings identify the targeted disease(s), the pathogen that causes the disease, and the immunogen(s) included in the final vaccine product. An overview of the methods used to produce each immunogen follows. Additional detail regarding the role(s) of each of the inactive vaccine ingredients used during manufacturing is discussed in the next chapter. The classification of vaccines according to the nature of the immunogen(s) used to produce them is also summarized in Table 3.1.

Disease: Respiratory infections caused by adenovirus

Pathogen(s) causing human disease: Adenoviruses types 4 and 7

Immunogen(s) used in the vaccine: Selective, live strains of adenoviruses types 4 and 7 (not attenuated)

Selected strains of adenovirus types 4 and 7 are amplified individually in cell culture using WI-38 human-diploid fibroblasts. The fibroblasts are supported in culture using medium containing glucose, mineral salts, amino acids, and vitamins that has been supplemented with fetal bovine serum. When ready for harvest, the viruses are purified using filtration, and dried by lyophilization. Replication-competent, lyophilized virus is used as the immunogen in the final vaccine product. The vaccine is provided to the end user as two tablets, one containing adenovirus type 4, the other type 7 formulated with an enteric-coating to allow passage through the stomach so that the live virus in released in the intestine.

Disease: Anthrax

Pathogen(s) causing human disease: *Bacillus anthracis*

Immunogen(s) used in the vaccine: Sterile filtrate from cultures of *Bacillus anthracis*

The immunogen included in anthrax vaccine is produced from cell-free filtrates collected from cultures of *Bacillus anthracis.* A characterized and defined strain of

Table 3.1 Classification of vaccines according to the nature of the active component Shading indicates where vaccine formulations for the prevention of the same disease are available from more than one category

Vaccines to prevent viral infections				Vaccines to prevent bacterial infections							
Whole virus			Viral products	Whole bacteria			Bacterial products				
Live	Live attenuated	Inactivated	Recombinant	Live	Live attenuated	Inactivated	Native protein		Capsular polysaccharide		Recombinant protein
							Mixed	**Toxoid**	**Native**	**Conjugated**	
Adeno	Influenza	Influenza	Influenza	BCG	Cholera	Whole cell pertussis	Acellular pertussis	Diphtheria	PPSV	PCV	Men-B
RV5	RV1	Hepatitis A	Hepatitis B		Typhoid		Anthrax[a]	Tetanus	Typhoid	HIB	Plague
Smallpox	Polio	Polio	HPV					MCV4			
	MMR	Rabies									
	Yellow fever	JEV									
	Varicella	TBE									
	Zoster		Zoster								
	Dengue[b]										
	Ebola[b]										

Adeno Adenovirus, *RV5* pentavalent rotavirus vaccine, *RV1* monovalent rotavirus, *MMR* measles, mumps, rubella, *JEV* Japanese encephalitis virus, *TBE* tick-borne encephalitis virus, *HPV* human papillomavirus, *BCG* Bacille Calmette-Guérin, *PPSV* pneumococcal polysaccharide vaccine, *PCV* pneumococcal conjugate vaccine, *MCV4* meningococcal conjugate vaccine quadrivalent A, C, Y, W-135, *Men-B* meningococcal serotype B, *HIB Haemophilus influenzae* type b

[a]As culture filtrate

[b]Live chimeric virus vaccines

Bacillus anthracis bacteria is grown under microaerophilic conditions in a chemically defined, protein-free culture medium consisting of a mixture of amino acids, vitamins, inorganic salts, and sugars. At harvest, the culture medium containing the 83 kDa protective antigen (PA) and other proteins produced by the bacterium are separated by filtration. Sterile filtrate is used as the immunogen in the final vaccine product.

Disease: Cholera

Pathogen(s) causing human disease: *Vibrio cholerae*

Immunogen(s) used in the vaccine: Live attenuated *Vibrio cholerae*

The live attenuated bacteria used as the immunizing agent in oral cholera vaccine were generated by genetically modifying the *Vibrio cholerae* serogroup O1 Inaba strain 569B. The attenuating modifications prevent the bacteria from synthesizing active cholera toxin while retaining the ability to synthesize the immunogenic, but nontoxic subunit of the protein.

The vaccine strain bacteria are grown under carefully controlled conditions in culture medium containing casamino acids, yeast extract, mineral salts, and an antifoaming agent. At harvest, the bacteria to be used as the immunogen for the final vaccine product are concentrated using ultrafiltration.

Disease: Dengue

Pathogen(s) causing human disease: Dengue viruses types 1, 2, 3, and 4

Immunogen(s) used in the vaccine: Chimeric live attenuated yellow fever-dengue viruses encoding the premembrane and envelope proteins from dengue virus types 1, 2, 3, and 4.

Each of the four viruses used in the manufacturing of the quadrivalent live attenuated dengue vaccine was produced using recombinant DNA technology. The genes encoding the premembrane and envelope proteins in yellow fever vaccine strain virus 17D204 were removed and replaced with those encoding the homologous sequences of dengue virus serotypes 1, 2, 3, and 4. Each of the four chimeric yellow fever/dengue viruses is cultured separately in Vero cells. At harvest, each of the 4 culture supernatants is purified and concentrated to produce individual lots of each of the 4 immunogens to be used in the final vaccine product. The final vaccine product is prepared from a bulk lot after the 4 immunogens are combined using the correct ratio, and a stabilizer is added.

Disease: Diphtheria

Pathogen(s) causing human disease: *Corynebacterium diphtheriae*

Immunogen(s) used in the vaccine: diphtheria toxoid

Diphtheria toxin is produced from large bacterial cultures of toxigenic *Corynebacterium diphtheriae* grown under carefully defined conditions. At harvest, toxin is concentrated from the culture medium using ultrafiltration, then purified by ammonium chloride precipitation, and dialysis. Toxin is inactivated with formaldehyde to produce the bulk lot of diphtheria toxoid for use in several different combination vaccine products.

Disease: Ebola hemorrhagic fever

Pathogen(s) causing human disease: Ebola virus

Immunogen(s) used in the vaccine: live chimeric vesicular stomatitis virus expressing ebolavirus envelope glycoprotein

The Ebola virus vaccine currently approved by the US Food and Drug Administration is a live chimeric vesicular stomatitis virus expressing the envelope glycoprotein of the Kikwit strain of *Zaire ebolavirus*. The genetically engineered recombinant virus is amplified in cell culture using Vero cells. The Vero cells are maintained in serum-free cell culture medium. When ready, virus is harvested from the culture medium. Concentrated virus is purified, and then resuspended in stabilizer solution. The final product is used to fill unit dose vials, which are stored frozen. The vaccine is preservative-free.

Disease: Meningitis and other invasive infections caused by *Haemophilus influenzae type b*

Pathogen(s) causing human disease: *Haemophilus influenzae type b*

Immunogen(s) used in the vaccine: Capsular polysaccharide polyribosyl-ribitol-phosphate conjugated to a carrier protein

The capsular polysaccharide of *Haemophilus influenzae* type b is the high molecular weight polymer polyribosyl-ribitol-phosphate (PRP). PRP is prepared from large-scale cultures of a designated strain of encapsulated *H. influenzae* type b grown in a synthetic medium. Following heat inactivation and purification, PRP is covalently linked (conjugated) to either tetanus toxoid, to form PRP-T, or to the outer membrane protein complex (OMPC) of the B11 strain of *Neisseria meningitidis* serogroup B to form PRP-OMP. PRP conjugated to diphtheria toxoid (PRP-D) is used in some parts of the world.

Disease: Viral hepatitis A

Pathogen(s) causing human disease: hepatitis A virus

Immunogen(s) used in the vaccine: inactivated hepatitis A virus

A known strain of hepatitis A virus (HM175) is amplified in MRC-5 human diploid cells. At harvest, the virus-infected cells are lysed, and then purified by ultrafiltration and chromatography. Purified virus is then inactivated with formaldehyde to generate the vaccine immunogen.

Disease: Viral hepatitis B

Pathogen(s) causing human disease: hepatitis B virus

Immunogen(s) used in the vaccine: recombinant hepatitis B surface antigen

The immunogen used in hepatitis B vaccines is hepatitis B surface antigen (HBsAg). Molecular techniques were used to clone the DNA coding sequence for HBsAg into *Saccharomyces cerevisiae* yeast. The recombinant HBsAg-expressing yeast strain is grown in large fermentation vats using a culture medium containing yeast extract, peptones, dextrose, amino acids, and mineral salts. When the culture is ready for harvest, the yeast cells are disrupted, releasing the recombinant HBsAg protein. The immunogen is purified by a series of physical and chemical methods, treated with formaldehyde, and then coprecipitated with aluminum sulfate. The lot is then used to complete production of monovalent and combination hepatitis B vaccine containing vaccine doses.

Diseases: Cancers of the anus, cervix, oropharynx, penis, vagina, and vulva; genital warts; laryngeal papillomatosis

Pathogen(s) causing human disease: High-risk oncogenic human papillomavirus types 16, 18, 31, 33, 45, 52, 58, and others. Low-risk types, including 6 and 11, cause genital warts and laryngeal papillomatosis.

Immunogen(s) used in the vaccine: Recombinant virus-like particles comprised of HPV type- 6, 11, 16, 18, 31, 33, 45, 52, and 58-specific L1 capsid proteins.

The immunogens used in HPV vaccines are recombinant major capsid (L1) proteins that self- assemble into virus-like particles as they are being produced in vitro. The 9-valent HPV vaccine currently used in the USA contains virus-like particles that express L1 proteins from HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Molecular techniques were used to clone each of the 9 L1 DNA-coding sequences into *Saccharomyces cerevisiae* yeast. Each of the 9 recombinant L1-expressing yeast strains is grown in large fermentation vats using a culture medium containing vitamins, amino acids, mineral salts, and carbohydrates. Each culture is harvested separately. The yeast cells are disrupted to release the recombinant viral-like particles, which are then purified by a series of chemical and physical techniques. Each of the purified immunogens is adsorbed onto amorphous aluminum hydroxyphosphate sulfate, and then combined with each of the others in defined ratios to produce the final bulk suspension product.

Disease: Seasonal influenza

Pathogen(s) causing human disease: Many different influenza A and B viruses

Immunogen(s) used in the vaccine: Standardized by quantity of measured hemagglutinin from 2 subtype strains of influenza A [A(H1N1) and A(H3N2)] and 1 or 2 lineage strains of influenza B [B(Victoria) and B(Yamagata)] viruses presented in one of the following formulations: (1) split, inactivated viruses, (2) live attenuated viruses, or (3) purified, recombinant protein.

Influenza vaccines are currently produced in trivalent and quadrivalent formulations. The immunogens used in quadrivalent influenza vaccines include 2 subtype strains of influenza A [A(H1N1) and A(H3N2)] and 2 lineage strains of influenza B [B(Victoria) and B(Yamagata)] viruses. Trivalent influenza vaccines include the same 2 subtype strains of influenza A [A(H1N1) and A(H3N2)] and 1 of the same 2 lineage strains of influenza B [B(Victoria) and B(Yamagata)] viruses. Each year, influenza vaccine formulations undergo strain modifications based on recommendations from the World Health Organization, and the US Centers for Disease Control and Prevention.

Inactivated Influenza Vaccines

Egg-based and cell-culture-based technologies are used to produce inactivated influenza vaccines. The process used to generate egg-based influenza vaccines starts with inoculating embryonated chicken eggs with each of the selected strains of influenza virus. When ready for harvest, allantoic fluid containing high

concentrations of the virus is collected. Next, the virus is inactivated by treatment with formaldehyde, then concentrated, and purified using gradient centrifugation. Virus is then disrupted with a nonionic surfactant to produce a split virus preparation. The split virus is further purified, and then resuspended in phosphate-buffered saline. Split virus preparations of appropriate strains are then combined to produce the final trivalent or quadrivalent vaccine products. Standard inactivated influenza vaccines contain 15 mcg of hemagglutinin from each of the virus strains included as immunogens. High-dose inactivated influenza vaccines contain 60 mcg of hemagglutinin from each strain.

Cell culture technology has emerged as an alternative to egg-based technology for the manufacturing of inactivated influenza vaccines. The production of cell-culture-based influenza vaccine starts with inoculating suspension cultures of Madin Darby canine kidney cells with each of the selected strains of influenza virus. At harvest, cell culture supernatant containing high concentrations of the virus is collected. Next, the virus is inactivated with ß-propiolactone, disrupted using a detergent, and then purified using chemical and mechanical techniques. As with egg-based production technology, each strain is produced and purified separately before being pooled to formulate the final trivalent or quadrivalent influenza vaccine product. Like other standard inactivated influenza vaccines, cell culture produced influenza vaccine contains 15 mcg of hemagglutinin from each of the included virus strains.

Live Attenuated Influenza Vaccine

The immunogens included in the live attenuated influenza vaccine are adapted to replicate well at 25 °C while being restricted in replication at or above human core body temperature. Each year, four reassortant influenza strains are developed for use based on vaccine strain selection for the upcoming seasonal quadrivalent influenza vaccine. Reassortant strain production starts with a master donor influenza virus that has already been engineered and characterized as cold adapted, temperature sensitive and attenuated. Gene segments that encode for the hemagglutinin and neuraminidase glycoproteins are derived from the selected, antigenically relevant pool of influenza viruses. Accordingly, each of the four viruses used as immunogens in the quadrivalent live attenuated influenza vaccine maintains the replication characteristics and phenotypic properties of the master donor virus while also expressing the hemagglutinin and neuraminidase of the wild-type viruses related to strains expected to circulate during the coming influenza season.

Embryonated chicken eggs are inoculated with each of the four reassortant influenza vaccine strains and then incubated to allow vaccine virus amplification. To harvest, the allantoic fluid is collected and purified using filtration. Next, the virus is concentrated using ultracentrifugation, and then diluted to a working concentration with a stabilizing phosphate buffer to obtain the final sucrose and potassium phosphate concentrations. The viral harvests of each of the four reassortants are then filter-sterilized. Each of the monovalent bulk preparations is tested and verified

to retain cold adaptation, temperature sensitivity, and attenuating phenotypes before being combined at the desired potency. The bulk lot of combined quadrivalent vaccine is then used to fill individual sprayers for nasal administration.

Recombinant Influenza Vaccine

The coding sequences for the hemagglutinin gene products of interest are cloned into baculovirus vectors. Each of the recombinant baculoviruses is then used to transfect Sf9 insect cells growing in a defined serum-free culture medium containing lipids, amino acids, vitamins, and mineral salts. When cultures are ready to harvest, the baculovirus-encoded hemagglutinin proteins are extracted from the insect cells with a surfactant, and then further purified using column chromatography. Each of the recombinant hemagglutinins is produced and purified separately before being pooled to formulate the final trivalent or quadrivalent influenza vaccine product. Recombinant influenza vaccine is formulated to contain 45 mcg of each hemagglutinin.

Disease: Viral encephalitis

Pathogen(s) causing human disease: Japanese encephalitis virus

Immunogen(s) used in the vaccine: Inactivated Japanese encephalitis virus

Production of inactivated Japanese encephalitis vaccine begins with inoculating Vero cell cultures with a seed stock of a known strain of Japanese encephalitis virus. Cells are incubated, allowing for virus replication. When ready for harvest, cell culture supernatants are pooled, filtered, and then concentrated. The suspension is then fractionated using sucrose density gradient centrifugation. Fractions containing the highest yield are pooled, and then treated with formaldehyde to inactivate the virus. Once the lot is brought to the specified antigen concentration used in the final product, and formulated with aluminum hydroxide, it is ready to be used to fill unit dose syringes.

Disease: Measles

Pathogen(s) causing human disease: Measles virus

Immunogen(s) used in the vaccine: live attenuated measles virus

In the USA, measles vaccine is currently only available in combination with mumps and rubella vaccines. The immunogen in measles vaccine is a live, attenuated measles virus derived from the Enders' attenuated Edmonston strain. The vaccine strain virus is propagated in cultures of primary chick embryo fibroblasts grown in a buffered salt solution supplemented with vitamins, amino acids, and fetal bovine serum and stabilized with sucrose, phosphate, glutamate, and recombinant human albumin. Neomycin is added to prevent bacterial contamination during manipulation. Harvested virus is purified, concentrated, and then brought to the concentration of virus desired in the final vaccine product. Sorbitol and hydrolyzed gelatin are added as stabilizers to complete the production of the bulk lot of monovalent measles vaccine.

Disease: Meningococcal meningitis, and other invasive infections including meningococcemia.

Pathogen(s) causing human disease: *Neisseria meningitidis*

Immunogen(s) used in the vaccine(s): Type-specific capsular polysaccharides conjugated to a carrier protein are used in serotype A, C, Y, and W135 vaccines. One serotype B vaccine uses outer membrane vesicles containing porin A in combination with recombinant factor H binding protein, *Neisseria* adhesin A, and *Neisseria* heparin-binding protein; another used four different recombinant-factor-H-binding proteins.

Worldwide, a variety of monovalent and combination meningococcal vaccines are available for protection against invasive meningococcal infection caused by different capsular serotypes of the pathogen. Currently, in the USA, quadrivalent vaccines are used to immunize against *Neisseria meningitidis* capsular types A, C, Y, and W135, while multicomponent, monovalent vaccines are used to immunize against capsular serotype B disease.

The immunogens used to manufacture quadrivalent A, C, Y, W135 vaccines are derived from the polysaccharides that make up the capsule for each of the four serotypes covalently linked (conjugated) to either diphtheria toxoid or CRM_{197} (cross-reacting material 197) protein, a nontoxic mutant of diphtheria toxin.

Known strains of *N. meningitidis* A, C, Y, and W-135 are each grown separately in defined bacterial culture media. When ready for harvest, the capsular polysaccharides are extracted using detergents and alcohols, and then separated from the bacterial cells using centrifugation.

After the polysaccharides undergo depolymerization by hydrolysis and reductive amination, they are filter-purified. The purified products are then covalently linked to either diphtheria toxoid or CRM197 protein (manufacturer dependent). The serogroup-specific glycoconjugates produced from each of the four bacterial cultures are combined in the correct ratios to produce the final quadrivalent conjugated meningococcal vaccine products.

Like *N. meningitidis* serotypes A, C, Y, and W-135, *N. meningitidis* serotype B produces a capsule that is rich in polysaccharides, but its specific biochemical structure is quite similar to human polysialic acid. The result of this molecular mimicry is that serogroup B capsular polysaccharide is poorly immunogenic because it is recognized as self. As a result, the currently available monovalent serotype B vaccines do not contain type-specific capsular polysaccharide. The two formulations of *N. meningitidis* serogroup B vaccines that are currently available are very different multicomponent products with only minimal overlap. Despite their differences in immunogens, they have been shown to be safe and effective in preventing invasive serogroup B disease. One combines four immunogens, all produced using recombinant technology. The other combines bacterial outer membrane vesicles (OMVs) with three recombinant proteins as immunogens.

The immunogens used for the production of four-protein recombinant meningococcal serogroup B vaccine include different variants of lipidated-factor-H-binding protein (fHBP). The genes for each of the four proteins were introduced into *E. coli* expression systems. Each of the four *E. coli* recombinants is grown in liquid media

under defined conditions to a specific density. The cultures are harvested, and the recombinant proteins are extracted and purified using chromatography. The four purified recombinant fHBP proteins are combined in the desired ratios in the presence of polysorbate 80 as an emulsifier, and loaded into syringes for use as individual doses.

The other available meningococcal serogroup B vaccine is produced using a single recombinant fHBP in combination with recombinant *Neisseria* adhesin A (NadA), and recombinant *Neisseria* heparin-binding antigen. The three recombinant proteins are produced from cultures of recombinant *E. coli,* and then extracted and purified using chromatography. Outer membrane vesicles are produced by culturing a characterized strain of *N. meningitidis* that expresses a known outer membrane porin protein, called PorA. At harvest, bacteria are inactivated with deoxycholate, a surfactant that also mediates the formation of OMVs. The primary immunogens included in the final vaccine include fHBP, NadA, *Neisseria* heparin-binding antigen, and PorA. The antigens are adsorbed onto aluminum hydroxide as an adjuvant.

The PorA- containing OMVs included in the final product also carry a number of lesser protein immunogens that are not clearly defined. The 3 purified recombinant immunogens are combined in the required rations with 25 mcg of the OMV preparation per dose to formulate the final vaccine product.

Disease: Mumps

Pathogen(s) causing human disease: Mumps virus

Immunogen(s) used in the vaccine: Live attenuated mumps virus

The immunogen used in mumps vaccine is the live attenuated Jeryl Lynn™ strain of mumps virus. The vaccine strain virus is propagated in cultures of primary chick embryo fibroblasts grown in a buffered salt solution supplemented with vitamins, amino acids, and fetal bovine serum and stabilized with sucrose, phosphate, glutamate, and recombinant human albumin. Neomycin is added to prevent bacterial contamination during manipulation. Harvested virus is purified, concentrated, and then brought to the concentration of virus desired in the final vaccine product. Sorbitol and hydrolyzed gelatin are added as stabilizers to complete the production of the bulk lot of monovalent mumps vaccine. In the USA, mumps vaccine is currently only available in combination with measles and rubella vaccines.

Disease: Pertussis, or whooping cough

Pathogen(s) causing human disease: *Bordetella pertussis*

Immunogen(s) used in the vaccine: Whole cell pertussis vaccines contain inactivated *Bordetella pertussis*. Acellular vaccines include inactivated pertussis toxin alone or together with one or more of the following purified native bacterial proteins: pertactin, filamentous hemagglutinin, and a mixture of fimbria agglutinogen types 2 and 3

Whole cell inactivated pertussis vaccines were introduced in the 1930s, and are still used throughout the developing world today. Acellular pertussis vaccine formulations became widely available in the early 1990s, gradually replacing the use of whole cell inactivated vaccines in most developed countries.

The manufacturing of whole cell inactivated pertussis vaccine begins with growing a characterized strain of *Bordetella pertussis* in a defined bacterial culture medium. The timing of harvest is dictated by the turbidity (opacity) of the liquid culture medium. Bacterial lots that meet quality control indices for purity and opacity are killed and detoxified using a method approved by the country's national regulatory authority, such as heat inactivation or chemical treatment with glutaraldehyde. Sterility and lack of toxicity are verified by culture and bioassay, respectively, and the final product is prepared by adjusting its opacity to a predefined optical density known to contain the desired concentration of killed bacterial cells. Whole cell pertussis vaccines are estimated to contain approximately 3000 different antigens. The number of these antigens that serve as immunogens when the vaccine is administered is unknown, but likely number in the hundreds.

Acellular pertussis vaccines used throughout the world have included between 1 and 5 of the following immunogens: pertussis toxin (inactivated), filamentous hemagglutinin, pertactin, fimbria type 2, and fimbria type 3. The manufacturing process starts with growing a characterized strain of *Bordetella pertussis* in defined bacterial culture media. Subsequent steps are carried out, as needed, depending on which of the 5 immunogens are to be included in the final vaccine product. Pertussis toxin (inactivated) and filamentous hemagglutinin are produced and released by the bacterium into the culture supernatant. Supernatant is collected and processed to concentrate them. Fimbrial agglutinogens and pertactin are extracted directly from the bacterial cells using heat and flocculation. Each of the pertussis antigens is then precipitated using ammonium chloride, and ultrafilter-purified. Filamentous hemagglutinin is treated with formaldehyde, and pertussis toxin is inactivated with glutaraldehyde. Residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed separately onto aluminum phosphate as an adjuvant, and then combined for use as a bulk stock for the production of acellular pertussis containing combinations vaccines (e.g., DTaP-HepB-IPV, DTaP-HIB-IPV) Monovalent pertussis vaccine is no longer available for use in the USA.

Disease: Plague

Pathogen(s) causing human disease: *Yersinia pestis*

Immunogen(s) used in the vaccine: Recombinant fusion product of *Yersinia pestis* F1 capsular and virulence (V) proteins expressed in *E. coli*

A vaccine for the prevention of plague, an infection caused by the bacterium *Yersinia pestis* was approved by the US Food and Drug Administration as an "orphan drug." The antigen used in the vaccine is a fused recombinant protein referred to as rF1V. The coding sequences for *Y. pestis* F1 capsular and virulence (V) proteins were cloned into *E. coli*. Recombinant *E. coli,* expressing the fused rF1V protein, are grown in a defined bacterial liquid culture medium. rF1V that is isolated and purified from the cultures is formulated with a 2% aluminum hydroxide wet gel suspension as an adjuvant to produce the immunogen for a final vaccine product.

Disease: Pneumococcal meningitis, pneumonia, bacteremia, and other forms of invasive disease.

Pathogen(s) causing human disease: *Streptococcus pneumoniae*

Immunogen(s) used in the vaccine: 13 purified serotype-specific pneumococcal polysaccharides conjugated to a carrier protein (conjugate vaccine) or 23 serotype-specific pneumococcal polysaccharides (pure polysaccharide vaccine)

Vaccines currently manufactured for the prevention of invasive pneumococcal disease are available as two different formulations. The immunogens included in the 23-valent pneumococcal polysaccharide vaccine are pure capsular polysaccharides. The immunogens included in the 13-valent conjugate pneumococcal vaccine are capsular polysaccharides that have been individually, covalently linked (conjugated) to CRM_{197} protein. For both vaccine formulations, the manufacturing process begins with culturing each of the desired *S. pneumoniae* serotypes in a defined soy peptone broth. When ready for harvest, the individual polysaccharides from each of the cultures are purified using physical and chemical means. From this point, the manufacturing steps differ between the 23-valent pneumococcal polysaccharide vaccine and the 13-valent conjugate pneumococcal vaccine.

To complete production of the 23-valent pneumococcal polysaccharide vaccine, purified polysaccharide immunogens representing pneumococcal serotypes, 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F, are combined in the correct ratio using saline. Phenol is added as a preservative to a final concentration of 0.25%.

To complete production of the 13-valent conjugate pneumococcal vaccine, each of the individual 13 purified polysaccharides is chemically depolymerized, and then conjugated to CRM_{197} protein using reductive amination. Each of the 13 resulting glycoconjugates is then purified using ultrafiltration and column chromatography before being combined in the desired saccharide to protein ratios, to formulate the final vaccine product containing pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F conjugated to CRM_{197}.

Disease: Paralytic poliomyelitis

Pathogen(s) causing human disease: Poliovirus type 1. Poliovirus type 2 was globally eradicated in 2015; poliovirus type 3 was globally eradicated in 2019

Immunogen(s) used in the vaccine: Live attenuated polio virus types 1, 2, and/or 3 or inactivated polioviruses types 1, 2, and/or 3

Inactivated trivalent polio vaccine remains the standard for polio prevention in the USA; however, live attenuated bivalent and trivalent vaccines continue to be used in other parts of the world.

The immunogens included in the manufacturing of inactivated trivalent polio vaccines are derived from well-characterized strains of the three poliovirus types 1, 2, and 3. Each virus is propagated individually in cell culture. The eukaryotic cells (e.g., Vero cells, WI-38 fibroblasts) used to support growth of the virus are grown in carefully formulated culture medium. When ready for harvest, cell culture supernatants containing high concentrations of each of the amplified polioviruses are clarified and concentrated using filtration, and then purified using liquid chromatography. Each of the monovalent viral suspensions is then inactivated using chemical exposure to formalin for a minimum of 12 days. Inactivated viral suspensions are then

adjusted to the desired immunogen concentration before being combined in ratios required in the final inactive polio vaccine formulation for injection.

Live-attenuated poliovirus vaccines are manufactured using cell culture to amplify specific Sabin strains of attenuated poliovirus types 1, 2, and/or 3 that are known to be derived from original seed stocks. The manufacturing processes used to amplify, harvest, clarify, and concentrate each strain of virus are similar to that used to produce inactivated polio vaccines. Instead of proceeding next to virus inactivation steps, the monovalent viral suspensions of Sabin strain viruses are used directly to produce doses of live attenuated mono-, bi-, and trivalent polio vaccines in formulations suitable for oral administration.

Disease: Rabies encephalitis

Pathogen(s) causing human disease: Rabies virus

Immunogen(s) used in the vaccine: Inactivated rabies virus

Both formulations of rabies vaccine that are currently used in the USA use inactivated rabies virus as the immunogen. The two vaccines are derived from separate and distinct strains of virus amplified using cell culture techniques. One manufacturer amplifies virus in MRC-5 fibroblasts, and the other uses primary chicken embryo fibroblasts. The fibroblasts are grown in synthetic cell culture medium containing human albumin. Antibiotics are included to prevent contamination. When ready for harvest, virus is concentrated and purified using physical techniques (ultrafiltration or centrifugation in a sucrose density gradient). Both manufacturers use β-propiolactone to inactivate the virus. A stabilizing solution is added and the final product is freeze-dried in unit dose vials without preservatives. The lyophilized vials are provided to the end user along with a 1 mL vial of sterile water for injection to be used for reconstitution.

Disease: Rotavirus gastroenteritis

Pathogen(s) causing human disease: Rotaviruses

Immunogen(s) used in the vaccine: Either live attenuated rotavirus serotype G1P[8] or five different live human-bovine reassortant viruses

The two oral formulations of live rotavirus vaccine currently available in the USA are formulated quite differently: one as a monovalent live attenuated human rotavirus and the other as five live human-bovine reassortant rotaviruses.

The immunogen included in the monovalent, live attenuated rotavirus vaccine is derived from a pathogenic G1P[8]-type human rotavirus. The attenuated vaccine strain is amplified in cell culture using Vero cells. The Vero cells are supported using liquid culture medium containing glucose, sodium pyruvate, L-cystine, L-tyrosine, L-glutamine, other amino acids, vitamins, and mineral salts. When ready, virus is harvested, concentrated, and purified. Sorbitol and sucrose are added as stabilizers prior to freeze-drying the final product. Lyophilized vaccine is provided to the end user along with a liquid diluent containing sterile water, calcium carbonate, and xanthan. The vaccine is preservative-free.

In contrast, the immunogens included in the pentavalent vaccine are reassortants derived from viruses that were originally isolated from humans and cows. Four of the reassortants in the vaccine express one of the outer capsid proteins (G1, G2, G3,

or G4) from the human rotavirus parent strain and the attachment protein (type P7) from the bovine rotavirus parent strain. The fifth reassortant virus expresses the attachment protein type P[8], from the human rotavirus parent strain and the outer capsid protein of type G6 from the bovine rotavirus parent strain. The result is a vaccine containing 4 human-bovine reassortant rotaviruses G1P7, G2P7, G3P7, G4P7, and G6P8 where either the attachment protein or the outer capsid protein is bovine-derived. The 5 reassortant viruses are amplified in Vero cells using techniques similar to those described above. When ready, virus is harvested, concentrated, and purified. The reassortants are resuspended in a buffered solution containing sucrose and polysorbate 80 as stabilizers to produce the final product. The vaccine is preservative-free.

Disease: Rubella infection including congenital rubella syndrome

Pathogen(s) causing human disease: Rubella virus

Immunogen(s) used in the vaccine: Live attenuated rubella virus

The Wistar RA 27/3 strain of live attenuated rubella virus is used as the immunogen for rubella vaccine. The vaccine strain virus is propagated in cultures of WI-38 human diploid lung fibroblasts grown in a buffered salt solution supplemented with vitamins, amino acids, and fetal bovine serum and stabilized with recombinant human albumin. Neomycin is added to prevent bacterial contamination during manipulation. Harvested virus is purified, concentrated, and then brought to the concentration of virus desired in the final vaccine product. Sorbitol and hydrolyzed gelatin are added as stabilizers to complete the production of the bulk lot of monovalent rubella vaccine. In the USA, rubella vaccine is currently only available in combination with measles and mumps vaccines.

Disease: Smallpox

Pathogen(s) causing human disease: Variola virus

Immunogen(s) used in the vaccine: Vaccinia virus

The smallpox vaccine that is currently approved for use in the USA is live vaccinia virus. The vaccine virus currently used as the immunogen in smallpox vaccine is derived from an archived stock of the vaccine used in the USA until the 1970s. Virus is amplified in Vero cells that are supported in defined cell culture medium that includes human serum albumin and antibiotics. When ready for harvest, virus is concentrated and purified, and then freeze-dried in vials as unit doses. Lyophilized vaccine is provided to the end user along with a vial of sterile water containing 50% glycerin as stabilizer and 0.25% phenol as a preservative. To administer the vaccine, the lyophilized virus is reconstituted with the diluent provided. A stainless-steel bifurcated needle is dipped into the reconstituted vaccine, and used to jab the skin 15 times, a technique called scarification. Smallpox remains the only vaccine administered in this manner.

Disease: Tetanus

Pathogen(s) causing human disease: *Clostridium tetani*

Immunogen(s) used in the vaccine: Tetanus toxoid

The production of tetanus vaccine requires growing *Clostridium tetani* in liquid culture medium under conditions that encourage optimal toxin production. When

ready to be harvested, the culture medium containing the toxin is separated from the bacteria by filtration, and then purified by fractionation with ammonium sulfate, dialysis, gel filtration, ion exchange chromatography, or a combination of these biochemical techniques. Next, the concentrated, now purified tetanus toxin is inactivated. Exposure to the proper concentration of formaldehyde for the proper period of time partially denatures the toxin. These changes in the tertiary structure of the toxin covert the toxigenic protein to a toxoid protein. The tetanus toxoid retains immunogenicity but is rendered nontoxic. Amino acids, such as lysine or glycine, may be added to facilitate crosslinking and prevent reversion. After purification and sterilization, the product is tested for sterility, purity, toxicity, and reversion to toxicity. During the final step, tetanus toxoid is adsorbed onto an aluminum salt adjuvant. The final product can be used, as is, to fill unit dose syringes for administration as monovalent tetanus vaccine, or combined with other immunogens. Final preparation of all tetanus-toxoid-containing combination vaccines, including Td, Tdap, DT, DTaP, DTaP-IPV, DTaP-HepB-IPV, DTaP-HIB-IPV, and DTaP-HepB-HIB-IPV, requires that each of the necessary immunogens be prepared and quality tested separately.

Disease: Tickborne encephalitis

Pathogen(s) causing human disease: Tickborne encephalitis virus

Immunogen(s) used in the vaccine: Inactivated tickborne encephalitis virus

The immunogen in tickborne encephalitis vaccine is whole inactivated virus. Vaccine manufacturing begins with amplifying a well-characterized TBE virus using cell cultures of chick embryo fibroblasts. Fibroblasts are grown in a defined cell culture medium with antibiotics added to prevent bacterial contamination. Harvested virus is concentrated by ultracentrifugation and purified using chromatography. Purified virus is inactivated using formaldehyde, and then adsorbed to aluminum hydroxide as an adjuvant. Improvements in purification procedures, including the addition of continuous flow zonal density gradient centrifugation, have substantially reduced vaccine reactogenicity.

Disease: Tuberculosis

Pathogen(s) causing human disease: *Mycobacterium tuberculosis*

Immunogen(s) used in the vaccine: Live bacteria in the form of Bacille Calmette-Guérin (BCG)

Bacille Calmette-Guérin (BCG) is the only vaccine available worldwide for the prevention of tuberculosis

The immunogens included in BCG are live, attenuated bacteria derived from well-characterized strains of *Mycobacterium bovis*. The TICE® strain of *M. bovis* that is used for the vaccine manufactured in the USA was developed at the University of Illinois from a strain originating from the Pasteur Institute in Paris, France. The TICE® BCG are grown in broth culture medium containing glycerin, asparagine, citric acid, potassium phosphate, magnesium sulfate, iron ammonium citrate, and lactose. When grown to the necessary density, the bacteria are lyophilized. The final vaccine product is provided to the end user in unit dose vials of freeze-dried bacteria

standardized to contain 1×10^8 colony-forming units along with a separate vial of sterile water for injection to be used as the diluent for reconstitution. BCG vaccine is preservative-free.

Disease: Typhoid or typhoid fever (not to be confused with typhus)

Pathogen(s) causing human disease: *Salmonella enterica subsp. enterica* serovar Typhi; less formally, and more frequently referred to as *Salmonella typhi*

Immunogen(s) used in the vaccine: Two formulations are available. One contains purified bacterial surface Vi polysaccharide, the other is a mixture of live and nonviable attenuated *S. typhi* bacteria.

Two formulations of vaccines are available in the USA for the prevention of typhoid, an infection caused by the bacterium *Salmonella enterica subsp. enterica* serovar Typhi. The immunogen used for the vaccine that is administered by injection is purified bacterial surface Vi polysaccharide. The alternative formulation is a live attenuated vaccine that is taken by mouth.

Manufacturing of the typhoid Vi polysaccharide vaccine starts with growing the well-characterized Ty2 strain of *S. typhi* in defined semisynthetic liquid culture medium supplemented early on with casein-derived proteins, carbohydrates, and amino acids. When the fermentation process is complete, the bacteria are inactivated by chemical treatment with formaldehyde. Capsular polysaccharide is extracted and precipitated from concentrated culture supernatant by adding hexadecyltrimethylammonium bromide. Extracted bacterial capsular polysaccharide is then purified using differential centrifugation. Phenol 0.25% is added as a preservative.

The live attenuated typhoid vaccine is manufactured using a bacterial strain known as *Salmonella typhi* Ty21a. This vaccine strain is grown in fermenters under controlled conditions using a broth culture medium supplemented with dextrose, galactose, yeast extract digest, and a digest of acid-treated casein. When fermentation is complete, the bacteria are separated from the culture medium using centrifugation, and then resuspended in a stabilizing solution containing sucrose, ascorbic acid, and amino acids to the desired concentration. The prepared live attenuated bacteria are freeze-dried, mixed with lactose and magnesium stearate, and then loaded into enteric-coated gelatin capsules.

Varicella and Shingles

Disease(s): Varicella, or chickenpox; zoster, or shingles

Pathogen(s) causing human disease: Varicella zoster virus

Immunogen(s) used in the vaccine: A live attenuated varicella virus vaccine is used to prevent chickenpox. Two formulations of vaccine are available for the prevention of shingles. One is a live attenuated varicella virus; the other contains recombinant varicella zoster virus surface glycoprotein E (gE)

The varicella vaccine used in the USA comprises the Oka/Merck strain of live attenuated varicella virus. The original, virulent wild-type varicella virus was isolated from a child with varicella infection. Attenuation was achieved using the classic method in virology of adapting the virus to grow in laboratory cell culture by

first growing it under ideal laboratory conditions using a human cell line. After the virus became well adapted to growing in a human embryonic cell line, it was passaged to embryonic guinea pig cell cultures. The adapted virus was then passaged to WI-38 cell cultures. Serial passage of the adapted, attenuated virus was completed in MRC-5 cells to prepare the seed stocks for manufacturing varicella vaccine. Manufacturing of varicella vaccine lots involves amplifying a seed stock of the live attenuated virus in cell cultures of MRC-5 cells maintained in culture media supplemented with bovine calf serum. Antibiotics are included to prevent bacterial contamination. When ready for harvest, the virus is concentrated and purified. Sucrose, processed porcine gelatin, and urea are added as stabilizers; then the virus is lyophilized and provided to the end user in unit dose vials containing a minimum of 1350 plaque-forming units (PFUs) of the live attenuated varicella virus. A vial of sterile diluent, to be used for reconstitution of the lyophilized vaccine virus, is provided with each dose. The vaccine is preservative-free.

The live attenuated zoster vaccine is manufactured using the same methodology used to produce varicella vaccine. The only major difference is that the unit doses of the final product contain a minimum of 19,400 PFUs of the Oka/Merck varicella virus (14 times more than varicella vaccine). Lyophilized vaccine is provided to the end user in unit dose vials paired with a vial of sterile diluent to be used for reconstitution. The vaccine is preservative-free.

The immunogen used for the recombinant zoster vaccine is a genetically engineered, varicella zoster virus surface glycoprotein E. A truncated form of the gene encoding the virus surface glycoprotein E was stably transfected into Chinese hamster ovary cells. Cells expressing the truncated surface glycoprotein E are grown in synthetic cell culture media supplemented with amino acids. When ready for harvest, the recombinant protein is concentrated and purified using column chromatography. Purified protein is formulated with sucrose as a stabilizing agent, and then lyophilized. Lyophilized vaccine is provided to the end user in unit dose vials paired with a vial of $AS01_B$ adjuvant suspension to be used for reconstitution. $AS01_B$ adjuvant suspension is a liposomal formulation of QS-21, a saponin purified from the plant *Quillaja Saponaria* and 3-O-desacyl-4′-monophosphoryl lipid A (MPL). The liposomes are composed of cholesterol and dioleoylphosphatidylcholine (DOPC) in phosphate-buffered saline. The vaccine is preservative-free.

Disease: Yellow fever

Pathogen(s) causing human disease: Yellow fever virus

Immunogen(s) used in the vaccine: Live attenuated yellow fever virus

Yellow fever vaccine is produced by amplifying the attenuated 17D-204 strain of yellow fever virus in embryonated chicken eggs. When ready for harvest, allantoic fluid containing the virus is collected and the virus is purified and concentrated, and then resuspended in a stabilizing solution containing sorbitol and gelatin. The product is lyophilized in unit dose vials containing a minimum of 4.74 log10 plaque-forming units of the live attenuated virus. Lyophilized vaccine is provided to the end user in unit dose vials paired with a vial of sterile saline for injection to be used for reconstitution. The vaccine is preservative-free.

References

Links to Package Inserts for US Food and Drug Administration Approved Vaccines

Adenovirus

https://www.fda.gov/media/80211/download.

Anthrax

https://www.fda.gov/vaccines-blood-biologics/vaccines/biothrax.

Cholera

https://www.fda.gov/media/128415/download.

Dengue

https://www.fda.gov/media/124379/download.

Diphtheria, Tetanus, Pertussis

https://www.fda.gov/media/75157/download.
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Ebola

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Haemophilus influenzae type B

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Hepatitis A

https://gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Havrix/pdf/HAVRIX.PDF.
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https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Twinrix/pdf/TWINRIX.PDF.

Hepatitis B

https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Engerix-B/pdf/ENGERIX-B.PDF.
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Human Papillomavirus

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Influenza

http://labeling.seqirus.com/PI/US/Afluria/EN/Afluria-Prescribing-Information-QIV.pdf.
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Japanese Encephalitis

https://www.fda.gov/media/75777/download.

Measles, Mumps, Rubella

https://www.merck.com/product/usa/pi_circulars/m/mmr_ii/mmr_ii_pi.pdf.
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Meningococcus

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Pneumococcus

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Polio

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Rabies

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Rotavirus

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Smallpox

https://www.fda.gov/media/75792/download.

Tickborne Encephalitis

http://mri.cts-mrp.eu/download/AT_H_0126_001_FinalPL.pdf.

Tuberculosis

https://www.merck.com/product/usa/pi_circulars/b/bcg_vaccine/bcg_pi.pdf.

Typhoid

https://www.vaccineshoppe.com/image.cfm?doc_id=9372&image_type=product_pdf.
https://www.fda.gov/media/75988/download.

Varicella and Shingles

https://www.merck.com/product/usa/pi_circulars/v/varivax/varivax_pi.pdf.
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https://www.merck.com/product/usa/pi_circulars/z/zostavax/zostavax_pi2.pdf.

Yellow Fever

https://www.vaccineshoppe.com/image.cfm?doc_id=13799&image_type=product_pdf.

Chapter 4
Vaccine Additives and Excipients

Joseph Domachowske

Introduction

Inactive substances included in vaccines are referred to as excipients. The microbiologic and biochemical methods needed to harvest, purify, and formulate vaccine immunogens for the end user are different for each vaccine. Specially formulated culture media containing various supplements are needed to support the growth of bacteria, yeast, and a variety of cell types. Chemical manipulations are performed to extract desired proteins, polysaccharides, or lipids. Treatment with inactivating agents may be necessary to neutralize viruses, bacteria, or toxins. During the final stages of vaccine production and formulation other substances, such as adjuvants, stabilizing solutions, buffers, and/or preservatives may be added. The goals of this chapter are to review the main categories of vaccine excipients, to list and define each of the specific excipients that are present in vaccines, and to describe why excipients are necessary and important for vaccine production.

Two Main Categories of Excipients

The two main categories of vaccine excipients are (1) residual concentrations of substances used during manufacturing and (2) substances added to the vaccine for a specific purpose.

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Residual Concentrations of Substances Used During Manufacturing

The vast majority of excipients listed as ingredients in vaccines belong to this category. These substances represent residual or trace amounts of every reagent used during the manufacturing process. A key concept, often overlooked, is that any substance not needed in the final product is reduced to microgram (mcg) or picogram (pcg) amounts, during subsequent purification steps. These excipients are present in such low amounts in the final vaccine product that many are listed by manufacturer's as present in "trace" or "residual" amounts (Table 4.1). The terms "trace" or "residual" may also be used to indicate that final concentrations are below the limit of detection using available assays. Any reagent that is used during vaccine production is listed as a vaccine excipient whether it is present in detectable amounts or not. Vaccines are complex products derived from biologic material grown in laboratories, involving large-scale cultures of bacteria, viruses, yeast, fertilized chicken eggs, insect cells, chicken fibroblasts, and a variety of different mammalian cell lines. Each culture type has different growth requirements. Carefully defined formulations of growth media are used to optimize the recovery of the desired immunogens from cultures of bacteria and yeasts. Viruses are obligate intracellular organisms that can only be cultured under laboratory conditions if target cells permissive to their infection are used. For example, embryonated chicken eggs have proven to be efficient incubation chambers for influenza viruses used to produce seasonal influenza vaccine. Other viruses, such as polio and hepatitis A, replicate very efficiently in cultures of eukaryotic cell lines specifically developed and propagated for this purpose. A variety of different cell lines are used to manufacture vaccines, each one supported by specially formulated culture medium specific to its growth requirements. Supplements, such as vitamins, amino acids, and fetal bovine serum, are added when necessary. Every component of culture medium used for vaccine manufacturing is considered an excipient.

Several different recombinant expression systems are also used in the mass production of vaccine immunogens. Recombinant technology has been used to introduce coding sequences for the immunogens of interest into bacteria, yeast, African green monkey kidney cells, and Chinese hamster ovary (CHO) cells. Each of these recombinant cell types has unique culture conditions and medium requirements that have been optimized for the recovery of the expressed protein(s).

Every ingredient used to manufacture a vaccine is listed in the product's prescribing information (package insert). Reading these long lists of ingredients can be disconcerting to those who do not understand the concept of an excipient, or the meaning of micro- or picogram amounts. Most of the chemicals and reagents listed have unfamiliar names (e.g., cetyl trimethylammonium bromide [CTAB], hexadecyltrimethylammonium bromide); some names are familiar, yet seem dreadfully out of context (e.g., yeast, gelatin, aluminum), some are clearly derived from animals (e.g., fetal bovine albumin, chick embryo protein), some are widely considered poisonous when present in much higher concentrations in other contexts, (e.g.,

Table 4.1 Vaccine excipients

Excipient	Category	Vaccine(s)[a]	Amount per dose[b]
2-Phenoxyethanol	Stabilizer	DTaP-HIB-IPV	3.3 mg
		DTaP-IPV	3.3 mg
		DTaP	3.3 mg
		TdaP	3.3 mg
	Preservative	IPV	0.5%
Albumin, bovine	Stabilizer	DTaP-HepB-IPV	trace
		DTaP-HIB-IPV	≤50 ng
		DTaP-IPV	trace
		Hepatitis A	<0.1 ng
		IPV	<50 ng
		JE	≤100 ng
		Rabies	trace
		Zoster	trace
Albumin, fetal bovine	Stabilizer	Pentavalent rotavirus	trace
		Varicella	trace
Albumin, human	Stabilizer and Diluent	MMR	≤0.3 mg
		MMR-V	0.31 mg
		Rabies	<100 mg
Albumin, egg (ovalbumin)	Medium ingredient	Influenza inactivated	≤1 mcg
		Influenza live attenuated	≤0.24 mcg
		Rabies	≤3 ng
Aluminum	Adjuvant	Anthrax	1.2 mg
		DTaP-HepB-IPV	≤0.85 mg
		DTaP-HIB-IPV	0.33 mg
		DTaP-IPV	0.33–0.6 mg
		DTaP	0.33–0.625 mg
		DT	1.5 mg
		HepA-HepB	0.45 mg
		Hepatitis A	0.45–0.5 mg
		Hepatitis B	0.5 mg
		HPV nonavalent	500 mcg
		JE	250 mcg
		Mening B	0.25–0.519 mg
		Pneumococcal 13-valent	0.125 mcg
		TD	0.33–0.53 mg
		TdaP	0.33–0.39 mg
Amino acid	Medium ingredient	Anthrax	Unspecified
		HepA-HepB	Unspecified

(continued)

Table 4.1 (continued)

Excipient	Category	Vaccine(s)[a]	Amount per dose[b]
		Hepatitis A	0.3% w/v
		Hepatitis B	Unspecified
		HPV nonavalent	Unspecified
		Influenza live attenuated	Unspecified
		Influenza recombinant quadrivalent	2.42 mg of arginine
		Mening B	10 mM or 0.776 mg of histidine
		MMR	Unspecified
		Rotavirus monovalent	Unspecified
		Typhoid, live attenuated	0.3–3.0 mg per capsule
		Zoster	Unspecified
Ammonium sulfate	Protein purifier	DTaP-HIB-IPV	Unspecified
		DTaP-IPV	Unspecified
		DTaP	Unspecified
		HIB	Unspecified
		Influenza live attenuated	Unspecified
		Meningococcal quadrivalent	Unspecified
		Pneumococcal 13-valent	Unspecified
		TdaP	Unspecified
		Td	Unspecified
Amphotericin	Antimicrobial	Rabies	<2 ng
$AS01_B$ suspension	Adjuvant	Recombinant zoster vaccine	50 mcg each of MPL and QS-21
Benzethonium chloride	Preservative	Anthrax	25 mcg
Beta-propiolactone	Virus inactivation	Influenza inactivated	≤0.5 mcg
		Influenza inactivated from cell culture	<0.5 mcg
		Rabies	<50 ppm
Calcium carbonate	Buffer	Rotavirus monovalent	Unspecified
Cetyl trimethylammonium bromide (CTAB)	Protein purifier	Influenza inactivated	≤12 mcg
		Influenza inactivated from cell culture	≤18 mcg

Table 4.1 (continued)

Excipient	Category	Vaccine(s)[a]	Amount per dose[b]
Chick embryo protein	Medium ingredient	Influenza inactivated	Trace residual
		MMR-V	Trace residual
		Varicella	Trace residual
		Yellow fever	Trace residual
Chicken fibroblasts	Medium ingredient	MMR	Trace residual
Chlortetracycline	Antimicrobial	Rabies	≤200 ng
Chinese hamster ovary cells	Medium ingredient	Recombinant Zoster vaccine	Trace residual
CpG 1018	Adjuvant	Hepatitis B Adjuvanted	3 mg
DOPC or dioleoyl phosphatidylcholine	Adjuvant carrier	Recombinant zoster vaccine	1 mg
Ethylenediaminetetraacetic acid (EDTA)	Medium ingredient	Influenza live attenuated	< 0.37 mcg
		Rabies	0.3 mg
		Varicella	Trace
Formaldehyde	Inactivating agent	Anthrax	<100 mcg
		DTaP-HIB-IPV	≤5 mcg
		DTaP-HepB-IPV	≤100 mcg
		DTaP-IPV	≤100 mcg
		DTaP	≤100 mcg
		DT	≤100 mcg
		HepA-HepB	≤100 mcg
		Hepatitis A	<0.8 mcg
		Hepatitis B	≤15 mcg
		HIB	<0.5 mcg
		Influenza inactivated	≤25 mcg
		JE	≤100 mcg
		Meningococcal quadrivalent	<2.66 mcg
		IPV	≤0.02%
		TdaP	≤100 mcg
		Td	≤100 mcg
		Typhoid inactivated	≤100 mcg
Gelatin	Stabilizer	Influenza live attenuated	2 mg
		JE	500 mcg
		MMR	14.5 mg
		MMR-V	11 mg
		Rabies	≤12 mg

(continued)

Table 4.1 (continued)

Excipient	Category	Vaccine(s)[a]	Amount per dose[b]
		Typhoid, live attenuated	Gelatin capsules
		Varicella	12.5 mg
		Yellow fever	Unspecified
		Zoster	15.58 mg
Gentamicin sulfate	Antimicrobial	Influenza inactivated	≤0.15 mcg
		Influenza live attenuated	<0.015 mcg/ml
Glutaraldehyde	Inactivating agent	DTaP-HIB-IPV	<50 ng
		DTaP-HepB-IPV	Unspecified
		DTaP-IPV	<50 ng
		DTaP	<50 ng
		TdaP	<50 ng
Hexadecyltrimethylammonium bromide	Protein purifier	Typhoid inactivated	Unspecified
Kanamycin	Antimicrobial	Influenza inactivated	≤0.03 mcg
		Mening B	0.01 mcg
MDCK cell residual	Medium ingredient	Influenza inactivated from cell culture	Unspecified
MF59C.1	Adjuvant	Influenza Adjuvanted	9.75 mg squalene in polysorbate 80
MPL or 3-O-desacyl-4′- monophosphoryl lipid A	Adjuvant	Recombinant zoster vaccine	50 mcg
MRC-5 cell residual	Medium ingredient	DTaP-HIB-IPV	Unspecified
		DTaP-IPV	Unspecified
		HepA-HepB	≤2.5 mcg
		Hepatitis A	≤5 mcg
		MMR-V	Residual
		Rabies	Unspecified
		Varicella	Residual
		Zoster	Residual
Neomycin	Antimicrobial	DTaP-HepB-IPV	≤0.05 ng
		DTaP-HIB-IPV	<4 pg
		DTaP-IPV	≤0.05 ng
		Hepatitis A	≤40 ng
		HepA-HepB	≤20 ng
		Influenza inactivated	≤81.8 ng
		MMR	25 mcg
		MMR-V	<16 mcg
		IPV	<5 ng

Table 4.1 (continued)

Excipient	Category	Vaccine(s)[a]	Amount per dose[b]
		Rabies	<150 mcg
		Varicella	trace
		Zoster	Trace
Phenol	Preservative	Pneumococcal 23-valent	0.25%
		Typhoid inactivated	0.25%
		Smallpox	0.25%
Polymyxin B	Antimicrobial	DTaP-HepB-IPV	≤0.01 ng
		DTaP-HIB-IPV	<4 pg
		DTaP-IPV	≤0.01 ng
		Influenza inactivated	≤3.75 mcg
		IPV	25 ng
QS-21	Adjuvant	Recombinant zoster vaccine	50 mcg
Sodium taurodeoxycholate	Protein purifier	Influenza inactivated	≤10 ppm
	Vesicle purifier	Meningococcal serotype B	Unspecified
Spodoptera frugiperda 9 (Sf9) cells	Medium ingredient	Influenza recombinant	Unspecified
Streptomycin	Antimicrobial	IPV	200 ng
Thimerosal	Preservative	DT	≤0.3 mcg
		Influenza inactivated	≤25 mcg from multidose vials only
		Td	≤0.3 mcg
		JE	0.007%
Vero cell residual	Medium ingredient	DTaP-HepB-IPV	Unspecified
		DTaP-IPV	Unspecified
		IPV	Unspecified
		JE	Unspecified
		Rotavirus monovalent	Unspecified
		Rotavirus pentavalent	Unspecified
WI-38 human fibroblast cell residual	Medium ingredient	Inactivated polio	Unspecified
		Rubella	Unspecified
Yeast	Medium ingredient	DTaP-HepB-IPV	≤5% yeast protein
		HepA-HepB	≤5% yeast protein
		Hepatitis B	≤5% yeast protein
		HPV nonavalent	<7 mcg

(continued)

Table 4.1 (continued)

Excipient	Category	Vaccine(s)[a]	Amount per dose[b]
		Pneumococcal 13-valent	trace
		Typhoid	Not specified

[a]Vaccines containing the same immunogens, but different excipients, are available because manufacturers use different processes to produce their final products. The excipients listed are included in one or more of the available formulations

[b]Amounts listed are collected from package inserts for vaccine formulations approved for use by the US Food and Drug Administration

formaldehyde, phenol), and some are derived from cells originating from fetal lung tissue (MRC-5 and WI-38 cells), African green monkey kidney (Vero) cells, insect (Sf9) cells, or other unusual sounding sources. Learning about the role that each of the excipients plays in vaccine manufacturing and understanding that remnants of these substances are present in vaccines at very low concentrations, if detectable at all, can help resolve questions from those expressing concerns about vaccine ingredients.

Substances Added to the Vaccine for a Specific Purpose

The second main category of excipients are those added near the end of the manufacturing process. These excipients are added in precise amounts. They are not diluted or removed subsequently because they are necessary for the formulation of the final vaccine product. For example, many vaccine immunogens are formulated with a stabilizing solution or buffer to maintain their integrity prior to use. Other vaccines require the addition of a substance called an adjuvant to improve vaccine immunogenicity. Finally, vaccines that are provided to the end user in multidose vials require the addition of a preservative to prevent bacterial contamination during use.

Adjuvants

Ingredients referred to as adjuvants are added to some vaccines near the end of the manufacturing process. An adjuvant is any substance that enhances or modulates the immune responses to an antigen. Historically, inorganic adjuvants, in the form of aluminum salts, were the first to be added to vaccines. Aluminum phosphate, aluminum hydroxide, and alum remain the most common vaccine adjuvants in use today. While their precise mechanisms of action are incompletely understood, aluminum salts are known to trigger the activation of dendritic cells. Activated dendritic cells upregulate and release interleukin-1β, which provides an important signal to B-cells to initiate antibody production.

Several new organic adjuvants were recently approved for use in vaccines. Organic adjuvants are a group of substances that are capable of mimicking

molecular patterns recognized by the innate immune system as pathogen-derived foreign material. Examples of molecules that are easily identified by the innate immune system as pathogen-derived include various components of bacterial cell walls, the outer bacterial membrane lipopolysaccharide of Gram-negative bacteria (also known as endotoxin), liposomes, double-stranded RNA, and unmethylated-CpG-dinucleotide-containing DNA. The innate immune system recognizes and responds to these and other pathogen-specific molecules. When a specific vaccine immunogen is presented to the immune system together with an organic adjuvant that mimics one of these pathogen-specific molecular patterns, the ensuing innate immune responses are robust. Dendritic cells, macrophages, and natural killer cells are engaged and activated, thereby augmenting and modulating the adaptive immune response triggered simultaneously by the vaccine immunogen. Organic adjuvants currently used in US-approved vaccines include the cytosine phosphoguanine motifs in CpG1018, MF59c.1, a squalene-based substance, and liposomes containing equal amounts of 3-O-desacyl-4′-*m*onophos*p*horyl *l*ipid A (*MPL*) and the purified *Quillaja saponaria* plant extract QS-21.

Stabilizers

The stabilizers added to many vaccine immunogens near the end of the manufacturing process serve to maintain the integrity of the formulation prior to use. Stabilizers that are commonly added include protein in the form recombinant human albumin, bovine albumin, bovine casamino acid, or porcine-derived gelatin; sugars in the form of lactose, sorbitol, sucrose, or xanthan; and/or nonionic surfactants and emulsifiers such as polysorbate 20 and polysorbate 80.

Preservatives

In the USA, most vaccines that are prepared for delivery as unit doses do not contain a preservative. Several vaccines are, however, available in multidose vials, most commonly containing 10 doses, although some contain enough vaccine to immunize 50 individuals. By design, multidose vials require repeated access by inserting a sterile needle through a stopper to withdraw each dose. Careful aseptic technique alone is insufficient to prevent contamination when the integrity of the stopper is disrupted repeatedly, so a preservative is added to all multidose vaccine vial preparations. Preservatives that are licensed by the US Food and Drug Administration for use in vaccines include thimerosal, 2-phenoxyethanol, benzethonium chloride, and phenol.

A list of excipients included in the package inserts of US Food and Drug Administration -approved vaccines is provided in Table 4.1. The category for each of the listed excipients identifies substances that are present in residual amounts as antibiotics, protein purifiers, chemicals used to inactivate pathogens or toxins, or ingredients used in culture medium. Excipients that are added to serve the specific

purpose of adjuvant, stabilizer, or preservative are likewise identified. The amount of excipient per unit dose of vaccine is also listed.

Vaccine Excipients: What Is It? Why Is It Listed as an Ingredient in Some Vaccines?

This section includes definitions of the excipients listed in the package inserts of all vaccines approved for use in the USA. A description of each substance is provided, including its specific role in vaccine manufacturing. Mineral salts and simple nutrients used in various formulations of culture media that are not described separately in this section or listed in Table 4.1 include calcium chloride, carbohydrates, dextrose, glucose, ferric (III) nitrate, galactose, magnesium sulfate, phosphate buffer, potassium chloride, sodium bicarbonate, sodium borate, sodium citrate, soy peptones, mineral salts, and vitamins.

2-Phenoxyethanol

2-Phenoxyethanol, $C_6H_5OCH_2CH_2OH$, is a phenol-derived aromatic ether substituted on oxygen by a 2-hydroxyethyl group. It is widely used in manufacturing of inks, dyes, insect repellents, and antiseptics. It is used as a preservative in cosmetics, perfumes, and a variety of pharmaceutical products including antibiotic creams, ear drops, and multidose vials of trivalent inactivated polio vaccine.

Albumin (Bovine, Fetal Bovine, Human)

Albumin is the most abundant protein found in plasma. It is widely used in vaccine manufacturing as a stabilizer to protect the integrity of the active ingredients during manufacture, storage, and transport. Bovine serum albumin is used simply because it is plentiful and inexpensive. Recombinant human serum albumin is also used as a stabilizer in some vaccines.

Albumin, Egg

Albumin is the most abundant protein found in eggs. The first step in manufacturing most influenza vaccines involves inoculating embryonated chicken eggs with vaccine strain influenza viruses. The eggs serve as the culture medium for the viruses, where they replicate until ready for harvest. Prior to 2016, chicken-egg-based

technology was the only process approved by the US Food and Drug administration for the production of influenza vaccines. In 2016, the first cell-culture-based influenza vaccine was introduced to the market.

Aluminum

Aluminum is a chemical element with the symbol Al, and atomic number 13. It is the most abundant metal, and third most abundant element on earth, accounting for 8% of the Earth's crust. Aluminum salts, such as aluminum hydroxide, aluminum phosphate, or potassium aluminum sulfate, are added to some vaccines to serve as adjuvants. Each of these aluminum salts occurs naturally in the environment. They are found in small amounts in food and drinking water. Aluminum salts are also one of the active ingredients in some antacids, and are used as stabilizers in many processed foods. Vaccines that contain aluminum are more painful when injected and more likely to cause self-limiting injection site redness and swelling compared with other vaccines.

Amino Acids

Amino acids are 20 related organic compounds that are used as the unit building blocks of protein. Humans can synthesize 11 amino acids de novo. The other nine, commonly referred to as "essential amino acids," are derived from digested dietary proteins. During vaccine manufacturing, amino acids are added to culture medium to support the replication of the bacteria, virus, or yeast cells being grown for the purpose of harvesting the desired immunogen.

Ammonium Sulfate

Ammonium sulfate is an inorganic salt $(NH_4)_2SO_4$ best recognized for its use as a soil fertilizer and other commercial agricultural purposes. In the chemistry laboratory, ammonium sulfate is used to purify proteins from complex mixtures. The technique, called ammonium sulfate precipitation, relies on a simple protein chemistry concept; protein solubility in a solution decreases as the ionic strength the solution increases. The method is called "salting out." After the ammonium sulfate is added to the solution containing the desired protein(s), centrifugation is used to separate the precipitate from the aqueous portion. The precipitated protein is then resolubilized using suspension buffers. Ammonium sulfate precipitation is a convenient, simple, and common technique used to fractionate complex protein mixtures during the early manufacturing steps for several vaccines.

Amphotericin

Amphotericin is a broad-spectrum antifungal agent. Several pharmaceutical formulations are available for intravenous use as medical treatment of invasive fungal infections in humans. It is also used in vaccine manufacturing as an additive to some culture media to prevent microbial cultures from becoming contaminated with mold.

AS01$_B$ Adjuvant Suspension

AS01$_B$ adjuvant suspension is a liposomal formulation comprised of equal amounts of 3-O-desacyl-4′-*m*onophos*p*horyl *l*ipid A (*MPL*) extracted from the bacterium *Salmonella minnesota* and QS-21, a plant extract purified from *Quillaja saponaria.* Liposomes are comprised of cholesterol and dioleoyl phosphatidylcholine (DOPC) suspended in phosphate-buffered saline.

Ascorbic Acid

Ascorbic acid is a synonym for vitamin C. It is found naturally in a variety of foods. It is used in vaccine manufacturing for its potent antioxidant properties.

Benzethonium Chloride

Benzethonium chloride is a synthetic quaternary ammonium salt with surfactant and antiseptic properties. Its broad-spectrum microbiocidal activity against bacteria, molds, and viruses makes it ideal for use in the restaurant industry as a hard surface disinfectant. It is an active ingredient found in many over-the-counter hand and body washes, mouthwash, topical first aid antiseptics, antibacterial wipes, and cosmetics. In the vaccine industry, it is used as a preservative in anthrax vaccine.

Beta-Propiolactone

β-Propiolactone ($C_3H_4O_2$) is an organic compound of the lactone family. It has excellent sterilizing activity against bacteria, fungi, and viruses. It has been used as a vapor-phase disinfectant for small, enclosed areas and to sterilize tissue grafts, surgical instruments, human plasma, water, and milk. In vaccine manufacturing, it is used to inactivate influenza virus during the production of some influenza vaccines.

Bovine Casamino Acids

Bovine casamino acids are a product derived from cow's milk casein. Bovine casein is digested using sulfuric or hydrochloric acid. The resulting hydrolysate consists chiefly of free amino acids. Bovine casamino acids are similar to tryptone. Tryptone is an incomplete casein hydrolysate that is used as a source of protein and amino acid in different formulations of bacterial culture media. In vaccine manufacturing, bovine casamino acids are used as an ingredient in bacterial culture medium early on in the production of some diphtheria vaccines. See also section "Amino Acids."

Calcium Carbonate

Calcium carbonate ($CaCO_3$) is a common, naturally occurring organic chemical compound found in limestone, coral reef structures, crustacean shells, and the eggs of reptiles and birds. It has a broad array of industrial applications. In the food industry, calcium carbonate is added to provide color, or as a buffer, stabilizer, or anticaking agent. It is approved as an additive to nondairy milk products (e.g., soy, almond) as a dietary calcium supplement, and it is the active ingredient in many over-the-counter antacids. The pharmaceutical industry relies on calcium carbonate as a filler "inactive ingredient" in the production of medications formulated as tablets. In vaccine manufacturing, calcium carbonate is used as a buffering agent for one of the oral formulations of rotavirus vaccine.

Cetyl Trimethylammonium Bromide (CTAB)

Cetyl trimethylammonium bromide $[(C_{16}H_{33})N(CH_3)_3]Br$ is a quaternary ammonium compound with surfactant properties. In the biochemistry laboratory, surfactants such as CTAB are used to extract proteins from cells and tissues. They do so by disrupting and disorganizing cell membrane lipid bilayers and solubilizing cellular proteins. Later biochemical steps are then used to purify the protein(s) of interest. Surfactants are used in industry for myriad practical applications that require dispersion, emulsification, foaming or antifoaming, and cleaning. While CTAB is most commonly used during protein purification steps in the biochemistry laboratory, a variety of other surfactants are used to manufacture soaps and laundry detergents, fabric softeners, inks, paints, waxes used for surfboards and skis, insecticides, spray and foaming sanitizers, and many others. The health and hygiene industry also depends on the use of surfactants for the manufacturing of cosmetics, liquid soaps and shampoos, hair conditioners, toothpaste, and spermicides. CTAB is used in the vaccine industry to extract

proteins from cultures of influenza virus during the manufacturing of some inactivated influenza vaccine formulations.

Chick Embryo Protein

Fertilized chicken eggs are used in the production of varicella, yellow fever, and most influenza vaccines. Vaccine strain viruses replicate efficiently in this system. When ready for harvest, the eggs, now containing amplified virus, are collected, combined, and subjected to a series of purification steps. The final preparations are highly purified, but do contain trace amounts of chick embryo proteins, including ovalbumin.

Chicken Fibroblasts

Chicken fibroblasts, or chick embryo fibroblasts (seen abbreviated as CEFs), are connective tissue cells derived from chicken embryos that grow and replicate in laboratory cultures containing cell culture medium. Harvested cells adhere to the culture dish, replicating to fill available space. Primary cells that are grown in laboratory cultures have a finite lifespan, but generally tolerate expansion by serial passage up to five times. CEFs are one of the many cell culture types used in laboratories to propagate viruses. In vaccine manufacturing, laboratory cultures of CEFs are used to support the manufacturing of measles and mumps vaccines.

Chinese Hamster Ovary Cells

Chinese hamster ovary (CHO) cells are a continuous epithelial cell line derived from the ovary of the Chinese hamster. Cell lines refer to well-characterized cells that are easily cultured and propagated in the laboratory, over time, using serial passage. Continuous cell lines, such as CHO cells, have been immortalized, allowing them to be passaged indefinitely. “Cell culture” refers to the process of growing animal (including human) cells in a suitable receptacle under laboratory-defined conditions. Culture conditions vary for each cell type, but generally include the use of a properly prepared liquid medium with careful regulation of temperature and pH. The culture medium for each cell line must be formulated to include all nutrients, growth factors, and hormones that are essential for its growth. As a laboratory tool, CHO cells are particularly efficient at expressing recombinant proteins. In vaccine manufacturing, genetically engineered CHO cells are used in the production of recombinant zoster vaccine.

Chlortetracycline

Chlortetracycline is a tetracycline class antibiotic used in veterinary medicine to treat bacterial conjunctivitis in dogs and cats, and a variety of bacterial infections in farm animals. In the vaccine industry, it is included in the cell culture media to prevent bacterial contamination during the manufacturing of rabies vaccine.

Citric Acid Monohydrate

Citric acid monohydrate $C_6H_8O_7{\cdot}H2O$ is a naturally occurring tricarboxylic acid present in citrus fruits. It is used as an excipient in some vaccine preparations for its antioxidant and pH-stabilizing properties.

Ethylenediaminetetraacetic Acid (EDTA)

Ethylenediaminetetraacetic acid is a chemical used for a broad array of industrial and medical applications. EDTA has a ring-like center that reacts with metal ions to form stable, water-soluble complexes. Chemicals that bind and sequester metal ions are called chelating agents. Solutions of EDTA are commonly used in biomedical laboratories during manipulation of cell cultures. The Ca^{2+} present in cell culture medium is necessary for cells to adhere to the culture flask and to adhere to one another. When EDTA is added, it chelates (sequesters, functionally removes) the Ca^{2+} from the culture media, causing the cells to detach from the flask for passaging or harvesting. During vaccine manufacturing, EDTA is often used during steps that require cell culture manipulation.

Formaldehyde

Formaldehyde CH_2O is a colorless, flammable, strong smelling organic compound that occurs naturally in the environment. When formed by the action of sunlight and oxygen on atmospheric methane and other hydrocarbons, it becomes part of smog. It is also formed as an intermediate during the combustion of fossil fuels. Formaldehyde is one of the many chemicals released and inhaled during cigarette smoking. It is a well-recognized component of air pollution and is classified as a known human carcinogen. Formaldehyde is used commercially in the manufacturing of industrial and household products such as particleboard, plywood, glues and adhesives, resins, plastics, paints and industrial fungicides, germicides, and disinfectants. It is, perhaps, best known for its use as a preservative in biology

laboratories and as a main chemical ingredient in embalming fluid. Perhaps unexpectedly, formaldehyde is also produced endogenously by most living organisms as part of normal metabolic processes. Biologically, it is essential for normal cellular metabolism. In humans, formaldehyde produced in the liver is used for the biosynthesis of purines, pyrimidines, and amino acids. Due to its rapid metabolic turnover, it does not accumulate in the body. Normal, healthy, endogenous production of formaldehyde in the human body results in stable blood concentrations of approximately 0.1 millimolar at all times. At this concentration, a healthy 6-month-old infant has approximately 2 mg, and an adult has approximately 15 mg of formaldehyde in their blood at all times.

Formaldehyde is used in the vaccine industry for the purpose of inactivating viruses and converting toxins into toxoids by altering their tertiary protein structure sufficiently to render them nontoxic, while retaining immunogenicity. Residual amounts of formaldehyde in amounts no greater than 100 micrograms (0.1 mg) may be present in the final vaccine products. Exposure to formaldehyde at the exceptionally low concentrations found in some vaccines is well below the physiologic range occurring from endogenous production.

Gelatin

Gelatin is a translucent, colorless, flavorless substance derived from animal byproducts of the meat industry, including skin, bones, and connective tissue. Commercially, it has a prominent role in the food industry as a gelling agent for flavored gelatin snacks, gummy candies and multivitamins, ice cream, and yogurt. It is also used to manufacture edible capsules that can be filled with medications or vitamin supplements. Outside of the food industry, gelatin is used in the manufacturing of cosmetics and in the production of film used for photography. Porcine gelatin is used as a stabilizer in several vaccines, and to manufacture the gelatin capsules used to formulate live attenuated typhoid vaccine. A bovine-gelatin-like product is used as a stabilizer in one of the available rabies vaccines. While true allergic reactions are uncommon events following receipt of vaccines, when they do occur, animal gelatin should be considered as the possible allergen.

Gentamicin Sulfate

Gentamicin sulfate is an aminoglycoside class antibiotic. Various pharmaceutical formulations are available to treat infections in humans including products for intravenous and intramuscular injection and topical treatment of infections localized to the eye, ear, or skin. Gentamicin sulfate is used in vaccine manufacturing as an additive to some growth media to prevent cultures from becoming contaminated with bacteria.

Glutaraldehyde

Glutaraldehyde ($C_5H_8O_2$) is a clear oily, strong smelling organic liquid chemical used for a variety of industrial, agricultural, and medical purposes. It plays a role in waste water treatment, disinfecting sugar mills, and fogging and disinfecting enclosures used to house poultry. It is used to disinfect hard surfaces, sterilize medical instruments that cannot be autoclaved, process radiographic film, and fix tissue for electron microscopy. Combined with methanol and formaldehyde, glutaraldehyde is one of the primary chemical ingredients used in embalming fluid. Glutaraldehyde is used in the vaccine industry for the purpose of inactivating bacterial toxins by converting them to toxoids. See also section "Formaldehyde."

Hexadecyltrimethylammonium Bromide

Hexadecyltrimethylammonium bromide is a chemical synonym for cetyl trimethylammonium bromide $[(C_{16}H_{33})N(CH_3)_3]Br$, a quaternary ammonium compound with surfactant properties. See also section "Cetyl Trimethylammonium Bromide."

Kanamycin

Kanamycin is an aminoglycoside class antibiotic. Pharmaceutical formulations are available for intravenous and intramuscular injection as medical treatment of serious bacterial infections in humans. It is used in vaccine manufacturing as an additive to some culture media to prevent cultures from becoming contaminated with bacteria.

Madin-Darby Canine Kidney (MDCK) Cells

Madin-Darby canine kidney cells were derived from the kidney of a normal adult cocker spaniel in 1958 for use as a cell-culture-based model of virus infection. This continuous "immortal" cell line has been propagated under laboratory conditions for more than 60 years. Cell biologists now use them to study cellular mechanisms necessary to establish polarity, signaling pathways important in cell-to-cell adhesion, and a variety of other epithelial cell functions.

In biomedical terms, "cell culture" refers to the process of growing animal (including human) cells in a suitable receptacle under laboratory-defined conditions. These conditions vary for each cell type, but generally include the use of a properly prepared liquid culture medium and careful regulation of temperature and pH. The culture medium for each cell line must be formulated to include all

nutrients, growth factors, and hormones that are essential for its growth. Cell lines refer to well-characterized cells that can be cultured and propagated in the laboratory, over time, using serial passage. Continuous cell lines, such as MDCKs, are cells that have been immortalized, allowing them to be passaged indefinitely. Growth of semicontinuous cell lines, like MRC-5 fibroblasts, can be supported across 30 or more serial passages, while the propagation of primary cells is typically limited to 3 passages or less.

The discovery and development of cell culture methods proved invaluable to the field of virology. Viruses are obligate intracellular pathogens. Viral replication is completely dependent on host cell machinery. Traditional diagnostic virology involves inoculating cell cultures with biologic samples collected from patients, and then monitoring the cells microscopically for visual evidence of infection such as virus-associated cytotoxicity and/or cytopathic effects. Because the process requires a high level of technical expertise and is time consuming, the use of viral cultures for diagnostic testing has been largely replaced by high-throughput molecular diagnostic tests. Viral cultures, however, remain fundamental and essential to the manufacturing of several vaccines. Large-scale cell cultures seeded with polio, influenza, live attenuated measles, live attenuated rubella virus, and live attenuated varicella virus serve as factories to amplify the viruses needed to produce the vaccines.

MDCK cells support the growth of influenza viruses, making them suitable for virology research, diagnostics, and vaccine production. Currently, it is the only cell line approved for use in the manufacturing of inactivated influenza vaccine. To distinguish MDCK-derived inactivated influenza vaccine from the long list of available chicken-egg-based inactivated influenza vaccines, the abbreviations ccIIV (cell culture inactivated influenza vaccine) and IIV (inactivated influenza vaccine) are used. See also sections "Chicken Fibroblasts," "MRC-5 Cells," "Vero Cells," and "WI-38 Cells."

MPL or 3-O-Desacyl-4′-Monophosphoryl Lipid A

The organic vaccine adjuvant MPL, or 3-O-desacyl-4′-monophosphoryl lipid A, is a detoxified form of endotoxin from the Gram-negative bacterium *Salmonella minnesota*. The adjuvant properties of MPL are explained by its proinflammatory interactions with toll-like receptor 4, triggering and enhancing the innate immune response. MPL is used as an adjuvant in the manufacturing of recombinant zoster vaccine.

MRC-5 Cells

MRC-5 (Medical Research Council cell strain 5) cells are a human diploid fibroblast cell line originally developed from the lung of a human fetus that was aborted at 14 weeks gestational age. This cell line has been propagated under

laboratory conditions since 1966 using established cell culture techniques. MRC-5 cells are currently used in the production of varicella and polio vaccines. See also sections "Chicken Fibroblasts," "MDCK Cells," "Vero Cells," and "WI-38."

Neomycin

Neomycin is an aminoglycoside class antibiotic. Pharmaceutical formulations are available for topical treatment of human eye, ear, and skin infections. It is used in vaccine manufacturing as an additive to some culture media to prevent cultures from becoming contaminated with bacteria.

Octoxynol-10

Octoxynol-10 is a nonionic chemical surfactant used primarily in the cosmetics and personal hygiene industry to aid in the formation of emulsions. It is found in hair dyes, hair conditioners, permanent wave products, and spermicides. In the biochemistry laboratory, surfactants such as octoxynol-10 are commonly used to extract proteins from cells and tissues. They do so by disrupting and disorganizing cell membrane lipid bilayers and solubilizing cellular proteins. Later biochemical steps are then used to purify the protein(s) of interest. In the vaccine industry, octoxynol-10 is used in the manufacturing of influenza vaccines, but subsequently removed during protein purification steps. Residual amounts may be detected in the final products.

Phenol

Phenol C_6H_5OH is a weakly acidic aromatic organic compound with a variety of industrial applications. It plays an important role in the synthesis of plastics, polycarbonates, epoxies, nylon, and some herbicides. In the molecular biology laboratory, phenol-chloroform extraction techniques are used to isolate DNA or RNA from cells and tissues. In the pharmaceutical industry, phenol is used as a precursor in the synthesis of a long list of medications, including acetylsalicylic acid (aspirin). Some over-the-counter oral analgesic sprays contain 1.4% phenol as an active ingredient. Phenol was also once widely used as an antiseptic. In the vaccine industry, phenol is added as a preservative to a final concentration of 0.25% in the 23-valent pneumococcal vaccine, the inactivated typhoid vaccine, and in smallpox vaccine.

Polymyxin B

Polymyxin B is an antibiotic with activity against most Gram-negative bacteria. Pharmaceutical formulations are available for intravenous and intramuscular injection to treat serious human infections caused by Gram-negative pathogens and for topical treatment of skin infections in combination with bacitracin and/or neomycin (e.g., triple antibiotic cream). It is used in vaccine manufacturing as an additive to some culture media to prevent cultures from becoming contaminated with bacteria.

Polysorbate 20, Polysorbate 80

Polysorbate 20 (Tween 20) and polysorbate 80 (Tween 80) are chemical surfactants and emulsifiers consisting of 20 and 80 repeat units of polyethylene glycol, respectively. Their stability and safety profiles identify them as excellent candidates for use in the health and hygiene industry for the manufacturing of cosmetics, liquid soaps and shampoos, hair conditioners, mouthwash, and toothpaste. They are also found as listed ingredients in soaps and laundry detergents, fabric softeners, inks, paints, waxes used for surfboards and skis, insecticides, spray and foaming sanitizers, and many other common household products. Stamp collectors use polysorbate 20 to remove adhesive and other residues from their collectables without damaging their quality or value. Industrial applications for polysorbates include a variety of manufacturing processes that require dispersion, emulsification, foaming, or cleansing. In the food industry, polysorbate 20 is used as a wetting agent in flavored mouth drops; polysorbate 80 is used as an emulsifier in ice cream. In the biochemistry laboratory, these agents are added to immunoassay wash buffers used to eliminate unbound proteins, and to lysing buffers used to extract proteins from cells and tissues. They do so by disrupting and disorganizing cell membrane lipid bilayers and solubilizing cellular proteins. In the pharmaceutical industry, polysorbates are used to stabilize emulsions and suspensions, including medications formulated for intravenous injection and more than a dozen different vaccine formulations.

QS-21

QS-21 is a purified plant extract from the soap bark tree *Quillaja saponaria.* In vaccine manufacturing, QS-21 is used as an adjuvant in the production of recombinant zoster vaccine in combination with MPL.

Sodium Taurodeoxycholate

Sodium taurodeoxycholate is a naturally occurring bile salt formed in the liver by conjugation of deoxycholate with taurine. Bile salts aid in the digestion of dietary fats by acting as anionic detergents and surfactants. The emulsification of dietary lipids in the small intestine leads to the formation of micelles, thereby facilitating intestinal absorption. In the biochemistry laboratory, sodium taurodeoxycholate and other surfactants (see also section "CTAB") are used to extract and purify proteins from cells and tissues. They do so by disrupting and disorganizing cell membrane lipid bilayers and solubilizing cellular proteins. In the vaccine industry, sodium taurodeoxycholate is used in the manufacturing of some inactivated influenza vaccines and in the production of the outer membrane vesicles used to produce one of the meningococcal serotype B vaccines.

Sorbitol

Sorbitol is a naturally occurring, sweet tasting, sugar alcohol found in berries, peaches, apples, and other fruits. Most of the sorbitol used commercially, however, is made from potato starch. Sorbitol is best known for its use in the food industry as a sweetener for sugar-free drinks, syrups, ice cream, and candies. Beyond its use as a sweetener, sorbitol is also used to reduce the loss of moisture over time from foods like peanut butter and fruit preserves, and to slow the staling process of baked goods. In the pharmaceutical industry, sorbitol is used to manufacture softgel capsules used to deliver single doses of liquid medicines. In the vaccine industry, sorbitol is added to several different products as a stabilizer.

Streptomycin

Streptomycin is an aminoglycoside class antibiotic. Pharmaceutical formulations are available for intramuscular injection as medical treatment of serious bacterial infections in humans. It is used in vaccine manufacturing as an additive to some growth media to prevent bacterial contamination.

Thimerosal

Thimerosal is an organic chemical that is approximately 50% ethylmercury by weight. It has played an important role as a preservative in vaccines and other pharmaceutical products since the 1930s by preventing bacterial and fungal

contamination during storage and use. Preservatives are particularly important as excipients in multidose vials of medications because of the need to enter and withdraw doses from the vial on more than one occasion. The history of thimerosal use as a vaccine preservative shows it to be both safe and effective. Mercury, however, is a heavy metal with no known physiologic role. Moreover, mercury is known to be toxic to humans when ingested as methylmercury in environmentally contaminated food. Organic methylmercury is present in many types of seafood, with the highest amounts accumulating in fish at the top of the food chain (e.g., sharks, swordfish, tuna). In contrast, thimerosal is metabolized to ethylmercury. Unlike methylmercury, ethylmercury is rapidly cleared from the body via the gastrointestinal tract. The amount of ethylmercury (as thimerosal) once included in childhood vaccines was not associated with toxicity. To offer added perspective on the amount of mercury-containing preservative once included in vaccine formulations administered to infants, consider the following: A single 0.5 mL dose of vaccine containing 0.01% thimerosal as a preservative contains 50 micrograms of thimerosal. This is equivalent to approximately 25 micrograms of mercury per vaccine dose. By comparison, this is roughly the same amount of elemental mercury contained in 1 ounce of swordfish or 3 ounces of canned albacore tuna.

Acknowledging that mercury has no physiologic function, and that methylmercury is known to be toxic, the FDA Modernization Act of 1997 recommended that, wherever feasible, mercury-containing preservatives must be removed from vaccines and other pharmaceutical products. The recommendation was not made because of any recognized toxicity of thimerosal or ethylmercury. In fact, the FDA noted its long safety history as a vaccine preservative stating that the recommendation was simply part of an ongoing effort to modernize vaccine formulations. The recommendation was made out of abundance of caution. Subsequently, thimerosal use was rapidly phased out as most vaccines were reformulated as single unit doses. Thimerosal remains FDA-approved for use as a preservative and continues to be used in the manufacturing of multidose vials of inactivated influenza vaccines, DT (diphtheria and tetanus), Td (tetanus and diphtheria), and Japanese encephalitis virus vaccine. Outside of the USA and most European countries, thimerosal is still used routinely. The World Health Organization has concluded that thimerosal is safe and that there is no need to change to the more expensive single-dose delivery via their Expanded Program on Immunization.

Thimerosal is also still used as a preservative in the manufacturing of the antivenins used to treat pit viper, coral snake, and black widow bites, and as a preservative in some immunoglobulin preparations.

Vero Cells

Vero cells are a lineage of African green monkey kidney cells initially established in 1962. Vero cells are interferon-deficient, so they do not secrete interferon alpha or beta when infected by viruses. They make excellent target cells for culturing viruses

needed for vaccine manufacturing and for a wide variety of experimental applications because they grow rapidly and continuously in cell culture. Vero cells are currently used in the production of some polio vaccines. See also sections "Chicken Fibroblasts," "MDCK Cells," "MRC-5 Cells," and "WI-38 Cells."

WI-38 Cells

WI-38 (Wistar Institute 38) cells are human diploid fibroblasts originally developed from the lung of a human fetus that was aborted at 12 weeks gestational age. This semicontinuous cell line has been propagated under laboratory conditions since the 1960s using established cell culture techniques. WI-38 cells are currently used in the production of rubella and polio vaccines. See also sections "Chicken Fibroblasts," "MDCK Cells," "MRC-5 Cells," and "Vero Cells."

Xanthan

Xanthan, or xanthan gum, is a complex polysaccharide used in the food industry as a thickening agent and as a stabilizer to prevent ingredients from separating. It is used in the vaccine industry to stabilize the active components in one of the available live, attenuated oral rotavirus vaccines.

Yeast

Yeast are single-cell, eukaryotic fungi that are widely used in the food industry and in the field of biotechnology. Fermentation of sugars by different types of yeasts is used to make bread and other baked goods, and in the fermentation steps needed to make beer and wine. Yeasts are one of the most widely used model organisms to study genetics and cell biology. A number of yeast species have been genetically engineered to efficiently produce large amounts of proteins used in the pharmaceutical industry including insulin and the immunogens used to produce hepatitis B and human papillomavirus vaccines.

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Links to Package Inserts for U.S. Food and Drug Administration Approved Vaccines

Adenovirus

https://www.fda.gov/media/80211/download.

Anthrax

https://www.fda.gov/vaccines-blood-biologics/vaccines/biothrax.

Cholera

https://www.fda.gov/media/128415/download.

Dengue

https://www.fda.gov/media/124379/download.

Diphtheria, Tetanus, Pertussis

https://www.fda.gov/media/75157/download.
https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert%2D%2D-DAPTACEL.pdf.
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https://www.vaccineshoppe.com/image.cfm?doc_id=13791&image_type=product_pdf.
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https://www.merck.com/product/usa/pi_circulars/v/vaxelis/vaxelis_pi.pdf.

Ebola

https://www.fda.gov/media/133748/download.

Haemophilus influenzae type B

https://www.vaccineshoppe.com/image.cfm?doc_id=13692&image_type=product_pdf.
https://gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Hiberix/pdf/HIBERIX.PDF.
https://www.merck.com/product/usa/pi_circulars/p/pedvax_hib/pedvax_pi.pdf.

Hepatitis A

https://gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Havrix/pdf/HAVRIX.PDF.
https://www.merck.com/product/usa/pi_circulars/v/vaqta/vaqta_pi.pdf.
https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Twinrix/pdf/TWINRIX.PDF.

Hepatitis B

https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Engerix-B/pdf/ENGERIX-B.PDF.
https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Twinrix/pdf/TWINRIX.PDF.
https://www.heplisavb.com/assets/pdfs/HEPLISAV-B-Prescribing-Information.pdf.
https://www.merck.com/product/usa/pi_circulars/r/recombivax_hb/recombivax_pi.pdf.

Human Papillomavirus

https://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_pi.pdf.

Influenza

http://labeling.seqirus.com/PI/US/Afluria/EN/Afluria-Prescribing-Information-QIV.pdf.
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https://www.azpicentral.com/flumistquadrivalent/flumistquadrivalent.pdf#page=1.
http://labeling.seqirus.com/PI/US//Fluvirin/EN/Fluvirin-Prescribing-Information.pdf.
https://www.vaccineshoppe.com/image.cfm?doc_id=14671&image_type=product_pdf.
https://www.vaccineshoppe.com/image.cfm?doc_id=14674&image_type=product_pdf.

Japanese Encephalitis

https://www.fda.gov/media/75777/download.

Measles, Mumps, Rubella

https://www.merck.com/product/usa/pi_circulars/m/mmr_ii/mmr_ii_pi.pdf.
https://www.merck.com/product/usa/pi_circulars/p/proquad/proquad_pi_4171.pdf.

Meningococcus

https://www.vaccineshoppe.com/image.cfm?doc_id=12580&image_type=product_pdf.
https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Menveo/pdf/MENVEO.PDF.
https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Bexsero/pdf/BEXSERO.PDF.
http://labeling.pfizer.com/ShowLabeling.aspx?id=1796.

Pneumococcus

https://www.merck.com/product/usa/pi_circulars/p/pneumovax_23/pneumovax_pi.pdf.
http://labeling.pfizer.com/ShowLabeling.aspx?format=PDF&id=501.

Polio

https://www.vaccineshoppe.com/image.cfm?doc_id=5984&image_type=product_pdf.

Rabies

https://www.vaccineshoppe.com/index.cfm?fa=anon.catalog&category=1&section=4&family=24#category=1&section=4.
https://www.vaccineshoppe.com/image.cfm?doc_id=5983&image_type=product_pdf.
https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Rabavert/pdf/RABAVERT.PDF.

Rotavirus

https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Rotarix/pdf/ROTARIX-PI-PIL.PDF.
https://www.merck.com/product/usa/pi_circulars/r/rotateq/rotateq_pi.pdf.

Smallpox

https://www.fda.gov/media/75792/download.

Tickborne Encephalitis

http://mri.cts-mrp.eu/download/AT_H_0126_001_FinalPL.pdf.

Tuberculosis

https://www.merck.com/product/usa/pi_circulars/b/bcg_vaccine/bcg_pi.pdf.

Typhoid

https://www.vaccineshoppe.com/image.cfm?doc_id=9372&image_type=product_pdf.
https://www.fda.gov/media/75988/download.

Varicella and Shingles

https://www.merck.com/product/usa/pi_circulars/v/varivax/varivax_pi.pdf.
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Chapter 5
The Process and Timeline to Develop a New Vaccine

Joseph Domachowske

Introduction

Theoretically, a safe and effective vaccine could be developed for the prevention of any infectious disease. Potential targets for vaccine development are identified and reviewed regularly by health officials in government, academia and research, and development teams across the pharmaceutical industry. The decision to begin development of a new vaccine typically begins with a general consensus across the major stakeholders regarding the need. The process required to bring an investigational vaccine candidate from preclinical research to regulatory approval and postlicense marketing is both costly and time consuming. A typical timeline to bring a vaccine from "bench to bedside" is 10–15 years at costs exceeding 1 billion US dollars. Vaccines are unlike the majority of medications, because they are administered to healthy individuals, including young children to prevent, not treat disease. Above all else, vaccines must be safe. Clinical trials designed to assess safety, and test efficacy are classified into four phases. Phase I trials, sometimes also referred to as "first in human" studies, include a small number of healthy subjects to evaluate whether the product meets the necessary safety criteria to progress to Phase II. Phase II studies continue to evaluate safety while beginning to assess "proof of concept." For vaccine studies, this is most often a preliminary evaluation of the vaccine's ability to induce the anticipated immune response. Investigational vaccines that pass Phase II safety and "proof of concept" advance to Phase III. The classic description of a Phase III trial is one that tests the efficacy of the investigational product. For many vaccine studies, measures of true efficacy are not possible because of the unpredictable nature of infectious disease outbreaks. In lieu of efficacy, many Phase III vaccine trials rely on vaccine immunogenicity as a surrogate. Safety outcomes remain

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a priority. Upon successful completion of Phase III studies in the USA, the vaccine manufacturer prepares and submits a biologic license application to the Food and Drug Administration (FDA). Following careful review of clinical trial data and other supporting documentation, the FDA renders a decision to approve or reject the request for licensure. Specific recommendations on the use of all licensed vaccines are developed by the Centers for Disease Control's (CDCs) Advisory Committee on Immunization Practices (ACIP). Post licensure, Phase IV trials to evaluate the vaccine's safety and effectiveness in the "real world" context have become routine.

The Preclinical Development and Testing of a Candidate Vaccine

Before an investigational vaccine can be administered to humans in clinical trials, a series of preclinical studies is performed. During this period, antigens are selected and generated in the laboratory from one or more natural or recombinant sources. Purified antigens are characterized, and different formulations tested for stability. Animal studies are performed to evaluate the immunogenicity of different formulations and dosing regimens while standardized toxicology and teratogenicity experiments are completed. Taken together, the results of preclinical testing help to determine whether a given formulation of the antigen has scientific merit for further development as an investigational vaccine. If so, in the USA, the preclinical data are presented to the FDA with a request for permission to develop the product as an Investigational New Drug (IND). IND designation is required before testing in human clinical trials can begin. Similar regulatory procedures are established in Canada, the European Union, and Japan.

The components of an IND application include manufacturing details, results of animal studies, any existing data from other countries about its use in humans, stability, and final composition of the candidate vaccine. The application also requires details on proposed human clinical trial protocols so that an assessment of risk can be determined. The applicant is required to develop an Investigator's Brochure for use as a resource by future clinical trial investigators. The FDA has up to 30 days to consider a new IND application. When the IND is granted, the Phase I, "first in human" clinical vaccine trial can begin.

Clinical Vaccine Trials: Phase I

Phase I vaccine trials are designed to test the safety, side effects, ideal formulation, and dosing regimen of the candidate vaccine. Only a small number of study subjects, typically between 20 and 80, are recruited and enrolled. Most

Phase I vaccine studies are performed using healthy adult volunteers. Following the informed consent process, subjects are enrolled, and protocol-defined baseline safety assessments are performed. Individuals who meet safety criteria to continue in the trial receive the investigational vaccine, are observed on site for possible side effects, and then followed closely by telephone contact until their scheduled return to the study site. Subjects are usually asked to keep a diary to document any adverse signs or symptoms experienced during the following week (or longer).

Phase I trials are often designed as dose-escalation studies where the first cohort of enrolled subjects, usually between 3 and 5 individuals, receive a low dose of the antigen. If safety monitoring shows an acceptable profile, the dose is increased stepwise. Subdivisions of Phase I clinical trials that involve a single ascending dose escalation are designated as Phase Ia, while those that include multiple stepwise dosing increases are referred to as Phase Ib. More than 70% of investigational vaccines that undergo Phase I testing meet the safety criteria required to progress to Phase II.

Clinical Vaccine Trials: Phase II

After a dose or dose range for a vaccine has proven safe in a Phase I study, the next step is to evaluate whether it can meet "proof of concept" as an immunogen in Phase II trials. Phase II trials continue to focus on the safety and side-effect profile of the candidate vaccine while beginning to assess whether it works. At this phase, studies are often performed as double-blind, randomized, placebo-controlled trials. Immunogenicity is most commonly evaluated by comparing vaccine-specific antibody responses before and 4 weeks after the study vaccine is administered. Compared with Phase I, Phase II studies include a larger number of subjects, typically between 300 and 1000, so that valid comparisons can be made between study groups. Most investigational vaccines fail to progress beyond Phase II; fewer than 30% advance to Phase III. Reasons for failure include undesirable side-effect profiles, serious safety concerns, identification of problems with the formulation not appreciated during Phase I, and/or failure to meet predefined immunogenicity criteria.

Phase II clinical trials are sometimes identified as Phase IIA or Phase IIB. Phase IIA studies are those designed to assess immunogenicity or other successful biologic outcomes. Phase IIB is used to describe drug studies that are designed to identify an effective dose associated with the fewest side effects. This designation rarely, if ever, applies to vaccine trials. It is not uncommon to see clinical vaccine studies that incorporate key aspects of both Phase I and Phase II trials. For example, a small dose-escalation trial that also includes immunogenicity as an outcome measure may be referred to as Phase Ib/IIa study.

Clinical Vaccine Trials: Phase III

Phase III studies are large randomized controlled multicenter trials designed to determine how well a vaccine works. Such studies are expected to be designed to allow comparisons with the current standard of care, if applicable. Phase III study enrollment targets usually range between 1500 and 3000 subjects, although some have included more than 12,000 subjects. To be considered for licensure in the USA, the FDA generally requires that results from two or more Phase III trials show the candidate vaccine to be both safe and effective. Here, "effective" can indicate a reduction in disease, but can also be interpreted to mean that the investigational vaccine is either noninferior to a current standard of care, and/or meets predefined immunogenicity criteria. Upon successful completion of Phase III studies in the USA, the vaccine manufacturer prepares and submits a biologic license application (BLA) to the FDA for review.

The FDA Review

A BLA is a request for permission from the FDA to market the vaccine candidate. The information required in the application includes details about the applicant, data about the product, its manufacturing processes, results obtained during preclinical testing, human clinical trial data, and proposed product labeling. BLA requests for approval of vaccines are regulated by the Center for Biologics Evaluation and Research (CBER), one of the six centers of the FDA. CBER is responsible for assuring the safety, purity, and effectiveness of vaccines and several other biologic products. Some biologic products, such as the monoclonal antibodies discussed in the chapter on Passive Immunization, are regulated by the FDA's Center for Drug Evaluation and Research (CDER).

Special Circumstance Designations for FDA Review: Fast Track

Fast track designates an investigational drug, such as a vaccine, for expedited review by the FDA. A request for fast-track designation can be made anytime during the process, but must be made by the manufacturer. This designation was first introduced by the FDA Modernization Act of 1997 to facilitate the development of drugs that address an unmet need and show promise in the treatment of serious or life-threatening diseases. Advantages of a fast-track designation include frequent meetings between the manufacturer and the FDA to ensure that all necessary data to support drug approval are being collected, regular written correspondence between the manufacturer and the FDA with ongoing feedback on clinical trial design at all

phases, and potential eligibility for priority review when the BLA is submitted. Priority review abbreviates the timeline of the process from 10 months to 6 months.

Special Circumstance Designations for FDA Review: Breakthrough Therapy Designation

The breakthrough therapy designation was created by Congress under the 2012 FDA Safety and Innovation Act. This designation allows the FDA to grant priority review for a submitted BLA if early clinical trials indicate that the drug has substantial advantages over existing therapies.

Requests by the manufacturer are reviewed by CBER (or CDER, as appropriate). Investigational products that are granted breakthrough status are given priority review.

Vaccines and Related Biological Products Advisory Committee

The Vaccines and Related Biological Products Advisory Committee, commonly referred to by its acronym VRBPAC, is comprised of 15 voting members appointed by the Commissioner of Food and Drugs for their expertise in infectious diseases, pediatrics, immunology, epidemiology, biostatistics, vaccine policy, vaccine safety, and related areas. Members of the advisory committee review and evaluate data concerning the safety, effectiveness, and appropriate use of all candidate vaccines and several related products, including the information provided in BLAs. Following a series of discussions, the committee votes on the disposition of each candidate vaccine and makes an appropriate recommendation to the Commissioner of Food and Drugs on whether to approve or reject the BLA. Between 20% and 30% of vaccine candidates that progress beyond Phase II either fail during Phase III study or are rejected by the FDA.

Developing Recommendations and Guidelines for FDA-Approved Vaccines

FDA approval of a vaccine includes labeling indications specific to the subset of the population that was evaluated during the clinical trials. Details on the formulation, manufacturing process, safety, efficacy, indications, contraindications, and precautions for its use are outlined clearly in the package insert included with each unit purchased by the end user. FDA labeling indications stop short of providing specific

recommendations on how the vaccine should be used across the population. Those recommendations are the responsibility of the Advisory Committee on Immunization Practices (ACIP). ACIP is a 15-member committee convened by the Centers for Disease Control and Prevention (CDC) for the purposes of providing detailed advice and guidance on controlling vaccine-preventable diseases in the USA. ACIP members have a broad array of expertise in the field of vaccinology, ranging from basic sciences to public health policy. At least one member must represent the perspective of consumers. Individuals with direct conflicts of interests, such as patent holders for vaccines and those employed by vaccine manufacturers, cannot be ACIP members. In addition to the 15 voting members, the ACIP also includes liaisons from more than 40 professional medical societies, such as the American Academy of Pediatrics, and ex officio delegates from 8 Federal agencies including FDA and the National Institutes of Health. Official vaccine recommendations from the ACIP are derived from the input of all stakeholders.

The Development of ACIP Vaccine Recommendations

In 2010, the ACIP began to use a systematic framework called "Grading of Recommendations Assessment, Development and Evaluation," or GRADE to develop and revise official vaccine recommendations. The process includes a comprehensive review of the epidemiology, morbidity and mortality of the targeted disease, an assessment of the vaccine's safety and efficacy based on the quality of available data, considerations and modeling of cost effectiveness, and discussion on the feasibility and logistics of integrating the vaccine into existing programs. To facilitate this process, ACIP appoints working groups to undertake comprehensive reviews of specific topics and to develop draft versions of vaccine recommendations in between regular meeting dates. Findings of each working group are presented and discussed during subsequent ACIP meetings.

Regular meetings of the ACIP are public forums held three times each year. Meeting dates and agendas are published in the Federal Register and posted on the CDC website at https://www.cdc.gov/vaccines/acip/index.html. Video recordings are posted for unrestricted viewing, and the meeting minutes are considered official government documents. Upon approval by the CDC Director, ACIP vaccine recommendations are published in Morbidity and Mortality Weekly Report and posted to https://www.cdc.gov/vaccines/hcp/acip-recs/index.html with unrestricted access. Recommendations to consider a vaccine for all individuals in a designated group (e.g., by age, gender, or risk factor) are assigned category A. Recommendations that encourage an individualized approach, based on discussions between the patient and physician, are assigned category B. In addition, updated versions of the ACIP-recommended pediatric and adult vaccination schedules are published at the beginning of each calendar year (see Fig. 5.1 and https://www.cdc.gov/vaccines/schedules/hcp/index.html).

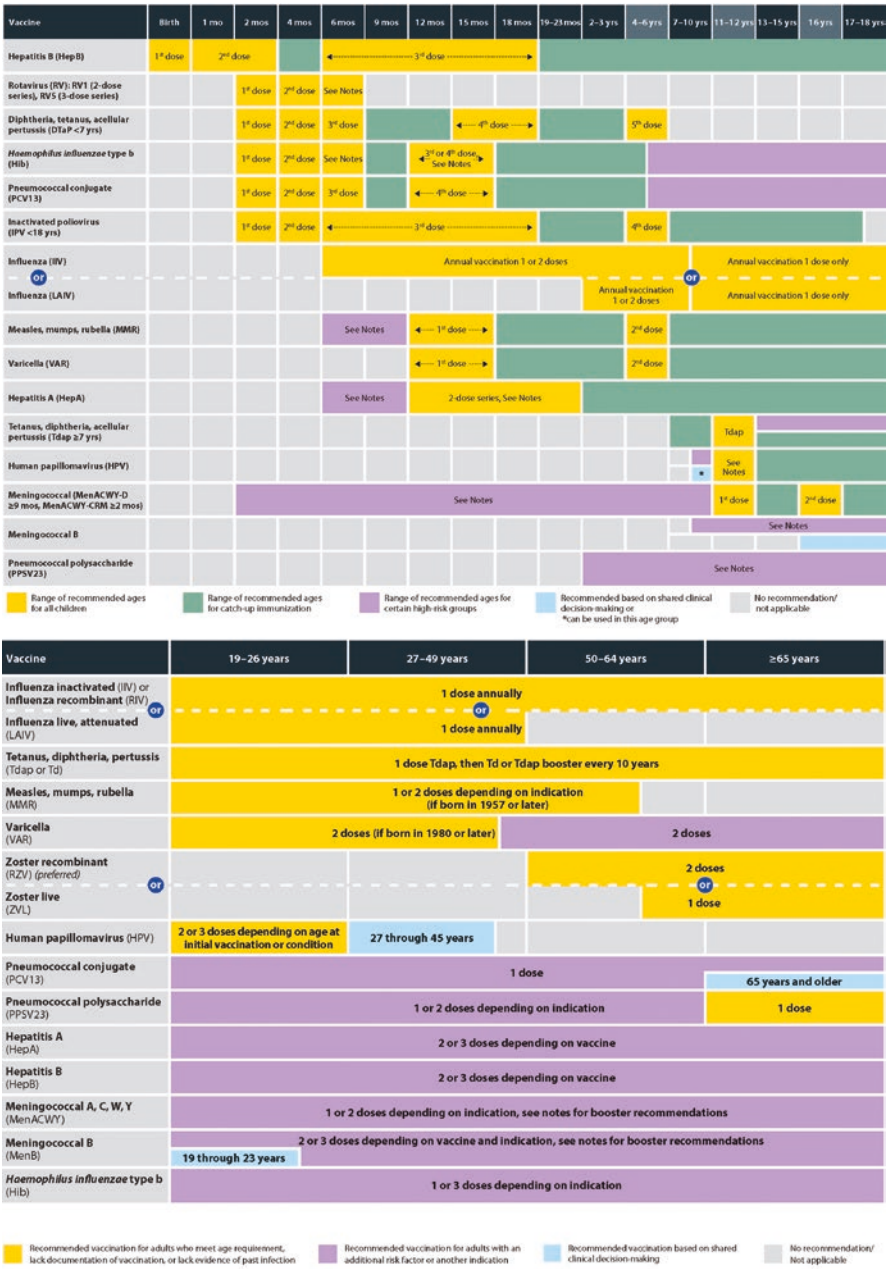

Fig. 5.1 2020 Recommended immunization schedules for children and adolescents (top panel) and for adults (bottom panel). (Source: Centers for Disease Control and Prevention. This material is available on the agency website at no charge: https://www.cdc.gov/vaccines/schedules/index.html. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the US Government, Department of Health and Human Services, or Centers for Disease Control and Prevention. https://www.cdc.gov/other/agencymaterials.html)

Tracking Vaccine Effectiveness and Safety

Careful and continuous monitoring of vaccine safety and effectiveness is essential to maintaining high-quality immunization programs. The CDC's Immunization Safety Office is responsible for assessing vaccine safety, identifying adverse outcomes that may be related to vaccines, and, when necessary, launching case-controlled studies to determine whether an observed adverse outcome is caused by a vaccine. Findings are reported regularly to the members of the ACIP. Federal partners that assist the CDC in tracking and communicating vaccine safety concerns include the FDA's CBER, and the Health Resources and Services Administration (HRSA). The HRSA oversees the National Vaccine Injury Compensation Program. Working together, the CDC and FDA use 3 major tools to monitor vaccine safety in the US population: The Vaccine and Adverse Events Reporting System (VAERS), the Vaccine Safety Datalink, and the Clinical Immunization Safety Assessment (CISA) Network.

Vaccine Adverse Event Reporting System

CDC and FDA share oversight of the Vaccine Adverse Event Reporting System (VAERS), a postmarketing surveillance repository maintained through the passive collection of data on adverse events that occur following the administration of vaccines. Providers who administer vaccines are required, by law, to file a VAERS report for certain adverse events, but anyone can submit a report using the open access portal https://vaers.hhs.gov/reportevent.html, including parents and patients. The system accepts all submissions, including those with incomplete or obviously erroneous data. The open design is meant to optimize the detection of suspected safety signals that appear temporally related to the timing of vaccine administration, including those that may be very uncommon. VAERS reports are monitored for patterns that could indicate true vaccine-associated adverse reactions, but the system is not designed to demonstrate cause and effect. Instead, it is designed to have a low threshold for detecting safety events worthy of further scrutiny. Knowingly filing a false VAERS report is a violation of Federal law (18 U.S. Code § 1001) punishable by fine and imprisonment. Of the more than 10 million doses of vaccines administered to Americans each year, VAERS receives up to 20,000 adverse event reports (0.2%). Major drawbacks of the VAERS system include the passive nature of the reports, inconsistent data quality, and the inability to assign causation. The strengths of the system include its size, comprehensive geographic representation, and potential to identify uncommon or rare events worthy of further scrutiny.

The Vaccine Safety Datalink Project

One powerful way to test the possibility that a safety signal identified using the VAERS system is caused by a vaccine is to perform a large-scale case-controlled study. The CDC's Vaccine Safety Datalink Project (VSD) allows such studies to be designed and executed quickly and efficiently. The VSD database includes detailed surveillance data representing approximately 7 million people, including a half million children. These data have proven invaluable in addressing a number of vaccine safety concerns in real time. For example, several months after the quadrivalent conjugate meningococcal vaccine was FDA-approved and ACIP-recommended for all adolescents, reports of Guillain–Barre syndrome that were temporally related to receiving the vaccine began to appear in reports from VAERS. Case-controlled studies were launched using the VSD Project to test the possibility that VAERS had detected an uncommon, but serious event caused by the new vaccine. VSD case-controlled study data were analyzed in real time as they became available. The results did not support causation, thereby allowing adolescent immunization programs to proceed according to the ACIP recommendation without interruption.

The National Vaccine Injury Compensation Program

In very rare instances, vaccines do cause serious problems. In such cases, with oversight of the HRSA, the National Vaccine Injury Compensation Program (VICP) has the authority to provide financial compensation for the vaccine-related injury. The VICP offers a no-fault alternative to traditional tort action civil liability action.

The VICP, funded entirely by the $0.75 excise tax imposed on each dose of vaccine sold, covers injuries associated with vaccines that are recommended by ACIP for routine administration to children or pregnant women. Compensable injuries are those that present for the first time during a defined postvaccination window period. Circumstances outlined in the Vaccine Injury Table are presumed to be caused by the vaccine even if the vaccine was not administered according to ACIP recommendations. Injuries and conditions that do not meet the criteria listed in the Vaccine Injury Table, found at https://www.hrsa.gov/sites/default/files/vaccinecompensation/vaccineinjurytable.pdf, may be deemed compensable upon presentation of additional evidence such as expert witness testimony.

Postlicensure Phase IV Vaccine Studies

Phase IV vaccine trials are those that are performed after licensure is granted. FDA approval of some vaccines comes with a stipulation that longer-term safety and/or effectiveness data be collected. Similarly, the vaccine manufacturer or Clinical

Investigators may take interest in designing postlicensure long-term, "real-world" studies to further assess aspects that were not able to be tested in a robust manner during Phase III assessments.

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Part II
Vaccine Preventable Infections

Chapter 6
Adenovirus

Cynthia Bonville and Joseph Domachowske

Adenovirus Infection

Etiology

Adenoviruses are nonenveloped, double-stranded DNA viruses. Their lack of a lipid bilayer envelope renders them remarkably stable to inactivation by detergents and other chemical agents, allowing them to remain infectious in the environment for prolonged periods of time. Human adenoviruses are classified into six groups, A through F. More than 79 serotypes have been identified. The vast majority of illnesses caused by adenoviruses are associated with mild-to-moderate respiratory and/or gastrointestinal symptoms. Disease morbidity is highest in young children, immunocompromised individuals, military recruits, and other groups living in crowded conditions. Lethal infection is uncommon, but well described, particularly among certain high-risk populations.

Epidemiology

Approximately 80% of all adenovirus infections occur in children less than 4 years of age. Other populations at high risk include military recruits and those with immunocompromising conditions. Adenoviruses circulate worldwide causing endemic and sporadic infections throughout the calendar year, with epidemics reported most commonly during late winter, spring, and early summer. Disease prevalence in the general population is difficult to determine with precision, since most illnesses are

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self-limiting and not reported. Adenoviruses account for more than half of all acute respiratory infections in military recruits worldwide where close living conditions and stressors related to training cause frequent, large outbreaks. The efficient spread of infection associated with crowded living conditions is also problematic in refugee and displacement camps of war-torn regions, where poor sanitation further exacerbates the problem.

Globally, circulating adenovirus serotypes differ region to region, and change over time. Serotypes 1 through 7 are responsible for more than 80% of infant and childhood infections, while infections caused by serotypes 1 through 5, 7, 14, and 21 are associated with the greatest morbidity. In Asia, a 30% mortality rate has been reported in children less than 3 years of age during outbreaks caused by serotypes 3 and 7. Among military recruits, disruptive outbreaks of moderate-to-severe respiratory infections are most commonly attributed to adenovirus serotypes 4 and 7. Significant outbreaks have also been described from serotypes 3, 11, 14, 17, and 55.

In the USA, the Centers for Disease Control and Prevention tracks adenovirus disease activity using two passive, voluntary, laboratory-based surveillance systems. Since 1989, the National Respiratory and Enteric Virus Surveillance System (NREVSS) has tracked and summarized adenovirus positive laboratory test results according to specimen type (e.g., respiratory sample, blood, urine, cerebrospinal fluid) and the geographic location where the sample was collected. NREVSS does not collect clinical or demographic data, or information related to virus serotype. In 2014, the National Adenovirus Type Reporting System (NATRS) began tracking demographic, clinical, and laboratory data, including virus serotype, on laboratory samples testing positive for adenovirus. The objectives for such enhanced surveillance included timely recognition of outbreaks according to virus serotype, and monitoring for serotype-specific trends in disease severity and geographic spread. Between 2003 and 2016, 1497 adenovirus positive samples were reported from 32 states and the US Virgin Islands. The distribution of adenovirus serotypes that were detected by year is shown in Fig. 6.1. The relative frequency of serotype detection during this 13-year surveillance period is shown in Fig. 6.2. Serotypes 1, 2, 3, 4, 7, and 14 were the most commonly detected serotypes, together accounting for 86% of all identified adenoviruses.

Transmission

Adenoviruses are remarkably stable to inactivation with many chemical and physical agents allowing for prolonged infectivity on environmental surfaces in homes, residence halls, military barracks, schools, hospitals, and others. They resist ultraviolet radiation and tertiary treatment procedures performed on urban wastewater. They are fairly resistant to standard concentrations of common household disinfectants, so industrial or industrial strength disinfectants such as 1% sodium

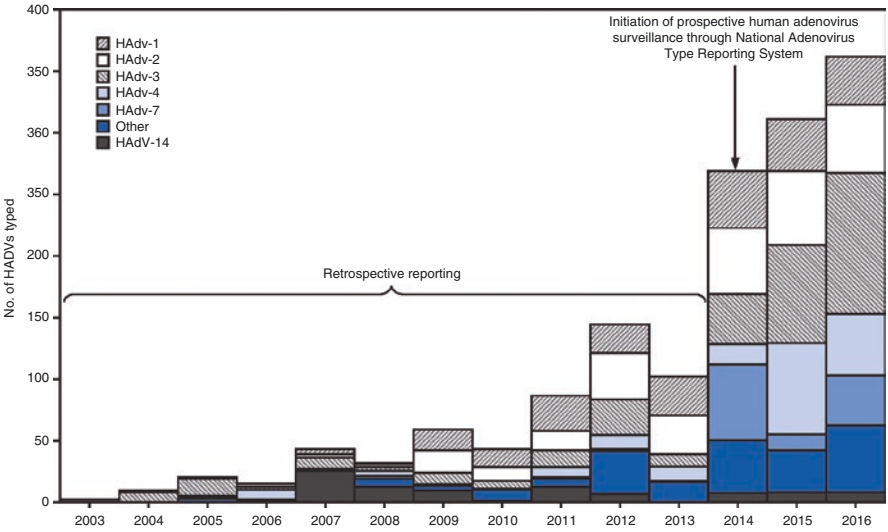

Fig. 6.1 Distribution of human adenovirus species (HAdVs) and types, by year of specimen collection. National Adenovirus Type Reporting System, 32 US states and the US Virgin Islands, 2003–2016. (Source: Centers for Disease Control and Prevention. This material is available on the agency website at no charge: https://www.cdc.gov/mmwr/volumes/66/wr/mm6639a2.htm. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the US Government, Department of Health and Human Services, or Centers for Disease Control and Prevention)

hypochlorite, 2% glutaraldehyde, 0.25% sodium dodecyl sulfate, or 95% ethanol solution must be used (Environmental Protection Agency List G disinfectants). They are also inactivated by heat or formaldehyde.

Transmission can occur from person to person or following exposure to a contaminated environmental source. Person-to-person transmission via direct contact or exposure to contaminated respiratory droplets is common. Self-inoculation from touching one's mouth, nose, or eyes after contact with a contaminated fomite (e.g., a doorknob) also occurs regularly. Adenovirus serotypes that are shed from the gastrointestinal tract are easily transmitted via the fecal-oral route. Serotypes 4 and 7 are transmitted quite efficiently via swimming pool or lake water. Ongoing asymptomatic infection of tonsils, adenoids, and intestines is fairly common among immunosuppressed individuals who can shed virus for prolonged periods of time. Transmission is especially efficient in settings where individuals have frequent and prolonged periods of close contact such as in hospitals, newborn nurseries, psychiatric centers, long-term care facilities, boarding schools, college dormitories, orphanages, day-care facilities, job-training centers, public swimming pools, and military barracks. Outbreaks can quickly escalate to epidemic proportions. Following exposure, adenoviruses have an average incubation period of 5–8 days, with a range from 2 to 14 days.

HAdV species	HAdV type	No. (%) of detections
A	12	t3 (0.2)
	31	3 (0.2)
B	3*	341 (22.8)
	7*	127 (8.5)
	11	6 (0.4)
	14*	89 (5.9)
	21	34 (2.3)
	34	2 (0.1)
	35	14 (0.9)
C	1*	248 (16.6)
	2*	293 (19.6)
	5	56 (3.7)
	6	20 (1.3)
D	8	54 (3.6)
	15	1 (0.1)
	19	1 (0.1)
	22	1 (0.1)
	29	1 (0.1)
	37	12 (0.8)
	56	1 (0.1)
E	4*	185 (12.4)
F	41	5 (0.3)
Total	22	1,497 (100)

*One of the six most common types detected, accounting for 1,283(85.5%) of reprts.

Fig. 6.2 Number and percentage of human adenovirus (HAdV) detections, by species and type. National Adenovirus Type Reporting System, 32 states and the US Virgin Islands, 2003–2016. (Source: Centers for Disease Control and Prevention. This material is available on the agency website at no charge: https://www.cdc.gov/mmwr/volumes/66/wr/mm6639a2.htm. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the US Government, Department of Health and Human Services, or Centers for Disease Control and Prevention)

Clinical Presentation

Infections of the Respiratory Tract

Adenoviruses cause a broad array of clinical illnesses. Specific disease manifestations depend on the tissue tropism of the infecting serotype and various host factors. A majority of serotypes target the respiratory tract. As a group, adenoviruses are responsible for up to 10% of acute respiratory tract infections in children and between 1% and 7% in adults.

Symptoms associated with infection of the respiratory tract may include fever, cough, red eyes, nasal congestion, sore throat, ear pain, shortness of breath,

headache, and fatigue. Manifestations can be consistent with common cold, keratoconjunctivitis, pharyngoconjunctival fever, pertussis syndrome, otitis media, tonsillopharyngitis, laryngotracheobronchitis, bronchitis, bronchiolitis, or pneumonia. Children may also develop concomitant gastrointestinal symptoms. Symptoms of acute adenovirus infection typically last up to 10 days. Pneumonia develops in up to 20% of infected newborns and infants, but is uncommon in immunocompetent adults. As many as 30% of infected immunocompromised individuals will develop pneumonia with severe respiratory failure. Fatality rate from adenovirus pneumonia in this high-risk population exceeds 50%.

Persistent infection of the lung in previously healthy adults and in those with associated chronic obstructive pulmonary disease has also been described. Adenovirus pneumonia occurs relatively frequently in military recruits. Approximately 25% of those who develop pneumonia require hospitalization for pneumonia. Adenovirus serotypes 4 and 7 are responsible for a majority of these cases.

Infections of the Eye

Infections caused by adenovirus serotypes 3, 4, 7, 11, and 14 may be associated with uncomplicated viral conjunctivitis. The eyes are bright red from the conjunctival hyperemia, but vision is not affected and the infection is self-limiting after 10–14 days. In contrast, epidemic keratoconjunctivitis, caused by adenovirus serotypes 8, 19, 37, 53, 54, and 56, lead to a gritty feeling in the eye with watery discharge, photophobia, and associated redness. Corneal involvement affecting visual acuity can persist for months. Outbreaks of epidemic keratoconjunctivitis have been described originating from day-care facilities, schools, outpatient clinics, chronic care facilities, and hospitals. Nosocomial transmission can occur via contaminated ophthalmic instruments or eye drops.

Infections of the Gastrointestinal Tract

Adenovirus-associated acute gastroenteritis is fairly common in children under 2 years of age. The clinical triad of fever, vomiting, and watery diarrhea is common, with the diarrhea persisting for 1–2 weeks. Most of these infections are caused by adenovirus serotypes 40 and 41. Very rare complications include hemorrhagic colitis, hepatitis, cholecystitis, and pancreatitis.

Infections of Other Organ Systems

Adenovirus infections beyond the respiratory and gastrointestinal tracts are uncommon.

Acute viral hemorrhagic cystitis mimics bacterial urinary tract infections. Serotype 11 is most commonly implicated.

Severe disseminated disease can be seen in newborns and in individuals with immunocompromising conditions. In newborns, disseminated adenovirus infection can cause meningitis, myocarditis, hepatic dysfunction, viral sepsis, and death. Similar complications have been described in immunocompromised children and adults. Between 10% and 30% of hematopoietic stem cell transplant patients who develop a respiratory tract infection with adenovirus will go on to develop disseminated infection. In this context, fatality rates up to 70% can be seen.

Management

No specific treatments for adenovirus infections are available. Symptoms that occur with mild-to-moderate infection, such as fever and pain, can be relieved using over-the-counter medications. The antiviral medication cidofovir is used to treat severe infections in immunocompromised individuals only.

Adenovirus Vaccine

The live bivalent adenovirus serotype 4 and 7 vaccine is approved for use by the US Food and Drug Administration (FDA) in military personnel, aged 17 through 50 years. The vaccine is required by the US Department of Defense for all military recruits entering basic training, and recommended for other high-risk military personnel. Its labeling indication is specifically for the prevention of acute febrile respiratory disease caused by human adenovirus serotypes 4 and 7. In the USA, the vaccine is only available for military personnel through the Department of Defense. The safety and efficacy of the vaccine have not been studied in the general population or in immunosuppressed individuals. Adenovirus vaccines are not currently available for civilian use anywhere in the world.

Vaccine Characteristics

The live adenovirus serotype 4 and 7 vaccine is manufactured by Teva Pharmaceuticals. It was licensed by the FDA in March 2011. The vaccine is a live virus product administered orally in the form of two enteric-coated tablets, one of each containing adenovirus serotype 4 and 7. Following ingestion of the vaccine, replication-competent virus is shed in stool, and can theoretically be transmitted to others. Each tablet contains at least 32,000 tissue-culture infective doses of virus. The vaccine may be given at the same time as other vaccines as necessary. Prior to use, it should be stored under refrigeration at temperatures between 2 °C and 8 °C. The vaccine should never be frozen.

Immunizing Antigen

Strains of adenovirus serotypes 4 and 7 are grown in WI-38 human-diploid fibroblast cell cultures maintained in Dulbecco's Modified Eagle's Medium, fetal bovine serum, and sodium bicarbonate. Virus is harvested, filtered to remove cellular material, formulated, and then lyophilized. The vaccine strain viruses are not attenuated.

Vaccine Additives and Excipients

Tablets contain monosodium glutamate, sucrose, D-mannose, D-fructose, dextrose, human serum albumin, and potassium phosphate. The inner tablet core contains anhydrous lactose, microcrystalline cellulose, potassium, magnesium stearate, and replication-competent live adenovirus. The outer tablet contains microcrystalline cellulose, magnesium stearate, and anhydrous lactose. The enteric-coating contains cellulose acetate, alcohol, acetone, and castor oil. The serotype 7 tablet also contains FD&C (Food, Drug and Cosmetic approved) Yellow#6 aluminum lake dye.

Vaccine Recommendations

The live bivalent adenovirus serotype 4 and 7 vaccine licensed for use in the USA is required by the US Department of Defense for all military recruits entering basic training, and recommended for other high-risk military personnel. Civilian access to the vaccine is not available. Both tablets should be swallowed whole at the same time without crushing or chewing them.

Contraindications to Vaccine

Like all other medical products, a known severe allergy to any component is a contraindication to using the bivalent adenovirus serotype 4 and 7 vaccine.
Like other live vaccines, bivalent adenovirus serotype 4 and 7 vaccine is contraindicated for use during pregnancy. Females of reproductive potential should have a pregnancy test performed prior to receiving the vaccine.

Warnings and Precautions for Vaccine Use

Warnings and precautions for vaccine use include individuals with weakened immune systems due to medical conditions, transplantation, radiation, or drug treatments. Females should avoid becoming pregnant for 6 weeks after vaccination.

Scheduled vaccination should be postponed for individuals with symptoms of vomiting or diarrhea, because vaccine effectiveness depends on multiplication of vaccine virus within the gastrointestinal tract during normal transit time. The vaccine strain viruses are shed in the stool from day 7 up to day 28 post vaccination. Attention to handwashing and personal hygiene is essential to prevent spread to others. This is especially important for household contacts less than 8 years old, those who are pregnant, and those with immune-compromising conditions.

Side Effects and Adverse Events

During clinical vaccine trials, potential side effects are monitored by collecting all reported adverse events (AEs) from all study subjects for a period of time, typically for 1 or 2 weeks following each dose of the study vaccine. If the vaccine is approved for use, these rates are included in the vaccine's package insert. The side effects reported are therefore temporally related to receiving vaccine, but may not be causally related to it. Since phase III efficacy trials, by design, include a control group of individuals that receive either the standard-of-care vaccine or placebo, it is important to compare the rates of AEs between the 2 groups to determine whether the rates of reported side effects are different between the 2 groups.

During clinical trials, recipients of the bivalent live adenovirus serotypes 4 and 7 vaccine reported the following AEs during the 2 weeks following administration of the vaccine: headache (33%), nasal congestion, sore throat, or joint pain (17%), abdominal pain, cough, or nausea (14%), diarrhea or vomiting (10%), and fever (1%). Rates in placebo recipients were almost identical. Rare reports of hypersensitivity reactions, anaphylaxis, and Guillain-Barre syndrome were also reported, but no causal relationship was identified.

Vaccine Efficacy

Results from a 2006 phase III, double-blinded, placebo-controlled, randomized clinical vaccine trial that included 4040 military recruits showed a vaccine efficacy of 99.3% (95% CI: 96.0%, 99.9%) in preventing adenovirus serotype 4 infection. No cases of adenovirus serotype 7 infection were identified in study subjects whether they received vaccine or placebo, so efficacy against serotype 7 infection could not be determined.

Serotype 7 immunogenicity, however, showed that 93.8% of vaccine recipients seroconverted, while only 5.3% of placebo recipients seroconverted.

A postlicensure evaluation of real-world vaccine effectiveness showed that routine vaccine implementation led to a reduction in adenovirus serotypes 4 and 7 infections from a baseline of 5.8 cases per 1000 person-weeks down to 0.02 cases per 1000 person-weeks.

The live bivalent adenovirus serotype 4 and 7 vaccine is safe and highly effective in reducing morbidity associated with adenovirus infections among military recruits. Other high-risks groups for serious infection with adenovirus include newborns, young infants, and individuals who are immunosuppressed. New approaches to adenovirus vaccine development would be necessary to target these groups for immunization, since replication-competent (live), nonattenuated vaccines should not be administered to these patient populations.

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Chapter 7
Anthrax

Cynthia Bonville and Joseph Domachowske

Anthrax Infection

Etiology

Anthrax is a serious infection of animals and humans caused by the Gram-positive anaerobic spore-forming bacterium *Bacillus anthracis*. Ancient Egyptian and Mesopotamian accounts of widespread pestilence affecting horses, cattle, sheep, camels, and oxen dating back to 700 BC are almost certainly descriptions about the devastating effects of animal anthrax. The organism, discovered in 1850, was subsequently used as the prototype for Koch's postulates on the transmission of infectious disease. In its vegetative form, the organism produces a number of virulence factors including a polysaccharide capsule, protective antigen (PA), edema factor, and lethal toxin.

Epidemiology

B. anthracis is naturally present in soil and ubiquitous across agricultural regions explaining why sporadic cases and outbreaks in grazing animals have the potential to occur anywhere in the world. The organism is infectious to most mammals, but animal anthrax is primarily a disease of herbivores, grazing livestock, and wild ungulates, such as cattle, goats, sheep, horses, antelope, deer, and bison. Animals become infected by ingesting contaminated soil as they graze. Outbreaks of human disease are driven by the ecological dynamics at the interfaces between wildlife and

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livestock. Worldwide, domestic livestock often share grazing areas with wild herbivores. Where used, national livestock vaccination programs interrupt disease transmission, but recent agricultural trends in some areas have been in favor of abandoning vaccination. Anthrax remains fairly common in regions lacking veterinary public health programs to promote routine anthrax vaccination of livestock and/or inspections of animals prior to slaughter.

Outbreaks occur regularly across the agricultural regions of sub-Saharan Africa, Central and Southwestern Asia, Western China, Southern and Eastern Europe, Central and South America, and the Caribbean. Small pockets of disease are also found in Canada and the Western United States. Factors that exacerbate the morbidity and mortality of human anthrax include regional limitations in knowledge of the disease, restricted access to health care, and food insecurity, resulting in the handling and consumption of contaminated meat. The World Health Organization estimates that 63.8 million economically disadvantaged livestock workers live in anthrax-susceptible regions, primarily in Africa and Eurasia (Fig. 7.1). Epizootics have the potential to cause substantial human morbidity and mortality. For example, in 1975, an epidemic of 448 cases of cutaneous anthrax in The Republic of The Gambia was associated with 12 deaths. The case fatality rate was similar during an epidemic of more than 10,000 cases in Zimbabwe between 1979 and 1985. Large epidemics resulting from food insecurity are also reported on a regular basis. In 2000, hundreds of Ethiopians were afflicted by oral and gastric anthrax after eating contaminated meat. In 2011, more than 500 Zambians developed cutaneous and gastrointestinal anthrax from handling or consuming meat from hippopotamuses that had died from the infection.

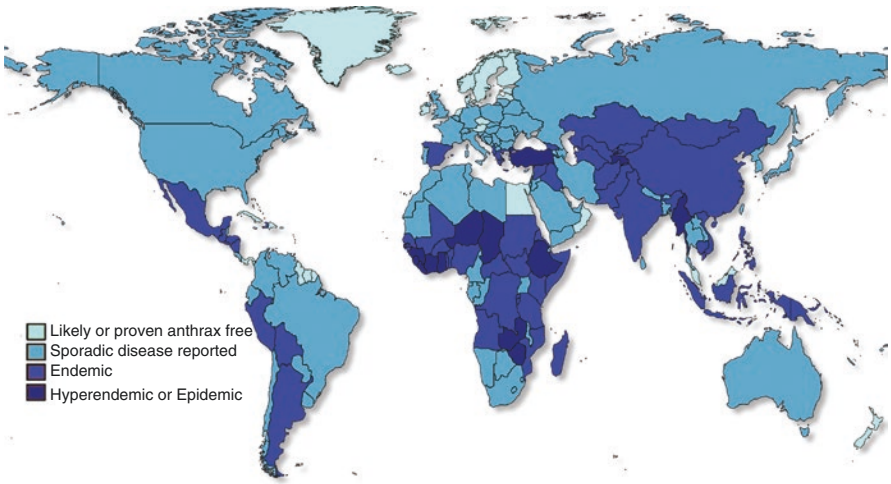

Fig. 7.1 This map illustrates global anthrax disease burden by country from 2005 to 2015. Countries are categorized as hyperendemic/epidemic, endemic, experiencing sporadic outbreaks of disease, or likely/proven to be anthrax-free

Cases of human anthrax are less common among those living in economically developed countries, but sporadic cases and outbreaks still occur. Approximately 20% of cutaneous anthrax cases are diagnosed in farmers, butchers, and veterinarians. The remaining cases of cutaneous anthrax and nearly all cases of inhalation anthrax are diagnosed among industrial workers exposed to imported animal hides, hair, wool, or bones that have been unknowingly contaminated at their source from enzootic disease. Sporadic cases of inhalational anthrax have also been reported in gardeners following exposure to contaminated bone-meal fertilizer.

Injection anthrax is a more recently described form of the disease that has been identified in heroin-injecting drug users. The clinical manifestations are similar to cutaneous anthrax, but infection may extend deeper into the soft tissues, including muscle. Injection anthrax is more likely to disseminate than the cutaneous form. Cases have been reported from Afghanistan, Denmark, England, France, Germany, Norway, Scotland, and Turkey. Case fatality rates as high as 37% have been reported.

Anthrax in the USA

Anthrax is a nationally notifiable disease in the USA. Prior to the 1960s, more than 80% of reported cases had epidemiologic ties to the manufacturing of products using imported goat hair, most notably among wool-sorters. The last fatal case of occupational inhalational anthrax in the USA occurred in 1976 in a weaver who had been working with contaminated yarn imported from Pakistan.

Epizootics still occur occasionally in livestock throughout the Great Plains and parts of California, Montana, Nevada, and New Mexico. In 2000, 32 farms in North Dakota went under quarantine. In total, 157 animals died, and 1 ranch worker survived cutaneous disease. Sporadic cases of human disease reported between 2006 and 2009 were linked to animal hides imported from Africa and Haiti for the purpose of drum making.

In 2001, in an act of domestic bioterrorism, weaponized anthrax spores were mailed via the US Postal Service, ultimately infecting 22 individuals, and killing 5 of them. The index case was a US Postal worker who died from anthrax meningitis. Individuals at increased risk for anthrax infection are summarized in Table 7.1.

Transmission

Transmission occurs during contact with bacterial spores that are present on animal products or on material that has been accidentally or intentionally contaminated. The route of exposure determines the manner in which the infection presents, at least initially. Exposures that occur through breaks in the skin lead to cutaneous anthrax. Breathing in spores while manipulating contaminated material causes inhalation anthrax. Consuming spores that are present in contaminated

Table 7.1 Individuals at increased risk for anthrax infection

Risk category	
Occupational	Recreational
Musicians who make or repair drums using animal hides or skins	
Weavers	
Tanners, leatherworkers, wool handlers	
Livestock producers and handlers	Travelers to endemic areas who have direct contact with animals or animal products
Veterinarians	
Microbiologists, laboratory personnel	
Military personnel	
First responders, postal workers	

meat, or incidental ingestion after handling spore-laden animal hides, results in gastrointestinal disease. Injection site anthrax is also well described in users of illicit substances as a result of exposure to contaminated heroin. *B. anthracis* joins variola virus (smallpox); ebola virus; and the bacterial causes of plague, tularemia, and botulism as a tier 1 select agent (see: https://www.selectagents.gov/SelectAgentsandToxinsList.html). Tier 1 select agents are pathogens and toxins that the Departments of Health and Human Services (HHS) and Agriculture (USDA) have identified as having the greatest risk of intentional misuse, resulting in mass casualties and/or devastating effects critical infrastructure.

The spores produced by *B. anthracis* are highly stable in the environment. They resist irradiation; exposure to a wide array of chemicals; extremes of heat, cold, and pH; and desiccation persisting in soil and other material for many decades, even centuries. Carbon dated bones containing intact spores that were unearthed during an archeological dig in South Africa were estimated to be at least 200 years old.

Portals of entry for human disease include breaks in the skin, ingestion of contaminated and undercooked meat, inhalation of spores during manipulation of contaminated materials, and inadvertent direct injection of contaminated heroin.

Very rarely, cutaneous anthrax can be transmitted from person to person with direct contact. Inhalation anthrax is not transferred from person to person.

Clinical Presentation

The clinical presentation of anthrax is dependent on the portal of entry for the bacterial spores. The 4 possible routes of entry are the skin, lungs, gastrointestinal tract, and injection site.

Cutaneous Anthrax

Cutaneous disease accounts for 95% of all anthrax cases worldwide. Infection is established through cuts or abrasions in the skin during the handling of contaminated animal hides, hair, wool, or leather. Most cases of cutaneous anthrax manifest as a single lesion, but multiple lesions can be present. The areas most commonly affected are the hands, forearms, face, and neck. The typical incubation period is 2–6 days, but can be as long as 3 weeks. After the spores enter the breaks in the skin, they germinate. The vegetative forms of the bacteria begin to multiply. Replicating bacteria produce a protective antiphagocytic capsule and begin to generate and release exotoxins. Bacterial toxins cause localized tissue injury and edema that manifests first as a small, pruritic papule or pustule. A ring of vesicular lesions surrounds the pustule as it begins to ulcerate. An adherent black eschar then appears over the ulcer. Despite the presence of extensive edema, the lesion of cutaneous anthrax is not painful. Some cases are, however, associated with the development of painful regional lymphadenitis. The eschar resolves slowly over a period of several weeks. Large eschars that require surgical excision may require skin grafting.

Cutaneous anthrax can be associated with systemic symptoms such as fever, headache, myalgias, and vomiting. Between 10% and 40% of untreated infections are fatal, while more than 98% of those who are treated with appropriate antibiotics will survive. Cutaneous anthrax is considered the least dangerous form of this infection.

Gastrointestinal Anthrax

Gastrointestinal anthrax occurs following the ingestion of contaminated meat. The typical incubation period is between 3 and 7 days. Early symptoms of infection, such as fever, chills, headache, and asthenia, are vague and nonspecific. Gastrointestinal symptoms, such as nausea, vomiting, mild diarrhea, and anorexia, are similar to those seen with food poisoning or viral gastroenteritis. A diagnosis of gastrointestinal anthrax may only be considered if an outbreak has already identified the cause in others, or if a history of ingesting contaminated meat is identified. This form of anthrax is often fatal, largely because it goes unrecognized until the infection is so advanced that antibiotics are no longer effective.

Gastrointestinal anthrax can cause ulcerative lesions anywhere along the alimentary canal, but they appear most frequently and in greatest abundance throughout the small bowel. The affected area becomes very edematous. Patients develop more severe abdominal pain with hematemesis and bloody diarrhea. Massive ascites develops. Intestinal perforation is not uncommon. Case fatality, even with appropriate antibiotic treatment, is 40% or higher. The average time between symptom onset and death is 2–5 days.

Inhalation Anthrax

Inhalation anthrax results from the direct inhalation of spores that become suspended in the air during the manipulation of contaminated material. People who work in wool mills, slaughterhouses, and tanneries, and those who work with animal hides, hair, and wool, are at risk for exposure in this manner. Following exposure by inhalation, an incubation period of 4–6 days is typical before the onset of symptoms, although incubation periods as long as 8 weeks have been described. Bacterial spores that germinate in the alveoli are taken up by tissue macrophages and brought to the draining lymph nodes in the mediastinum where they replicate and release exotoxins. The ongoing infection and intense inflammatory response cause hemorrhagic mediastinitis. Like gastrointestinal disease, inhalation anthrax is often fatal, because the early symptoms are nonspecific and the infection advances so quickly. The first symptoms of inhalation anthrax mimic an influenza-like illness with abrupt onset of fever, chills, sweats, nausea, malaise, and nonproductive cough. Symptoms evolve quickly as the patient develops worsening respiratory distress, disorientation, and septic shock. Even with appropriate antibiotic treatment, 90% of patients do not survive the infection unless the diagnosis is suspected and treated early.

Injection Anthrax

Injection anthrax first appears as a cluster of small blisters at the site where illicit drug was injected. The almost pathognomonic findings of central ulceration and formation of a painless adherent black eschar that is seen with cutaneous anthrax may not manifest, but the area does become edematous. Abscesses may develop deep under skin or in the underlying muscle. Systemic symptoms are similar to the cutaneous form, but here, the infection progresses more rapidly and is more likely to disseminate causing sepsis. If antibiotics are initiated prior to dissemination, the prognosis for survival is quite good, mirroring cutaneous anthrax. Disseminated disease is almost always fatal.

Management of Anthrax

Cases of anthrax that are diagnosed and treated early generally respond well to antibiotic treatment. Infections resulting from occupational or recreational exposures can be treated with ciprofloxacin, clindamycin, doxycycline, levofloxacin, or moxifloxacin. If the isolate is known to be penicillin susceptible, penicillin or amoxicillin can also be used. Known or suspected exposures are also treated, a process referred to as *postexposure prophylaxis*, or PEP. If the source of exposure is unclear, suspicious, or suspected to be an act of bioterrorism, recommended PEP antibiotic options include ciprofloxacin, clindamycin, doxycycline, levofloxacin, and moxifloxacin. Anthrax vaccine should also be administered. PEP is administered for 42

or 60 days with the goal of preventing infection until vaccine can elicit a protective immune response.

Anthrax Vaccine

Vaccines Available in the USA

In the USA, anthrax vaccine is marketed under the name BioThrax by Emergent BioSolutions/BioDefense Operations. FDA approval for pre-exposure prophylaxis (PrEP) was granted in 1970. Approval for use as postexposure prophylaxis (PEP), in combination with antibiotics, was granted in 2015. This product is the first vaccine to receive approval for human use under the FDA's Animal Rule. Human clinical trials were not performed prior to licensure. The FDA's Animal Rule (21 CRF 601 Subpart H for biological products, 21 CRF 314 Subpart I for drugs) enables licensure of biologics for life-threatening conditions where human efficacy trials are deemed unethical or impractical.

Anthrax vaccine is derived from the avirulent, nonencapsulated *B. anthracis* strain V770-NP1-R. The vaccine itself does not contain any bacteria, live or killed. Instead, the vaccine is made from a filtrate of bacteria culture media rich in *B. anthracis*-specific 83 kDa protective antigen (PA) protein. The vaccine is approved for pre-exposure use in 18- to 65-year-old persons at high risk and for postexposure use in conjunction with a 42- or 60-day course of appropriate antibiotics. Vaccine is administered intramuscularly in the deltoid muscle. In individuals at risk of hematoma formation from intramuscular injections, the vaccine may be given subcutaneously into the fatty tissue overlying the deltoid muscle.

Vaccine Recommendations

Since 2008, most doses of anthrax vaccine have been administered by the Department of Defense as PrEP to high-risk members of the military. Anthrax vaccine is not recommended for the general public, and not recommended for or available to civilian travelers. The US Strategic National Stockpile stores vaccine and antibiotics, so they are immediately available if needed, to address public health emergencies. The FDA has approved 2 scenarios:

Scenario 1

PrEP: Intramuscular administration of vaccine to 18- to 65 -year-old adults at risk by occupation:

- Laboratory professionals who work with anthrax
- Veterinarians, farmers, ranchers, livestock handlers, and abattoir workers
- Members of the US military as determined by the Department of Defense
- Emergency responders, on a voluntary basis

The recommended PrEP vaccination schedule includes five doses over an 18-month period, with additional boosters to maintain protection. The first 3 doses, given at 0, 1, and 6 months apart, are considered the primary series. Once the primary series is complete, the vaccine recipient is considered protected, and can start work in at-risk areas with appropriate personal protective equipment and biosafety practices. Documentation of seroconversion is not required. The fourth and fifth doses are given 12 and 18 months after the first dose. The 2019 Advisory Committee on Immunization Practices (ACIP) recommendations state that following the 5 dose series administered at time 0, 1, 6, 12, and 18 months, individuals who remain at high risk should receive annual booster doses of vaccine. Those not at high risk require boosters every 3 years. PrEP with anthrax vaccine is not recommended for pregnant women.

Scenario 2

In the event of an act of bioterrorism involving the large-scale release of anthrax spores, the FDA has approved PEP to be administered *subcutaneously* over the deltoid muscle in unvaccinated individuals *of all ages:*

- Subcutaneous route is preferred when administering vaccine as PEP, because achievable antibody titers are higher at 4 weeks when compared with intramuscularly dosing.
- Requires 3 injections in the first month. The first dose is given at the time of exposure, followed by doses at 2 weeks and 4 weeks.
- Immunocompetent individuals 18–65 years of age should also receive antibiotic prophylaxis for 42 days starting at the time of the first vaccine dose.
- Immunocompromised individuals 18–65 years of age should also receive antibiotic prophylaxis for 60 days starting at the time of the first vaccine dose.
- Children less than 18 years old, adults more than 65 years old, and women who are pregnant or nursing should also receive antibiotic prophylaxis for 60 days starting at the time of the first vaccine dose.

  Coadministration with other vaccines has not been evaluated.

Immunizing Antigen

The immunizing antigens in anthrax vaccine are derived from cultures of an avirulent, nonencapsulated *B. anthracis* strain grown in protein-free medium

supplemented with amino acids, vitamins, inorganic salts, and sugars. Vaccine is formulated using filtrates of sterilized bacterial culture medium containing the bacterial proteins that were released during incubation, including the 83 kDa protective antigen (PA) protein.

Additives and Excipients

Additives and excipients included in the final vaccine formulation include 1.2 mg/mL of aluminum adjuvant, as aluminum hydroxide in saline, 25 μg/mL benzethonium chloride as preservative, and 100 μg/mL formaldehyde as an inactivating ingredient.

The vial stopper contains natural rubber latex.

Vaccine Storage, Preparation, and Administration

The vaccine is formulated in multidose vials and appears as a milky white suspension. It should be stored under refrigeration between 2 °C and 8 °C, and should not be frozen. Administration is by intramuscular or subcutaneous injection.

Contraindications to Vaccine

Anthrax vaccine should not be used as PrEP in anyone who had a serious life-threatening reaction to a previous anthrax vaccine, who had a severe allergy to any anthrax vaccine component, including latex, aluminum, benzethonium chloride, and formaldehyde, or who are pregnant.

The use of anthrax vaccine for PEP during pregnancy and for those who developed a serious reaction to a previous dose can be considered if the potential benefits outweigh potential risks.

Warnings and Precautions for Vaccine Use

Individuals who are recovering from a moderate-to-severe illness are advised to postpone vaccine when used as PrEP. Individuals with a past history of natural anthrax infection may be at increased risk for developing a severe local reaction to the vaccine.

The immune response to vaccine may be diminished in those with underlying immunocompromising conditions.

Side Effects and Adverse Events

Common Side Effects

The most common reported local adverse reactions, occurring in 10% or more of all recipients, are injection site tenderness, pain, erythema, and edema. The most common systemic adverse events, occurring in 5% or more of all recipients, include muscle ache, fatigue, and headache.

In a 5-year open-label safety study of PrEP involving the administration of 15,907 doses to 7000 textile workers, 24 (0.15%) developed severe local reactions defined as induration measuring more than 120 mm, marked limitation in arm movement, or axillary node tenderness. Four (0.06%) serious adverse events were reported including 1 subject who developed transient fever, chills, nausea, and general body aches.

The most common adverse events reported in an open-label PEP study involving 200 healthy adults were headache (4.0%), fatigue (3.5%), skin hyperpigmentation (3.5%), decreased joint range of motion (2.5%), and myalgia (2.5%).

Vaccine Immunogenicity

Efficacy justification for the use of anthrax vaccine was based on animal models of inhalation anthrax under the FDA's Animal Rule, since challenge studies in humans are not ethical. Animals (rabbits, then nonhuman primates) were given two doses of vaccine 4 weeks apart, and then subsequently challenged with aerosolized anthrax spores at 200 times the 50% lethal dose. Serologic correlates of immune protection were calculated from the survival data.

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Chapter 8
Cholera

Cynthia Bonville and Joseph Domachowske

Cholera

Etiology

Cholera is a small intestinal infection caused by certain toxin-producing strains of the Gram-negative bacillus, *Vibrio cholerae*. The organism is a facultative anaerobe with a single unipolar flagellum that occurs in both freshwater and marine habitats where they attach themselves to the chitin-containing exoskeletons of crabs, shrimp, and other shellfish. Cholera occurs when toxigenic strains of *V. cholerae* are ingested, colonize the small intestine, and begin to express the 2-subunit cholera toxin cyxA/cyxB. The toxin stimulates the movement of fluid and electrolytes across the epithelium into the intestinal lumen, causing profuse watery diarrhea. Cholera is endemic in areas with poor sanitation where sporadic cases can quickly lead to epidemics. Disease is uncommon in developed countries, where occasional small outbreaks are easily controlled.

Many serogroups of *V. cholerae* have been identified, but only serogroups O1 and O139 cause cholera epidemics. Before 1992, when serogroup O139 was first identified in Bangladesh as the cause of a regional outbreak, serogroup O1 was the only pathogen known to cause cholera. *V. cholerae* serogroup O1 continues to be responsible for nearly all cholera outbreaks and epidemics globally. Sporadic cases of infections caused by serogroup O139 continue to be reported from Asia, with only rare reports from other areas of the world. During cholera epidemics, both disease incidence and mortality are highest among children younger than 5 years of age.

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Epidemiology of Cholera

Globally, cholera epidemics are caused by toxigenic strains of *Vibrio cholerae* serogroup O1. Outbreaks and sporadic cases caused by serogroup O139, first identified from Bangladesh, have not spread outside of Asia. The World Health Organization has identified cholera as pandemic in Africa, Asia, and Latin America for more than 50 years. Sub-Saharan Africa carries the greatest global burden accounting for 60% of the world's nearly 12 million cases between the years of 2008 and 2012. Southeast Asia carries the second highest burden globally, accounting for 30% of cases. In 2017, case fatality rates were highest in the African nations of Chad (6.8%), Angola (5.2%), and Zambia (3.2%). Densely populated areas of the Indian subcontinent, especially across India and Bangladesh, are home to the world's greatest numbers of individuals at risk for developing cholera. Outbreaks and epidemics of cholera are indicators of inadequate access to clean water and sanitation and a general lack of social development. Globally, 2.4 billion people live in unsanitary conditions, 2 billion use water sources that are contaminated with human and animal waste, and 950 million practice open defecation due to the lack of toilets or latrines. The highest risk areas for cholera outbreaks include urban slums and camps for displaced persons or refugees. Of the estimated 1.3–4 million people infected with cholera each year worldwide, between 21,000 and 143,000 die. In 2017, 34 countries reported cases of cholera to the WHO, but a single large epidemic in Yemen, related to civil unrest, conditions of war, and ongoing conflicts with neighboring countries, was responsible for causing 84% of all cases and 41% of deaths worldwide that year.

Global Cholera Pandemics 1 Through 7

Cholera is one of the oldest known diseases with potential to cause pandemics. Cholera-like illnesses are described in ancient writings from India and Greece dating back as early as the fifth century BC. Throughout recorded history, endemic cholera is described from areas of the Ganges and Brahmaputra river deltas in Eastern India and Bangladesh.

The first pandemic to be described began in 1817 at the Ganges River delta, then spread via trade routes, across Asia to the Persian Gulf, and throughout Southern Europe over a 6-year period, ending in 1823. The world's second pandemic endured much longer, again originating in India from the delta of the Ganges River. From 1829 to 1851, cholera spread throughout Asia to the Middle East, and for the first time crossed the Atlantic spreading to North America and Latin America. The third global pandemic proved to be the deadliest to date. Its origin was again traced to India, this time spreading through Europe, including Great Britain where the infection killed more than 23,000 people. In 1854, British physician John Snow carefully mapped out cases of cholera that were occurring in a London neighborhood,

subsequently identifying contaminated water from the public well on Broad Street as the source of the outbreak. Global pandemics 4 (1863–1875), 5 (1881–1896), and 6 (1899–1923) also had their origins in India. Robert Koch first isolated the bacterium in culture in 1883, during the fifth pandemic.

More than a half million people died from cholera in India alone between 1918 and 1919. The world's seventh and current cholera pandemic, caused by *V. cholerae* O1 El Tor biotype, began in 1961. Its origin was in Indonesia, not India. After spreading through Asia, the pandemic reached Africa, the Middle East, southern Europe, and the former USSR in 1971. Punctuated by periods of emergence and re-emergence, the O1 El Tor biotype was first identified in Latin America in 1991.

The global burden from cholera during 2018 is shown in Fig. 8.1. During 2018, outbreaks continued throughout much of Africa where 16 nations reported a total of 120,000 cases to the WHO. Nigeria, Zimbabwe, and the Democratic Republic of the Congo were disproportionately affected. An epidemic in Yemen that began in late 2016, fueled by ongoing conflict with Saudi Arabia, civil war, famine, and lack of access to clean water and basic health care, saw an additional 370,000 cases of cholera in 2018 alone. Cholera in the Western Hemisphere paled in comparison during 2018, but notable for the 3777 cases reported from Haiti where thousands of cases continue to be reported annually since 2010. In stark contrast, 3 sporadic cases of cholera were reported in 2018 from Vancouver, Canada. The infections were acquired locally following the consumption of herring eggs collected in a nearby creek. Disease did not spread beyond the 3 primary cases.

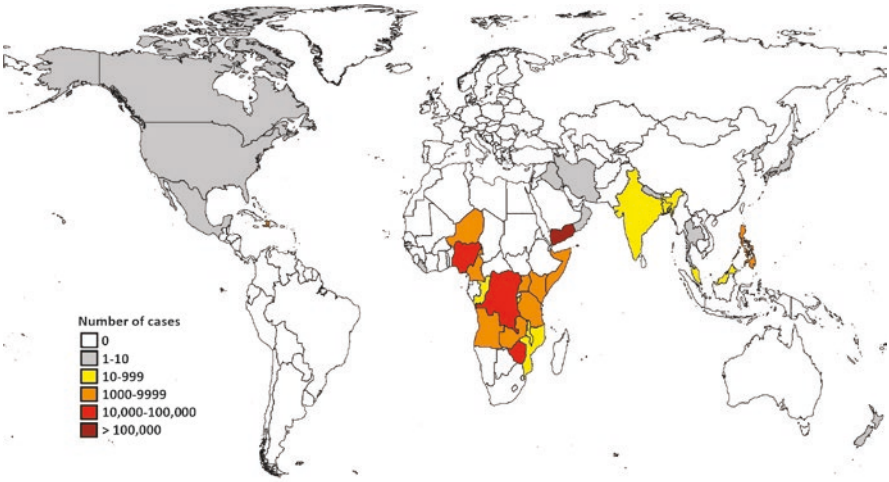

Fig. 8.1 Global burden of cholera 2018. Shown is a world map indicating the total numbers of cholera cases reported during 2018 by country. Note that "0" is used to indicate either that no cases were reported (no report submitted), or that 0 cases were reported. (Source of data used to generate the original figure: https://www.who.int/immunization/diseases/typhoid/en/)

Cholera in the USA

During the early and mid-1800s, cholera was endemic to the USA. By the mid-1800s, the introduction of modern water and sewage treatment systems had virtually eliminated the spread of disease via contaminated water. Reports of sporadic cases tapered quickly. Currently, with one exception, fewer than 20 cases per year are reported. Identified cases over the past six decades are usually in travelers returning from areas where disease remains endemic, or from the ingestion of raw or undercooked seafood from the Gulf Coast. At-risk individuals include health-care workers who treat cholera patients, mission response workers in areas where cholera has been identified, and travelers to endemic regions who do not practice safe food and water precautions.

In 1989, the US Centers for Disease Control and Prevention started COVIS, a Cholera and Other Vibrio Illness Surveillance program, in close collaboration with the FDA and the Gulf Coast states of Alabama, Florida, Louisiana, and Texas. From 1989 to 2006, only infections shown to be caused by toxigenic *V. cholerae* serogroup O1 or O139 were nationally notifiable. In 2007, surveillance expanded to include all infections caused by members of the *Vibrionaceae* family. Such infections are classified as vibrioses to distinguish them from cholera. Between 2010 and 2014, 96 cases of cholera were reported in the USA through COVIS. The majority of cases were associated with travel to endemic regions and/or consumption of seafood. The higher than expected numbers during this period of time were caused, at least in part, by the close proximity of the USA to Haiti where cholera had become epidemic following the earthquake of 2010. Of the 96 cases of cholera reported to COVIS in the USA, between 2010 and 2014, 64 (67%) had a history of recent travel to Haiti or the Dominican Republic. Given the magnitude of the epidemic in Haiti, and the close geographic proximity between Haiti and the USA, it is surprising that more cases have not spread to the USA.

Transmission

Fresh, brackish, and marine waters are the natural environment for *Vibrio cholerae* where the organism closely associates itself with crustaceans and mollusks. Infection is transmitted through ingestion of contaminated food or water via the fecal-oral route, often where sanitation practices are poor. The majority of individuals who become infected with *V. cholerae* do not develop symptoms, but still shed bacteria in their stool for as long as 10 days. Crowded living conditions, especially those with poor sanitation, facilitate spread. Bacteria closely associate with zooplankton and chitin-containing shells of crustaceans (crabs, shrimps, lobsters) and molluscs (clams, oysters) shellfish, explaining why individuals who consume raw or undercooked seafood have an increased risk for infection.

Clinical Presentation

The clinical presentation of cholera ranges from asymptomatic infection with shedding to life-threatening, rapidly progressive secretory diarrhea. Approximately 10% of those infected develop severe manifestations of disease. Severe infection is characterized by profuse watery diarrhea with very frequent, large volume rice-water stools with or without vomiting. Fever is usually absent. Untreated, between 25 and 50% of those with severe disease develop complications that may include severe electrolyte imbalances, renal failure, hypovolemic shock, circulatory collapse, and death. Young children, pregnant women, and their fetuses are at highest risk for mortality.

Following exposure, the median incubation period is 1.4 days with a range between 8 hours and 5 days. Re-exposure can lead to reinfection, but the infection is not associated with the development of a carrier state.

Management

Rehydration is paramount. The most severe cases require rapid treatment with intravenous fluids and antibiotics. Mild-to-moderate, and some severe, infections are managed successfully with oral rehydration solution supplemented with intravenous fluids with electrolytes as needed. With fluid and electrolyte support and replacement, rapid recovery is expected without long-term sequelae. Zinc therapy for children under 5 years of age reduces the duration of the illness. Antibiotics should be used in combination with hydration therapy. When choosing an antibiotic, it is important to consider local antibiotic susceptibility patterns, because antimicrobial resistance is becoming more common. In most circumstances, the first-line antibiotic options are doxycycline for adults and azithromycin for children and pregnant women. The use of antibiotic prophylaxis is generally discouraged during outbreaks. Prevention of spread requires careful attention to toileting practices and personal hygiene.

Cholera Vaccine

WHO-qualified cholera vaccines include the brand names Dukoral (SBL Vaccin AB), Shanchol (Biotechnics Limited), Euvichol-Plus (Eubiologics), and Vaxchora (PaxVax Bermuda Ltd). Vaxchora is the only cholera vaccine available for use in the USA where it was approved for use by the FDA on June 10, 2016. It is licensed for use as an orally administered active immunization against *Vibrio cholerae* serogroup O1. The recipient should avoid eating or drinking for 60 minutes before and after ingesting the vaccine. Each dose is supplied as 2 components. Packet 1 contains a vaccine buffer and packet 2 contains the live attenuated bacteria. Both components should be stored at 2 °C to 8°, protected from light and moisture. Prior to

administration, the vaccine must be reconstituted. Using a clean disposable cup, 100 mL cold water is added to the contents of the buffer packet. Effervescence will occur. The buffer solution is stirred until completely dissolved. Next, the contents of packet 2, containing the lyophilized attenuated bacteria, are added to the buffer solution, and stirred for a minimum of 30 seconds. The final suspension is slightly cloudy and may contain white particulates. The entire 100 mL volume should be consumed within 15 minutes of reconstitution. The vaccine is licensed for use as a single dose in adults to be administered at least 10 days prior to potential exposure. Booster doses are not recommended. Vaccine strain, live attenuated bacteria are shed in stools of recipients for at least 7 days.

Immunizing Antigen

The immunizing antigen included in cholera vaccine is a live attenuated serogroup O1 classical Inaba strain of *V. cholerae*. Attenuation was achieved by deleting the catalytic domain sequence of both copies of the ctxA toxin gene, thereby preventing the synthesis of active cholera toxin. The immunogenic nontoxic B subunit of cholera toxin encoded by ctxB is unaltered. For epidemiologic purposes, a marker has been inserted into the hemolysin gene locus (hlyA) to facilitate the differentiation between vaccine strain and wild type *V. cholerae* in the laboratory.

The attenuated bacteria are grown in fermenters in a culture medium containing casamino acids, yeast extract, mineral salts, and an antifoaming agent. Bacteria are then collected by filtration, diafiltered, and concentrated. The formulation is stabilized using a solution containing the antioxidant ascorbic acid, and 2 cryoprotectants: hydrolyzed casein and sucrose. The bacteria are lyophilized, milled, and blended with dried lactose as a desiccant and bulking agent. The vaccine buffer component consists of sodium bicarbonate to neutralize gastric acid, sodium carbonate, ascorbic acid, and dried lactose.

Additives and Excipients

The final formulation of cholera vaccine contains no more than 8.6 mg ascorbic acid, 17.1 mg hydrolyzed casein, 165 mg sucrose, 2 g dried lactose, 2.4 g sodium bicarbonate, and 0.5 g sodium carbonate per dose. It is preservative-free.

Vaccine Recommendations

A single, one-time dose of cholera vaccine is recommended for adults 18 to 64 years of age who will be traveling to an area with any cholera activity reported within the last year unless otherwise contraindicated. Vaccination is not required as a condition for entry into any country or region.

Contraindications to Vaccine

Cholera vaccine is contraindicated in those individuals who developed a life-threatening allergic reaction to a previous dose, and those with a known severe allergy to any vaccine component. Individuals with a moderate or severe acute illness should postpone immunization until they recover.

Warnings and Precautions for Vaccine Use

Cholera vaccine should not be administered to individuals who are currently being treated with or were treated with systemic antibiotics in the last 14 days. If needed for malaria prophylaxis, treatment with chloroquine should not be started until at least 10 days after cholera vaccination. Vaccine strain bacteria are shed in feces for at least 7 days after receipt, indicating the potential for transmission to nonvaccinated close contacts. Attention to proper hand washing, especially after bathroom use and during food handling, is important to prevent transmission to others. Safety and effectiveness have not been established in immunocompromised people, and careful consideration should be given when administering vaccine to individuals with immunocompromised close contacts.

Side Effects and Adverse Events

Cholera vaccine is well tolerated. When side effects occur, the vast majority are mild and self-limiting, resolving within a few days. In clinical trials, the most common AEs (incidence >3%) occurring within 7 days of vaccination included fatigue (31%), headache (29%), abdominal pain (19%), nausea/vomiting (18%), decreased appetite (17%), and diarrhea (4%). Pooled analyses of results from 4 randomized, controlled clinical trials indicated that the overall rate of severe adverse events was 0.6% in vaccine recipients and 0.5% in control groups. None of the serious adverse events were considered to be related to the vaccination.

Estimated Effectiveness or Efficacy from Clinical Vaccine Trials

A placebo-controlled efficacy trial of cholera vaccine that included 197 healthy adult volunteers showed 90.3% efficacy at 10 days post vaccination, and 79.5% efficacy at 3 months post vaccination. An immunogenicity trial in US and Australian adult volunteers showed that 93.5% of all vaccine recipients developed protective antibody responses.

Impact of Vaccine on Disease Burden

Mathematical modeling suggests that maintaining community immunization rates of 70% or higher among residents of Bangladesh 1 year of age and older is sufficient to interrupt cholera transmission. Since the creation of a global oral cholera vaccine stockpile in 2013, more than 50 million doses have been used in mass vaccination campaigns in efforts to interrupt transmission during outbreaks. Between 2014 and 2017, 18 million doses of vaccine were shipped to 15 countries including Cameroon, Democratic Republic of the Congo, Ethiopia, Guinea, Haiti, Iraq, Malawi, Mozambique, Nepal, Niger, Somalia, South Sudan, Sudan, Tanzania, and Zambia. The rationale for distribution included humanitarian crises (37%), outbreak control (36%), and ongoing endemic disease (27%). Targeted shipments to the most affected regions of Africa continued through 2018 and 2019.

Civil war and ongoing conflict with neighboring Saudi Arabia quickly escalated to a massive humanitarian crisis in the Middle Eastern country of Yemen. The associated unsanitary and crowded living conditions, famine, and malnutrition incited the largest and fastest spreading cholera outbreak in recorded history. From late 2016 to the end of 2019, nearly 2.5 million cases and 4000 deaths have occurred in Yemen. Approximately 25% of those affected are children under 5 years of age. During early October 2018, a pause in fighting, known as the "*Days of Tranquility*," allowed the opportunity for public health workers to vaccinate more than 300,000 individuals, including 164,000 children. The campaign was life-saving for many, but the benefits will be short-lived unless or until the root cause of the massive crisis can be solved.

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Chapter 9
Dengue

Cynthia Bonville and Joseph Domachowske

Dengue Infection

Etiology

Dengue, or dengue fever, is a mosquito-borne infection endemic to tropical and subtropical areas of the world caused by dengue virus. Dengue viruses are enveloped, single-stranded RNA members of the family *Flaviviridae*, genus *Flavivirus*. Four serologically and genetically distinct serotypes, 1, 2, 3, and 4 exist. Natural disease is believed to confer life-long immunity to the infecting serotype but only partial and temporary protection against the other 3 serotypes. Following the bite of an infected mosquito, the disease has an incubation period of 4–7 days, occasionally longer.

Epidemiology: Global Burden of Disease

Dengue is the most common and most rapidly spreading arbovirus infection in the world, presenting major public health challenges in tropical and subtropical regions. Seasonal outbreaks are affected by rainfall, temperature, relative humidity, and urbanization. Specific regions can be hyperendemic for any or all four dengue serotypes. Worldwide, cases of dengue are underreported because most infections are asymptomatic or mild, and therefore easily managed without seeking medical care. Globally, of the estimated 300–500 million people infected with dengue each year, approximately 100 million develop symptomatic disease, 0.5 million develop severe

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illness requiring hospitalization, and 20,000 die. Prior to 1970, only 9 nations worldwide reported widespread dengue epidemics. Now, just 50 years later, dengue has become endemic to more than 100 countries in tropical and subtropical regions of Asia, Africa, Central and South America, the Caribbean, and island nations of the Western Pacific. The 30 countries that reported the greatest numbers of dengue cases to the WHO between 2006 and 2015 are shown in Fig. 9.1**.** Infection is likely to be just as widespread, or even more so, throughout parts of Africa despite the overall lower numbers that are reported. Dengue has also spread to areas along the Gulf Coast of the USA, and to the most northern coastal areas of Australia.

More than three million people were infected with dengue during the 2019 epidemic in the region of the Americas. Of those infected, nearly 1% developed severe disease and 1,538 died. At least 34 countries were affected. In early 2020, ongoing higher-than-usual number of dengue cases led the US Centers for Disease Control and Prevention (CDC) to issue a level 1 travel alert for the nations of Belize, Brazil, Colombia, Costa Rica, Dominican Republic, El Salvador, Guadeloupe, Guatemala, Honduras, Mexico, Nicaragua, Peru, and Saint Martin. During this same period, increased dengue activity across areas of Asia and the Western Pacific disproportionately affected the countries of Bangladesh, Sri Lanka, Nepal, Pakistan, the Philippines, Singapore, Micronesia, French Polynesia, the Marshall Islands, and Palau. Problematic areas of Africa included the countries of Benin, Ivory Coast, Réunion, and Tanzania.

Epidemiology: Burden of Disease in the USA

In 2010, with the recognition that the epidemiology was changing quickly, the CDC added dengue to the list of nationally notifiable diseases. Infection had already been endemic in Puerto Rico for at least 50 years where 60% and 80% of the island's

Fig. 9.1 Shown is a world map indicating the 30 countries that reported the highest numbers of dengue cases to the World Health Organization between 2006 and 2015. (Source of data used to generate figure: https://www.who.int/activities/improving-data-for-dengue)

population are infected by at least one serotype before age 20 or 30 years, respectively. Similarly, dengue is endemic in the US Virgin Islands and sporadically endemic in American Samoa, Northern Marianas, and Guam.

Prior to World War II (prestatehood), dengue was also endemic to Hawaii where autochthonous transmission was once very common. Since World War II, only three outbreaks of dengue have been described. The most recent Hawaiian cluster, reported in 2015, involved 107 cases, 15 hospitalizations, and no deaths. Similarly, dengue was once endemic to the region of the Gulf Coast. Outbreaks in Texas, for example, were a regular occurrence until mosquito prevention campaigns, started in the 1940s, effectively eliminated disease transmission in the region. As reports of disease waned, mosquito prevention campaigns slowed, until eventually being discontinued altogether. As a result, mosquito populations resurged, resulting in dengue outbreaks in 1980, 1999, and 2005. More recently, in 2013, a cluster of 53 cases in Texas followed a much larger outbreak of more than 5,500 cases in the neighboring Mexican state of Tamaulipas. The states of Texas and Tamaulipas share a 200-mile-long border extending along the Rio Grande from Brownsville to Loredo, Texas. Sporadic cases, and occasional small outbreaks, are also described from the state of Florida. Despite the potential for autochthonous transmission of dengue in the USA, most cases reported outside of Puerto Rico and other island territories are related to leisure travel to endemic areas including the islands of the Caribbean (Fig. 9.2). In addition to the 1,183 travel-associated infections reported in 2019, 20 locally transmitted cases of dengue were reported from 3 US states and the District of Columbia (DC): 1 each from North Carolina and DC, 2 from Texas, and 16 from Florida.

The rapid spread of dengue worldwide, fueled by the proliferation of its mosquito vector, has been linked to population growth and higher population densities, human migration from rural to urban settings, absence of readily available clean water, inadequately funded or organized public mosquito control programs, global travel, and climate change that favors mosquito survival, leading to longer transmission seasons and further geographical spread. Together, these and other factors have been associated with a 15-fold increase in reported dengue cases since 2000. Epidemiologic modeling estimates that between 3.5 and 4 billion people worldwide are currently at risk for dengue infection. Prediction models show that during the next 30 years, dengue is likely to expand further into the southeastern United States, along coastal regions of China, Japan, Turkey, and Spain, and into northern Argentina, southern Africa, and inland Australia.

Transmission

Dengue is transmitted primarily by the bite of infected female *Aedes aegypti* mosquitoes. *Ae. aegypti* mosquitoes are daytime biters and are also recognized as the primary vector for the transmission of Zika, yellow fever, and chikungunya viruses. The less efficient vector of transmission, *Ae. albopictus*, has a geographic spread across 32 US states due to its tolerance of colder conditions.

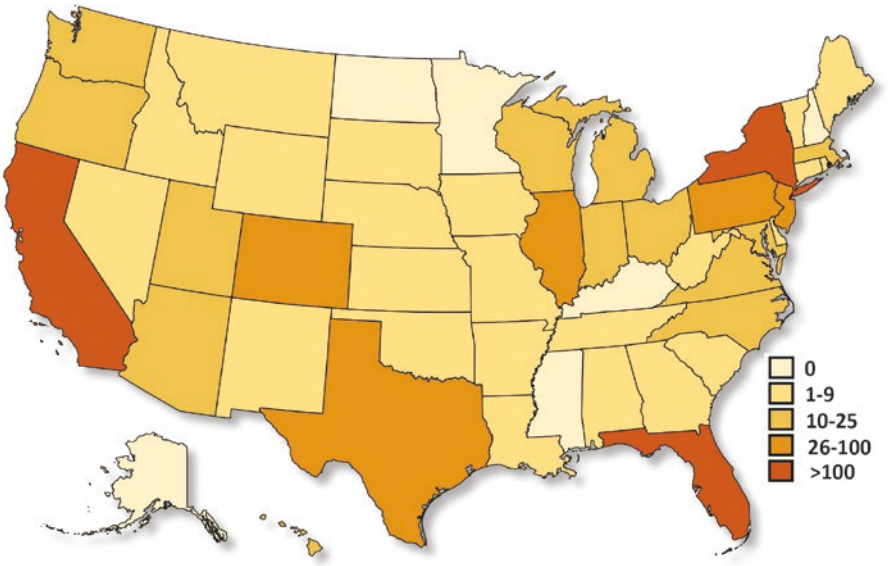

Fig. 9.2 Shown is a state by state distribution map of travel-associated dengue cases reported to the US Centers for Disease Control in 2019. (Source of data used to generate figure: Centers for Disease Control and Prevention, https://www.cdc.gov/dengue/statistics-maps/2019.html. This material is available on the agency website at no charge: Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the US Government, Department of Health and Human Services, or Centers for Disease Control and Prevention)

The transmission cycle of infection begins when a female *Ae. aegypti* mosquito takes a blood meal from a dengue-infected individual. Virus, present in the blood meal, replicates in the mosquito midgut and then disseminates to the mosquito's salivary glands. During her next blood meal, virus from the mosquito's salivary glands infects the new human host. After the bite of the infected mosquito, virus replicates in local dendritic cells and tissue macrophages. Infected cells migrate to the lymphatics and the bloodstream, resulting in the dissemination of the infection to multiple target tissues and organs.

Clinical Presentation

The illness is very mild or completely asymptomatic in 75% of those infected. The remaining 25% of cases can be divided into two general categories: dengue fever and severe dengue.

Dengue fever is a mild-to-moderate disease that presents as an acute influenza-like illness. Symptoms usually last no more than 2–7 days. The nonspecific, and often vague symptom, complex overlaps those of many other viral illnesses. Most cases of

dengue are self-limiting and resolve without sequelae. The World Health Organization defines dengue as an illness associated with the abrupt onset of high fever and 2 or more of the following additional clinical findings: severe headache, retro-orbital pain, generalized myalgia, arthralgia and bone pain, abdominal pain, nausea, vomiting, anorexia, altered taste sensation, adenopathy, or a generalized maculopapular rash.

Severe dengue, a condition previously referred to as dengue hemorrhagic fever, is a dengue illness with a critical phase that develops between 3 and 7 days after symptom onset. Severe dengue develops in approximately 5% of symptomatic individuals. This risk is increased during an individual's second heterotypic dengue infection when the 2 bouts of illness are separated by more than 18 months. Severe dengue can develop in anyone, but approximately 95% of severe cases are associated with the second dengue infection. Severe infection can be explained, at least in part, by the phenomenon referred to as antibody-dependent enhancement (ADE) of disease. Pre-existing antibodies that were formed in response to the first dengue infection that cross-react with the second dengue virus bind to it, thereby facilitating its entry into dendritic cells, and macrophages via the antibody's Fc receptor. This early virus-host interaction allows the newly infecting virus to evade the host responses that normally limit infection. The resulting higher viral burden and imbalanced immune response trigger capillary endothelial pathology that leads to vascular leakage and bleeding. In regions hyperendemic for dengue, ADE is seen primarily in children less than 15 years of age. Across low endemic regions, ADE is more commonly seen in adults. Pregnancy is another well-recognized risk factor for the development of severe dengue, especially during the third trimester.

Severe dengue is a medical emergency. Signs for the development of this complication are usually first noticed at the time of defervescence, then last for 24–48 hours. Warnings signs for severe dengue include intractable abdominal pain, persistent vomiting, fluid accumulation, tachypnea, bleeding of the gums or nose, hematemesis, hematochezia, fatigue, restlessness, irritability, and the development of hepatomegaly.

Patients with marked vascular permeability develop severe disease within hours with rapid development of pleural effusions, ascites, hypoproteinemia, and hemoconcentration. Bleeding from the mucous membranes and gastrointestinal tract may be severe and difficult to control. Hypovolemic, hemorrhagic shock leads to severe organ impairment, coma, and death. If proper, aggressive supportive care can be maintained for 48–72 hours, the vascular leakage will resolve. This subgroup of patients generally recovers completely, although adults may have prolonged weakness and myalgias that last for several months.

Management

There is no specific treatment or cure for dengue infection. Infected individuals should pay close attention to maintaining hydration. Headache, bone pain, and fever should be managed with acetaminophen, not aspirin or other nonsteroidal

anti-inflammatory medications such as ibuprofen. Early detection of severe dengue by recognizing the early warning signs is the key to improving survival rates. Hospitalization with maintenance of proper fluid volume reduces fatality from 20% to less than 1%.

Prevention

Mosquito control and bite prevention is a key component to dengue prevention programs. Environmental controls known to reduce or eliminate mosquito breeding include managing or removing sources of free-standing water, the proper disposal of solid waste, weekly emptying and cleaning of domestic water storage vessels, and application of insecticide to outside water storage containers. Environmental measures that reduce the risk for mosquito bites include the use of window screens, insect repellants, and insecticide-treated materials. Clothing that minimizes skin exposure should be worn when possible. Community engagement and education on the importance and logistics of mosquito control can be highly effective.

Dengue Vaccine

The commercially available dengue vaccine is a replication-competent, tetravalent product known as CYD-TDV. Its name is based on the unique manner in which the vaccine is formulated. The first three letters, CYD, are used to denote that the vaccine is a *C*himeric derivative of the live, attenuated *Y*ellow fever vaccine strain 17*D*. Yellow fever and dengue are both flaviviruses. Basic similarities in their genomes allowed for genetic manipulation of the live attenuated yellow fever virus whereby coding sequences for surface proteins could be removed and replaced with the homologous sequences from each of the four dengue virus serotypes. The second three letters in the vaccine name, TDV, reflect the change by denoting *T*etravalent *D*engue *V*accine. The chimeric viruses included in the CYD-TDV vaccine are, therefore, capable of inducing the production of antibodies directed against the surface proteins of all 4 dengue serotypes. When administered to dengue-naïve individuals, CYD-TDV partially mimics primary dengue infection, thereby increasing the risk for severe dengue during their first natural dengue infection. This risk is similar to that observed epidemiologically among individuals who develop a second dengue infection. CYD-TDV is, therefore, only recommended for individuals who have already had their first natural infection with dengue. The vaccine is given as three injections over a year. It was first licensed in 2015 for use in Mexico. In its 2018 position paper, the World Health Organization recommended that the vaccine be administered to individuals between the ages of 9 and 45 years who live in endemic regions with a high burden of disease, defined as seroprevalence of greater than 70% in the target age group. Vaccine is not recommended in endemic regions

where seroprevalence is below 50% in the target age group. Vaccine should only be administered to individuals with documentation of at least one previous dengue infection or a positive serologic test result at the time of vaccination. The CYD-TDV dengue vaccine was approved by the US FDA on May 1, 2019, and added to the World Health Organization's list of prequalified vaccines on March 25, 2020.

Type of Vaccines Available in USA

In the USA, the CYD-TDV dengue vaccine is marketed by Sanofi Pasteur under the trade name Dengvaxia. The vaccine is approved for use in children between the ages of 9 and 16 years who live in dengue endemic regions and who have laboratory-confirmed evidence of previous infection with at least one dengue serotype. The vaccine is a live attenuated, recombinant tetravalent (representing four serotypes) product comprised of a yellow fever virus 17D strain backbone. It is considered a genetically modified organism (GMO).

Each dose of the vaccine contains between 4.5 and 6.0 log10 median cell culture infectious doses of each of the four chimeric yellow fever-dengue virus serotypes. The three-dose vaccine series is administered as 0.5 mL injections at 6-month intervals (at month 0, 6 and 12). Each dose is provided by the manufacturer in two vials: one containing the lyophilized vaccine immunogens and the other containing the 0.4% sodium chloride diluent for reconstitution. Prior to use, vaccine should be stored under refrigeration between 2 °C and 8 °C protected from light. Vaccine should never be frozen.

To prepare a dose for injection, the caps from both vials are removed. The top stoppers are cleaned with alcohol before withdrawing 0.6 mL from the diluent vial and transferring it to the vial containing the lyophilized vaccine. The vaccine is suspended using a gentle swirling movement. The reconstituted product is clear and colorless. Trace amounts of white to translucent proteinaceous particles are acceptable, cloudy solutions should be discarded. Once the fluid appears homogeneous, 0.5 mL is drawn into a syringe. Vaccine should be administered immediately after reconstitution; however, refrigeration at 2 °C to 8 °C for 30 minutes is acceptable if necessary. Vaccine not administered within 30 minutes of reconstitution should be discarded.

Immunizing Antigen

Researchers developed the CYD-TDV dengue vaccine using recombinant DNA technology. They began with the live attenuated virus used to manufacture yellow fever 17D204 vaccine. The sequences of DNA encoding the yellow fever vaccine virus premembrane (prM) and envelope (E) proteins were removed, then replaced with the homologous coding sequences from dengue virus serotypes 1, 2, 3, and 4, resulting in

the formation of four new chimeric viruses. Each chimeric virus has the same yellow fever vaccine virus "backbone" with one of the four dengue virus serotype-specific prM and E gene sequences. Each of the four chimeric viruses is grown separately in Vero cell cultures under serum-free conditions, then harvested, and purified by membrane chromatography and ultrafiltration. A proprietary stabilizer solution is added, producing four monovalent drug substances. The four monovalent substances are combined, sterilized by filtration, filled into vials, and freeze-dried.

Additives and Excipients

The final vaccine product contains 2 mg sodium chloride, 0.56 mg essential amino acids 0.2 mg nonessential amino acids, 18.75 mg sucrose, 9.38 mg D-sorbitol, 0.18 mg, and 0.63 mg urea per 0.5 mL dose. No adjuvant or preservatives are added.

Vaccine Recommendations

US Pediatric Immunizations

The vaccine is approved for use in children 9–16 years old living in US regions with endemic disease including American Samoa, Guam, Puerto Rico, and the US Virgin Islands, who have laboratory-confirmed evidence of prior infection with at least one dengue serotype. Formal ACIP recommendations are pending discussion at an upcoming meeting.

Contraindications to the CYD-TDV Dengue Vaccine

The contraindications to receiving the CYD-TDV dengue vaccine include a history of a severe allergic reaction to a previous vaccine dose or to any vaccine component and the presence of a known immunodeficiency or treatment with immunosuppressive medications.

Warnings and Precautions for Vaccine Use

The CYD-TDV dengue vaccine is not approved for use in dengue seronegative or unknown serostatus individuals, because it may place those individuals at increased risk for the development of severe disease from natural dengue infection. This caveat is complicated by the lack of FDA-approved serologic tests to determine

dengue serostatus. Available non-FDA-cleared tests may produce false-positive results from cross-reacting antibody to other flaviviruses. Vaccine may not protect all vaccinees. It is important to maintain personal protective measures against mosquito bites when visiting or living in a dengue endemic region.

Data are not available on the safety and efficacy of the vaccine when administered concomitantly with other recommended adolescent vaccines. Safety has not been established for use during pregnancy. Inadvertent administration during pregnancy should be reported to the pregnancy registry maintained by the manufacturer at 1-800-822-2463.

Side Effects and Adverse Events

Common Side Effects

Adverse events reported from the administration of a three dose series to 2000 clinical trial subjects, aged 9–16 years from Latin America over a 12-month period, included pain (23–32%), erythema (2–4%), and/or swelling (2–4%) at the injection site. Systemic reactions included headache (30–40%), myalgias (20–29%), malaise (19–25%), asthenia (16–25%), and fever (6–7%). Over the course of nine clinical trials performed in children aged 9–16 years, serious adverse events were reported in 0.6% of vaccine recipients and 0.8% of placebo recipients. None of the serious adverse events were considered to be related to the CYD-TDV dengue vaccine.

Estimated Effectiveness or Efficacy from Clinical Vaccine Trials

Two phase III vaccine trials in Latin America showed similar efficacies of 81% and 77% against symptomatic, virologically confirmed dengue caused by any serotype, among subjects who were seropositive for dengue at baseline. Estimated vaccine efficacy derived from post licensure experience outside of the USA, prior to US licensure, showed 76% efficacy against confirmed symptomatic dengue in baseline seropositive recipients at 2-year follow-up, but only 39% efficacy against confirmed symptomatic dengue in baseline seronegative recipients. Seronegative recipients also showed an increased risk of hospitalization for severe dengue 18 months after vaccination. Follow-up 5-years later in areas with 70% or higher seroprevalence showed one excess case of severe dengue in seronegative vaccine recipients for every four cases of severe dengue that were prevented in the seropositive vaccine recipients. These data led to the US labeling indication for the CYD-TDV dengue vaccine to be used only in children 9–16 years of age who are confirmed to be dengue seropositive prior to vaccination.

In September 2018, 51 childhood deaths were reported during a large-scale vaccination campaign in the Philippines that involved 830,000 children. During review,

it was determined that 15 deaths were caused by dengue infection. The WHO reviewed the deaths, but was unable to make a causality determination. Unfortunately, despite the vaccine's potential to reduce dengue morbidity in this hyperendemic region of the world, vaccine confidence was eroded, ultimately leading to the revocation of its license in the Philippines.

Conclusion

Dengue is the most common and most rapidly spreading arbovirus infection in the world. The global burden of disease is associated with substantial morbidity and mortality, especially among children. Severe dengue can develop in anyone, but approximately 95% of severe cases are associated with the second dengue infection, largely explained by the enhancement of disease in presence of pre-existing antibody. Vector control efforts, and protection from mosquito bites, help to prevent the spread of dengue and related arbovirus infections. The tetravalent, chimeric dengue vaccine, CYD-TDV, has been shown to be safe and modestly effective at preventing disease when administered to children who have already been infected by natural dengue virus. In the absence of previous dengue exposure, however, the CYD-TDV vaccine partially mimics primary infection and increases the risk of severe dengue during subsequent infection.

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Chapter 10
Diphtheria

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Diphtheria Infection

Etiology

Diphtheria is caused by toxin-producing strains of *Corynebacterium diphtheriae*. The bacterial pathogen is an aerobic, Gram-positive, pleomorphic, non-spore-forming bacillus. The organism's key virulence factor, diphtheria toxin, is a potent exotoxin encoded by a bacteriophage that is present in toxigenic strains. After the bacteriophage infects the bacterium, phage DNA integrates into the bacterial genome. Nontoxigenic strains of *C. diphtheriae* can cause disease, but are much less virulent. Some strains of *C. pseudotuberculosis* and *C. ulcerans* are also infected with the phage, explaining how they produce illness so similar to diphtheria.

Diphtheria toxin comprises two segments, A and B. After segment B recognizes and binds to the target cell surface receptor, segment A enters the cell's cytoplasm and inactivates the host tRNA translocase (elongation factor 2). Loss of this enzyme blocks cellular protein synthesis in all cell types, but disproportionately affects cardiac myocytes, renal tubular cells, and neurons. Toxin also triggers the formation of a pseudomembrane at the site of the initial infection.

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Epidemiology

Worldwide, although outbreaks of diphtheria are uncommon, they still occur in countries with poor routine vaccination coverage and/or substantial pockets of unimmunized children. In the USA, during the prevaccine era, between 100,000 and 200,000 cases of diphtheria and 15,000 associated deaths occurred annually, with most of the disease burden among children under 5 years of age. Diphtheria vaccines emerged during the mid-1930s, but global uptake across low- and middle-income countries was not widespread until 1974 when the World Health Organization included diphtheria, tetanus, and whole cell pertussis (DTP) vaccine as a component of the Expanded Programme on Immunization. In 1980, 97,160 cases of diphtheria were reported to the World Health Organization, 80% of which occurred in just 6 countries (Table 10.1). Since 1980, the general trend has been a gradual decline in diphtheria cases, largely due to widespread immunization efforts (Fig. 10.1). By 2010, the total number of cases reported had reached historic lows, dropping 95% to fewer than 5000 cases per year. National crises such as civil unrest and/or war-like conditions are associated with outbreaks such as the 2018 surges in cases in Yemen and Venezuela, while other areas struggle more consistently to control the disease. For nearly four decades, year after year, the nation of India has ranked number one in reported cases, at times accounting for nearly 75% of the world's total cases. Other nations that have regularly ranked in the top six for the numbers of reported cases include Pakistan, Indonesia, and Nigeria. Nations that rank in the top six repeatedly are highlighted using a country-specific color (Table 10.1; India in blue, Pakistan in green, Indonesia in orange, and Nigeria in pink).

Transmission

Humans are the only known reservoir for *C. diphtheriae.* The primary modes of transmission are via respiratory droplets and through direct contact with infected skin lesions. The usual incubation period between exposure and development of symptoms is 2–5 days. The diagnosis of diphtheria is made primarily on clinical

Table 10.1 Countries reporting the most cases of diphtheria in 1980, 1990, 2000, 2010, and 2018

	1980		1990		2000		2010		2018	
Rank	Nation	Cases Reported	Nation	Cases Reported	Nation	Cases Reported	Nation	Cases Reported	Nation	Cases Reported
1	India	39231	India	8425	India	5125	India	3434	India	8788
2	Pakistan	14328	Indonesia	2200	Nigeria	3995	Indonesia	432	Yemen	2609
3	China	9767	Nigeria	1768	Russia	771	Nepal	146	Nigeria	1870
4	Kenya	6395	Pakistan	1371	Ukraine	365	Philippines	107	Indonesia	1026
5	Brazil	4646	Sudan	1342	Nepal	268	Iran	106	Venezuela	775
6	Indonesia	3674	Russia	1211	Latvia	264	Thailand	77	Pakistan	413
Global		97160	Global	22127	Global	11615	Global	4603	Global	16651

*Nations that rank in the top 6 repeatedly are highlighted using a country -specific color; India in blue, Pakistan in green, Indonesia in orange, and NIgeria in pink).

Nations that rank in the top 6 repeatedly are highlighted using a country-specific color; India in blue, Pakistan in green, Indonesia in orange, and Nigeria in pink

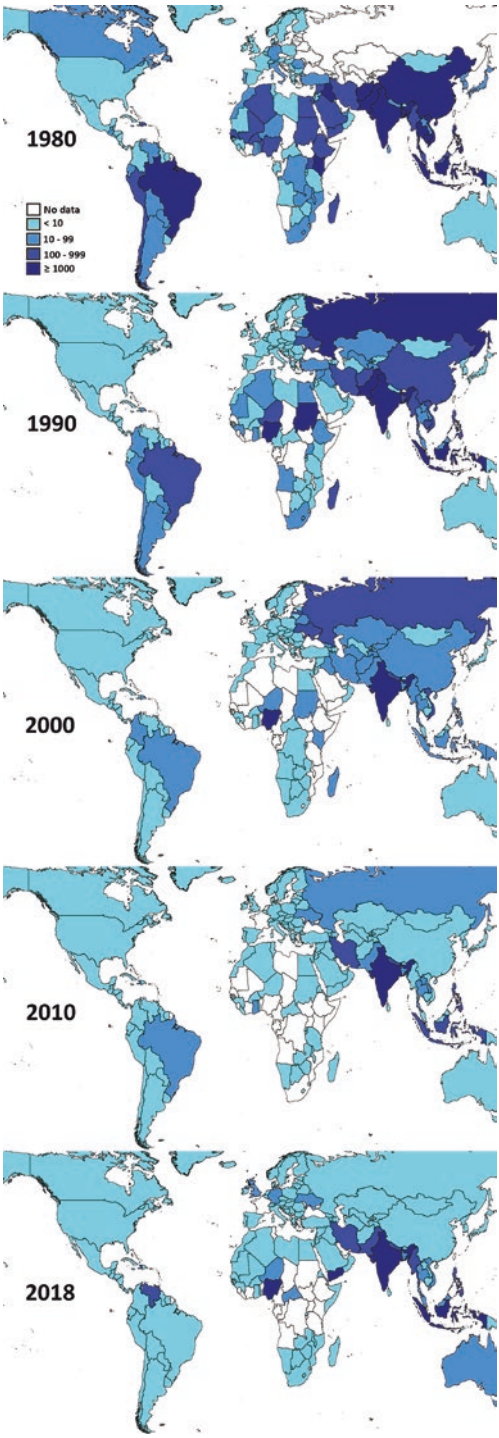

Fig. 10.1 Diphtheria cases reported to the World Health Organization in 1980, 1990, 2000, 2010, and 2018 by country. See also Table 10.1. (Data Source to generate maps: World Health Organization https://apps.who.int/immunization_monitoring/globalsummary/timeseries/tsincidencediphtheria.html)

Table 10.2 Forms of diphtheria based on anatomic site involved

Cutaneous diphtheria
Respiratory diphtheria
Pharyngeal and tonsillar
Nasal and nasopharyngeal
Laryngeal
Conjunctival

grounds based on the classic presentation; however, diagnostic microbiology studies provide confirmation of toxin production and an isolate for epidemiologic tracking. Droplet precautions are necessary for patients with pharyngeal diphtheria until two consecutive negative cultures are obtained from both the nose and the throat 24 hours after completing antibiotic therapy. Contact precautions are sufficient for those with cutaneous diphtheria until two negative skin lesion cultures are obtained 24 hours apart, 24 hours after completion of therapy. The only effective control measure against diphtheria is immunization using a diphtheria-toxoid-containing vaccine. Close contacts of patients diagnosed with diphtheria should receive a booster dose of vaccine in addition to a 7- to 10-day regimen of oral erythromycin. Another 10-day course of erythromycin may be indicated if posttreatment pharyngeal cultures are positive, indicating persistent colonization. A single intramuscular dose of benzathine penicillin may be given as an alternative.

Clinical Presentation

Diphtheria is classified into different clinical forms based on the location of the disease (Table 10.2). Fever, when present, is of low grade. The respiratory infection caused by *C. diphtheriae* usually presents with membranous pharyngitis with or without bloody nasal discharge. Patients with pharyngeal diphtheria may develop palatal palsy, a condition that can be recognized when the patient develops a highly nasal quality to their speech. Laryngeal and/or conjunctival involvement is less common. Anterior and posterior cervical lymphadenopathy and the associated soft tissue edema can give the appearance of a "bull neck" in severe cases. Cutaneous diphtheria is a much less common form of the infection that presents as a nonhealing skin ulcer. In all forms of the infection, diphtheria toxin causes the formation of a local pseudomembrane that is comprised of fibrin clots and necrotic cellular debris. This dense, gray, friable matted collection adheres to the local mucosa or skin.

Management

Careful attention to maintaining airway patency is the most essential aspect of managing patients with respiratory diphtheria. In addition, treatment with diphtheria antitoxin and appropriate antibiotics should not be delayed. A single dose of

Table 10.3 Available combination vaccines that include diphtheria toxoid

Combination vaccine	Brand name	Manufacturer	Diseases targeted for prevention
DT	None	Sanofi Pasteur	Diphtheria Tetanus
Td	Tenivac	Sanofi Pasteur	Tetanus Diphtheria
DTaP	Daptacel Infanrix	Sanofi Pasteur Glaxo Smith Kline	Diphtheria Tetanus Pertussis
TdaP	Adacel Boostrix	Sanofi Pasteur Glaxo Smith Kline	Tetanus Diphtheria Pertussis
DTaP, Hep-B, IPV	Pediarix	Glaxo Smith Kline	Diphtheria Tetanus Pertussis Hepatitis B Polio
DTaP, IPV	Kinrix Quadracel	Glaxo Smith Kline Sanofi Pasteur	Diphtheria Tetanus Pertussis Polio
DTaP, IPV, Hib	Pentacel	Sanofi Pasteur	Diphtheria Tetanus Pertussis Polio *Haemophilus influenzae* type b
DTaP, IPV, Hep-B, Hib	Vaxelis	MSP Vaccine Company	Diphtheria Tetanus Pertussis Polio Hepatitis B *Haemophilus influenzae* type b

equine-derived diphtheria antitoxin should be given any time the clinical suspicion for diphtheria is high, even without laboratory confirmation of the infection. A scratch test should be performed prior to administration to determine whether the patient has pre-existing hypersensitivity to horse serum. Diphtheria antitoxin should be administered intravenously in an effort to neutralize systemic diphtheria toxin as quickly as possible. Antibiotics are administered to stop toxin production, eradicate *C. diphtheriae* from the respiratory tract, and prevent further transmission to others. Oral or intravenous erythromycin is the drug of choice.

Diphtheria Vaccine

Diphtheria vaccine is among the most simple and elegant immunizations available. The vaccine immunogen, diphtheria toxoid, is a derivative of diphtheria toxin that has been rendered nontoxic. Monovalent vaccine formulations of diphtheria toxoid are not

currently available anywhere in the world. Instead, diphtheria toxoid is 1 of 2 or more components included in a growing variety of combination vaccine formulations. All formulations of diphtheria vaccine in use presently also include tetanus toxoid (abbreviated DT and Td) and all those that contain immunogens beyond diphtheria and tetanus toxoids all include pertussis antigens (DTaP and TdaP) (see Table 10.3). Lower case "d" is used to indicate the lesser amount of total diphtheria toxoid included in vaccines used in formulations given as booster doses to individuals older than 7 years (Td and TdaP). The DT vaccine formulation is not commonly used, but is available to provide protection against diphtheria and tetanus in infants and young children for whom pertussis vaccination is contraindicated. For younger children, quadrivalent (adding in polio immunogens; abbreviated DTaP-IPV), pentavalent (adding either hepatitis B or *Haemophilus influenzae* type B; DTaP-IPV-Hep-B and DTaP-IPV-HIB), and hexavalent (adding both hepatitis B or *Haemophilus influenzae* type B immunogens; DTaP-IPV-Hep-B-HIB) combination vaccines are also widely used throughout the world. During young childhood, five doses of diphtheria- (capital "D") and tetanus-toxoid-containing vaccines are recommended to be administered at ages 2, 4, 6, and 15–18 months and 4–6 years. The first dose may be administered as early as 6 weeks of age. The use of pentavalent or hexavalent vaccines at 2, 4, and 6 months has the benefit of reducing the number of injections needed at each immunization visit (Fig. 10.2). Other benefits of combination vaccines are discussed in Chap. 35.

Starting at age 7 years, and throughout adulthood, vaccine formulations that contain the lesser amount of diphtheria toxoid, as indicated in the vaccine abbreviation with a lower case "d," as in Td and TdaP, are used. The immune systems of older children and adults have already been primed and boosted with diphtheria toxoid at 2, 4, 6, 15–18 months and 4–6 years of age, so the lower antigen dose is more than sufficient to boost existing immunity. The unintentional administration of a vaccine formulation containing the higher amount of diphtheria toxoid beyond age 6 years is not harmful, per se, but would likely be associated with a high rate of self-limiting injection site reactions. Such reactions result, at least in part, from the robust immune memory response to the prior doses. Pediatricians are keenly aware of the relative frequency with which this occurs already following the appropriate administration of DTaP-containing vaccines, particularly in preschool-aged children 1–2 days after receiving their fifth dose.

The Advisory Committee on Immunization Practices (ACIP) recommends that booster injections of diphtheria toxoid be given every 10 years for life. TdaP vaccine is recommended for all 11- or 12-year-old children, primarily to boost their pre-existing immunity to pertussis. ACIP recommendations state that either Td or TdaP vaccine may be used for subsequent, every 10-year boosters. Td or TdaP vaccine is also used for tetanus wound prophylaxis, since monovalent tetanus toxoid vaccine is no longer available. Anytime a diphtheria-toxoid-containing combination vaccine is used in such contexts to boost immunity to tetanus or pertussis, the dose is valid to reset the 10-year clock for the next recommended dose. This guidance aligns nicely with the routine booster recommendations for tetanus toxoid booster vaccines every 10 years and explains why monovalent tetanus toxoid vaccines are no longer made available for use.

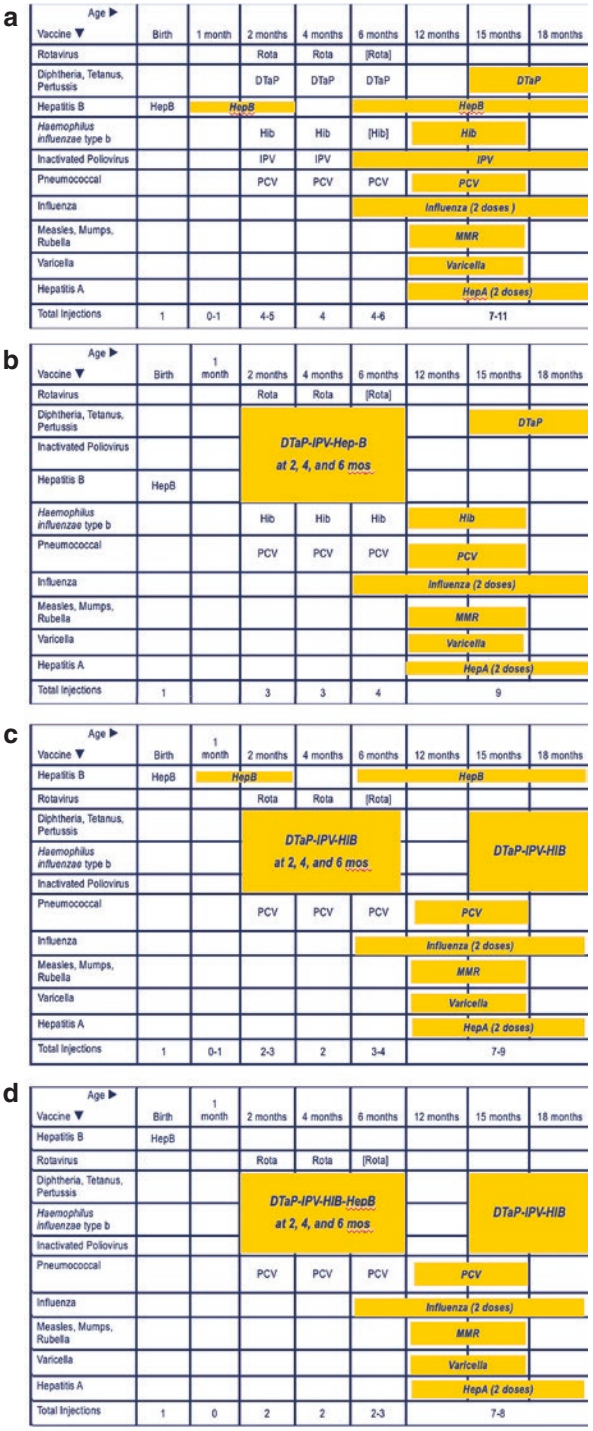

Fig. 10.2 Pediatric immunization schedule from birth to 18 months of age when using (**a**) DTaP with individual component vaccines, (**b**) DTaP-IPV-Hep-B combination vaccine, (**c**) DTaP-IPV-HIB combination vaccine, and (**d**) DTaP-IPV-HIB-Hep-B combination vaccine

Immunizing Antigen

Diphtheria toxoid is used as the immunogen in all combination vaccines that include diphtheria antigen. Diphtheria toxoid is derived from diphtheria toxin produced in industrial cultures of toxigenic *C. diphtheriae* grown under carefully defined conditions. When the bacterial cultures are ready for harvest, diphtheria toxin is concentrated from the culture medium using ultrafiltration, then purified by ammonium chloride precipitation, and dialysis. Toxin is then inactivated with formaldehyde to produce a bulk lot of diphtheria toxoid for use in all of the available combination vaccine products.

Additives and Excipients

All diphtheria-toxoid-containing vaccines include an aluminum salt adjuvant that is added during the final manufacturing steps. Monovalent diphtheria toxoid vaccines are not available for use. For a list of additives and excipients in diphtheria-toxoid-containing vaccines, see details provided in Chap. 4.

Contraindications to Vaccine

Diphtheria-toxoid-containing vaccines are contraindicated for use in individuals who developed a severe allergic reaction to a prior dose, and for those with a known severe allergy to any vaccine component.

Side Effects and Adverse Events

Mild-to-moderate, self-limiting local injection site reactions are common with all diphtheria-toxoid-containing vaccines. Since infants who receive diphtheria-toxoid-containing vaccines also typically receive other vaccines during the same visit, vaccine-specific and antigen-specific side effects are usually difficult to identify with any certainty. Fortunately, all of the diphtheria-toxoid-containing vaccines are very well tolerated. For example, in one study involving more than 27,000 infants who received DTaP at 2, 4, and 6 months of age, crying for 3 hours or longer was reported at a rate of 0.44 per 1000 doses, fever ≥40 °C at a rate of 0.35 per 1000 doses, seizures at 0.07 per 1000 doses, and no reported episodes of hypotonic-hyporesponsive episodes (an uncommon reaction known to occur following the administration of whole cell DTP vaccine at rates of 0.67 per 1000 doses). Adolescents and adults who receive Td vaccine experience injection site pain

(75–80%), redness (16–26%), or swelling (15–17%), which are rarely severe in nature. Fever between 38 °C and 39 °C occurs uncommonly (0.8–1.6%). Headache (23–25%), weakness (17–32%), malaise (15–17%), and joint pains (11–16%) are self-limiting and only rarely severe in quality.

Vaccine Immunogenicity

Protection against diphtheria results from the development of neutralizing antibodies to the diphtheria toxin/toxoid. Serum antibody at concentrations of 0.01 IU/mL is the lowest level to provide some degree of protection; a serum concentration of 0.1 IU/mL or higher is considered protective. Clinical trials consistently show that diphtheria-toxoid-containing vaccines induce protective antibody concentrations in the protective range in 100% of recipients who have completed a three-dose primary series. The global epidemiology of diphtheria from 1980 to the present (Fig. 10.1, Table 10.1) is quite telling. Diphtheria can be controlled by prioritizing and paying careful attention to vaccination. Lack of attention and/or a failure to prioritize vaccination will, eventually, lead to the emergence or re-emergence of disease. The immune response to diphtheria vaccination provides excellent protection against the effects of diphtheria toxin, but the induced immunity does not eliminate the pathogen's natural reservoir, because it has no effect on reducing human nasopharyngeal colonization with *C. diphtheriae*. Regions that struggle most with outbreaks are those that are most densely populated (India), are experiencing war or war-like conditions (Yemen), have undergone a recent collapse in infrastructure (Venezuela), and/or continue to suffer from extreme poverty (Haiti, Nigeria).

References and Suggested Reading

World Health Organization

https://www.who.int/immunization/diseases/diphtheria/en/

U.S. Centers for Disease Control and Prevention

https://www.cdc.gov/diphtheria/index.html

Vaccine Information Sheets

https://www.cdc.gov/vaccines/hcp/vis/visstatements/dtap.html
https://www.cdc.gov/vaccines/hcp/vis/vis-statements/tdap.html
https://www.cdc.gov/vaccines/hcp/vis/vis-statements/td.html

FDA Aapproved Package Inserts

Daptacel

https://www.fda.gov/vaccines-blood-biologics/vaccines/daptacel

DT vaccine

https://www.fda.gov/media/119411/download

Infanrix

https://www.fda.gov/vaccines-blood-biologics/vaccines/infanrix

Kinrix

https://www.fda.gov/vaccines-blood-biologics/vaccines/kinrix

Pediarix

https://www.fda.gov/media/79830/download

Pentacel

https://www.fda.gov/media/74385/download

Quadracel

https://www.fda.gov/vaccines-blood-biologics/vaccines/quadracel

Tenivac

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Vaxelis

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Chapter 11
Ebola

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Ebola Virus Disease

Etiology

Ebolaviruses are enveloped, single-stranded, negative-sense RNA viruses belonging to the *Filoviridae* family. The genus *Ebolavirus* includes six species, each named based on the region where it was first identified: Bundibugyo ebolavirus, Reston ebolavirus, Sudan ebolavirus, Taï Forest ebolavirus, Bombali ebolavirus, and Zaire ebolavirus. Four of these species are known to cause Ebola virus disease in humans, a type of viral hemorrhagic fever. Of those, Zaire ebolavirus has caused the majority of human cases and deaths from Ebola virus disease, and was the cause of the 2014–2016 epidemic in West Africa that resulted in more than 28,000 cases and 11,310 confirmed deaths.

Epidemiology

Ebola virus disease typically occurs as outbreaks in tropical regions of sub-Saharan Africa. Figure 11.1 shows the total cumulative cases of Zaire and non-Zaire ebolavirus disease reported by country from one or more outbreaks that occurred between 1976 and 2018. The small number of cases that have been reported from other African nations can almost always be traced back to an ongoing outbreak in a neighboring country. For example, during the 2014–2016 Zaire ebolavirus epidemic in Guinea, Sierra Leone, and Liberia, small numbers of epidemiologically linked cases

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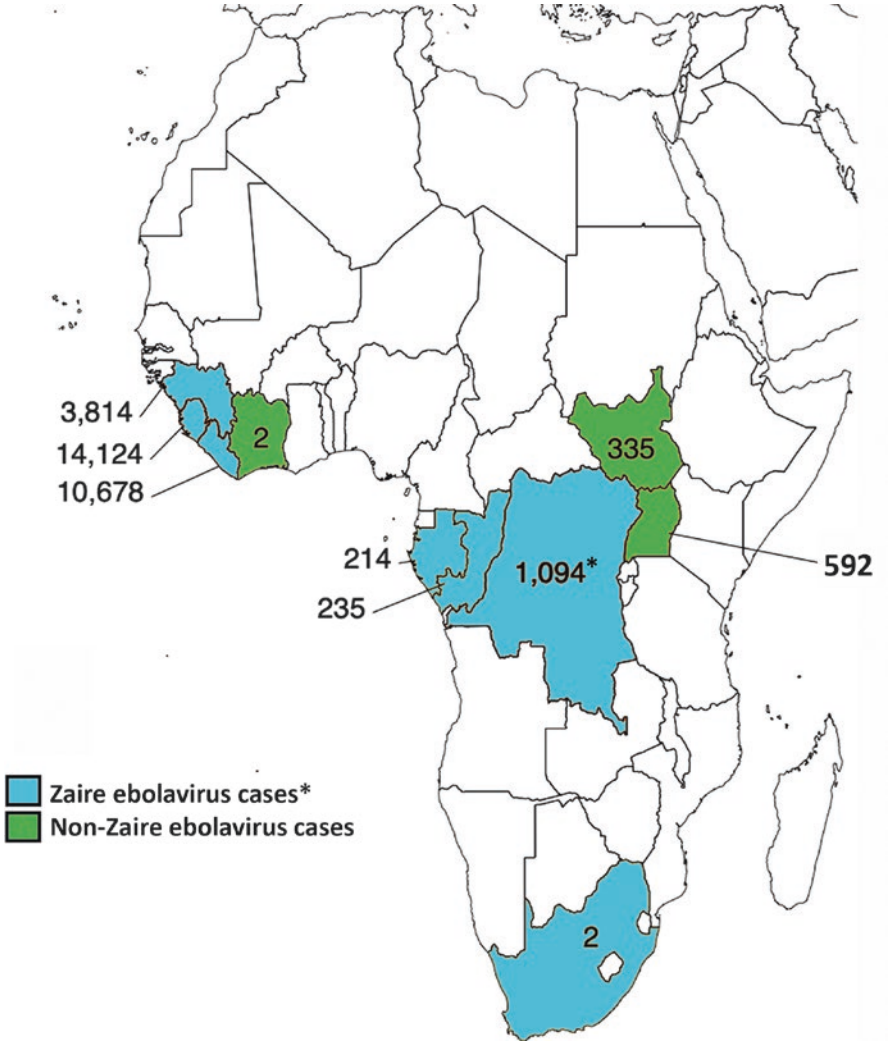

Fig. 11.1 This map of Africa shows the total cumulative cases of Zaire and non-Zaire ebolavirus disease reported by country from 1976 to 2018. *Note that 36 of the cases reported from the Democratic Republic of the Congo were caused by the non-Zaire Bundibugyo ebolavirus. See also Tables 11.1 and 11.2. (Source of data to develop Fig. 11.1, Tables 11.1 and 11.2: Centers for Disease Control and Prevention. The data are available on the agency website at no charge: https://www.cdc.gov/vhf/ebola/index.html. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the US Government, Department of Health and Human Services, or Centers for Disease Control and Prevention)

were identified in nearby Senegal, Mali, and Nigeria. Zaire ebolavirus has been responsible for all outbreaks of disease that have occurred in Gabon and the Republic of the Congo, and all but one of the eight large outbreaks in the Democratic Republic of the Congo (Table 11.1) since 1976. In addition, Zaire ebolavirus was responsible

Table 11.1 Zaire ebolavirus cases and outbreaks: 1976–2018

Country or countries	Year(s)	Cases	Deaths
Democratic Republic of the Congo	2018–present	Ongoing	Ongoing
	2018	54	33
	2017	8	4
	2014	66	49
	2008	32	15
	2007	264	187
	1995	315	250
	1977	1	1
	1976	318	280
Sierra Leone	2014–2016	14,124	3956
Liberia	2014–2016	10,678	4810
Guinea	2014–2016	3814	2544
Republic of Congo	2003	35	29
	2002	143	128
	2001	57	43
Gabon	2001	65	53
	1996	60	45
	1996	37	21
	1994	52	31
South Africa	1996	2	1
Total	1976–2018	30,125	12,480

Table 11.2 Non-Zaire ebolavirus cases and outbreaks: 1976–2018

Country	Year	Cases	Deaths	Species
Democratic Republic of the Congo	2012	36	13	Bundibugyo ebolavirus
Uganda	2012	6	3	Sudan ebolavirus
	2012	11	4	Sudan ebolavirus
	2011	1	1	Sudan ebolavirus
	2007	149	37	Bundibugyo ebolavirus
	2000	425	224	Sudan ebolavirus
South Sudan	2004	17	7	Sudan ebolavirus
	1979	34	22	Sudan ebolavirus
	1976	284	151	Sudan ebolavirus
Ivory Coast	1994	2	1	Taï Forest ebolavirus
Totals	1976–2018	965	463	

for the massive multicountry epidemic of infection between 2014 and 2016. Taken together, this species accounts for more than 96% of all Ebolavirus disease cases and deaths recorded since the virus was discovered. The countries of Uganda and South Sudan have both experienced multiple outbreaks of Ebola virus disease caused by non-Zaire ebolaviruses (Table 11.2), but have not yet been affected by the Zaire ebolavirus. The only two known cases of human disease caused by the non-Zaire Taï Forest ebolavirus were reported from the Ivory Coast in 1994.

Transmission

Transmission of the ebolaviruses between their natural animal reservoirs and humans is rare. Outbreaks of human Ebola virus disease can often be traced to an index case who handled a dead gorilla, chimpanzee, fruit bat, or small antelope called a duiker. The index case then spreads the virus to a family member or community contact through person-to-person direct contact.

Person-to-person transmission of Ebola virus disease is thought to spread only by direct contact with the blood or body fluids of an infected person. The level of contagion appears to increase as the disease advances. Health-care providers attending to infected individuals are at increased risk for infection and are recommended to wear enhanced personal protection when caring for infected patients. Dead bodies remain infectious to anyone handling the remains for the purposes of immediate postmortem care, traditional burial rituals, or embalming.

Clinical Presentation

The incubation period between exposure to the virus and the development of symptoms is typically 4–10 days, but can be as long as 21 days. The first symptoms of infection are nonspecific, and include fever, headache, sore throat, joint and muscle aches, and weakness. As the infection progresses, most patients develop abdominal pain in association with nausea, vomiting, and diarrhea. Patients become confused and begin to show signs of edema. Many become extremely dehydrated. Half of those infected develop a maculopapular rash approximately 1 week after symptom onset. Moderate-to-severe coagulopathy is a near-universal finding. Associated symptoms begin to manifest between days 5 and 7 of the infection. At first, petechiae may appear at tourniquet or blood pressure cuff sites. As the coagulopathy worsens, patients show signs of easy bruisability, gingival bleeding, and/or subconjunctival hemorrhages. Excessive bleeding at needle puncture sites or from around intravenous catheters occurs in up to 50% of cases. Gastrointestinal bleeding may lead to hematemesis and/or hematochezia. Death from moderate blood loss coupled with hypovolemia from severe dehydration is seen in 25–90% of cases. Outcomes differ with each outbreak. The highest fatality rate (90%) was seen during the 2002 outbreak in the Republic of the Congo. The case fatality rate observed during the world's largest outbreak, involving three countries in West Africa from 2014 to 2016, was 40%. Most survivors experience a protracted period of convalescence with continued, often profound weakness. Persistent anorexia makes it difficult for those in convalesce to regain strength and to return to their preillness body weight.

Management

Treatment is primarily supportive. Close attention to rehydration and subsequent meticulous management of fluid status improves survival. The World Health Organization recommends avoiding the use of aspirin, ibuprofen, and other nonsteroidal anti-inflammatory medications for pain management because of their known effects of inhibiting platelet function. Patients often require infusions of blood products, including packed red blood cells, platelets, and fresh frozen plasma. Specific antiviral medications are not yet available for the treatment of Ebolavirus disease; however, two investigational monoclonal antibody products, REGN-EB3 and mAb114, showed promise when used on a compassionate basis during an outbreak in the Democratic Republic of the Congo in 2018–2019.

Ebola Vaccine

A recombinant Ebola virus vaccine was approved by the Food and Drug Administration for use in the USA in December 2019. The vaccine is marketed by Merck & Company under the trade name ERVEBO. ERVEBO is indicated for the prevention of disease caused by Zaire ebolavirus in individuals 18 years of age and older. The product is a live recombinant viral vaccine that was developed using a vesicular stomatitis virus backbone. The gene encoding the envelope glycoprotein of the backbone virus was deleted and replaced with the homologous envelope glycoprotein from the Zaire ebolavirus. Recombinant vesicular stomatitis virus expressing the envelope glycoprotein of the Zaire ebolavirus on its surface is grown in serum-free Vero cell cultures. Virus is harvested and purified from cell culture medium, then formulated with a stabilizing solution of 10 mM Tromethamine (Tris) and 2.5 mg/mL of rice-derived recombinant human serum albumin. The final product is used to fill single dose vials, each containing a minimum of 72 million plaque-forming units of vaccine virus. Each 1 mL dose may contain residual amounts of host cell DNA (≤10 ng), benzonase (≤15 ng), and/or trace amounts of rice protein. The vaccine is preservative-free. The vial stopper does not contain natural rubber latex.

Vaccine Storage, Preparation, and Administration

The vaccine should be stored frozen, as provided, until immediately prior to use. The vial should be thawed at room temperature, not in the refrigerator. The product is a colorless to slightly brownish-yellow liquid. The dose should be administered immediately after thawing, but may be stored for up to 4 hours at room temperature,

up to 25 °C, protected from light. Thawed vaccine should never be refrozen. The vaccine is administered intramuscularly as a 1 mL dose into the deltoid muscle of the nondominant arm.

Contraindications to Vaccine

The vaccine is contraindicated in anyone with a known severe allergic reaction to any of the vaccine components.

Warnings and Precautions for Vaccine Use

Immunized persons should also adhere to standard infection control practices used to prevent Zaire ebolavirus infection. Vaccine virus RNA has been detected in the urine, blood, and saliva of immunized persons. Person-to-person transmission of the vaccine virus is theoretically possible, but not demonstrated as of this writing. The safety and effectiveness have not been studied in immunocompromised individuals or in pregnant women. As with other live virus vaccines, the potential risks and benefits of vaccinating immunocompromised individuals and pregnant women should be weighed against their risk of the disease.

Side Effects and Adverse Events

During clinical trials, the most common local adverse events were injection-site pain (70%), swelling (17%), and redness (12%). The most common systemic adverse events included headache (37%), fever (34%), muscle ache (33%), fatigue (19%), joint pain (18%), and nausea (8%). Four vaccine-related serious adverse events were reported among 15,399 individuals who received the vaccine. Two of the serious adverse reactions were high fevers, and two were anaphylaxis-like allergic reactions. None of these serious adverse events were fatal.

Vaccine Efficacy

Vaccine efficacy was evaluated in an open-label, randomized cluster trial conducted in the Republic of Guinea during the 2014 Ebola outbreak in West Africa. Each cluster was composed of direct contacts and contacts of direct contacts of individuals known to be infected with Ebola virus. Clusters were randomized to receive vaccine immediately, or to receive vaccination 21-days later. A total of 3537 adults

were enrolled. Of those, 2108 were included in clusters randomized to receive vaccine immediately and 1429 were included in clusters randomized to receive vaccine 21 days later. Zero cases of Ebola infection were observed in the immediate vaccination clusters, and 10 cases were observed in the delayed vaccination clusters, yielding a vaccine efficacy of 100%, with a 95% confidence interval of 64–100%. The vaccine is currently being used to help control the ongoing Ebola epidemic in the Democratic Republic of the Congo. Interim analyses estimate the vaccine to be at least 95% effective at preventing disease.

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https://www.who.int/health-topics/ebola/#tab=tab_1

U.S. Centers for Disease Control and Prevention

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Chapter 12
Haemophilus influenzae Type B

Manika Suryadevara

Haemophilus influenzae Type B

Etiology

In 1892, German bacteriologist, Richard Pfeiffer, first isolated *Haemophilus influenzae* from the sputum of patients with flu-like illnesses, mistaking this newly discovered Gram-negative pleomorphic coccobacillus for the cause of influenza. Influenza viruses weren't discovered as the cause of influenza until 4 decades later. In the meantime, Margaret Pittman further characterized *H. influenzae* showing that isolates of the bacterium could be encapsulated (types a–f) or nonencapsulated (non-typeable). She found that *H. influenzae* type b was the most common type isolated from the cerebrospinal fluid and blood of children. The bacterial polyribosylribitol phosphate (PRP) polysaccharide capsule was identified early on as a primary virulence factor capable of facilitating hematogenous spread of infection and preventing phagocytes from engulfing and killing the bacteria. Antibodies directed against PRP were subsequently found to correlate with both short-term and long-term protection from invasive disease.

Pre-vaccine epidemiology

Hib infection occurs worldwide, in both developing and developed countries. While nearly all invasive Hib diseases occur in children younger than 5 years, the majority of infection is seen in those younger than 18 months of age. Globally, each year during the pre-vaccine era, Hib caused an estimated eight million cases of invasive disease and more than 370,000 deaths among children younger than 5 years [4]. In the early and mid-1980s, in the USA, it was estimated that 20,000 cases of invasive Hib disease occurred each year. Infecting 1 in 200 children younger than 5 years of age, Hib was the leading cause of bacterial meningitis among US children.

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Table 12.1 Factors associated with increased risk of invasive Hib disease

Factors associated with increased risk of invasive Hib disease
Underlying health conditions
Sickle cell disease
Asplenia
Human immunodeficiency virus infection
Hypogammaglobulinemia
Complement deficiency
Malignancy
Host demographics
Alaskan Natives
Native American Indians
Males
Social factors increasing risk of exposure to Hib
Childcare attendance
Crowded living conditions
Low socioeconomic status
Low parental education status
School-age siblings

Table 12.1 lists the factors associated with an increased risk of acquiring invasive Hib infection [5]. One subpopulation known to be in this category is the Alaskan Natives. While the incidence of invasive Hib disease among children less than 5 years old in the general US population was 40–50 per 100,000, the incidence among the Alaskan Native population was closer to 332 per 100,000 [6, 7]. On the other hand, breastfeeding has been found to protect against invasive Hib disease, particularly in the first six months of life. Secondary cases of infection may occur among under- or unimmunized children residing in the same house or attending the same childcare center as an infected person; however, these account for less than 5% of all invasive Hib diseases.

Transmission

Hib transmission occurs from person to person through respiratory droplets or direct contact with respiratory secretions. Neonatal acquisition of infection through contact with genital tract secretions has also been reported. Pharyngeal colonization is thought to precede infection (through subsequent bacteremia and seeding of distal sites or contiguous spread of respiratory mucosa) and contribute to community spread.

Clinical presentation

The six most common presentations of invasive Hib disease include meningitis, bacteremic pneumonia, epiglottitis, septicemia, cellulitis, and osteoarticular infections [8]. Prior to the use of vaccine, more than half of all invasive Hib infections resulted in meningitis. In fact, Hib was the leading cause of bacterial meningitis among children younger than 5 years old. Of children who developed Hib meningitis, 4 % succumbed to disease, despite appropriate therapy. Of those who survived,

Table 12.2 Indications for chemoprophylaxis to prevent secondary cases of invasive Hib disease

Populations for whom rifampin is indicated after exposure to invasive Hib disease
Household contacts if:
At least one child is younger than 4 years old and has not received the complete primary vaccine series and booster dose
At least one child is younger than 12 months old and has not received the complete primary vaccine series
At least one child is immunocompromised
Childcare contacts
All attendees (regardless of age and vaccination status) should receive chemoprophylaxis if at least two cases of invasive Hib disease occur at the center within 60 days
Index patient if:
Younger than 2 years of age and treatment course did not include at least a single dose of cefotaxime or ceftriaxone; rifampin prophylaxis should be given after treatment is complete

15–30% still suffered from hearing impairment or other neurologic sequelae. Less common manifestations of Hib infection include purulent pericarditis, endocarditis, and peritonitis.

Management

The treatment for invasive Hib disease includes intravenous administration of either ampicillin (if the isolate is beta-lactamase negative) or a third-generation cephalosporin (ceftriaxone, cefotaxime, if the isolated is beta-lactamase positive) for 7–10 days. For patients with Hib meningitis, administering dexamethasone before or at the same time as the first dose of antibiotics has been shown to reduce the rates of sensorineural hearing loss.

Prevention

The primary approach to community-wide Hib prevention includes the routine administration of Hib vaccine to infants starting at 2 months of age. Some circumstances require that close contacts of an index case of invasive Hib disease receive antibiotic prophylaxis to prevent secondary spread of infection (Table 12.2). Rifampin is the drug of choice for most individuals who require chemoprophylaxis. Rifampin (and other antibiotics like ceftriaxone) is effective at eradicating nasopharyngeal colonization of Hib in 95% of carriers and is effective in reducing the number of secondary cases of infection.

Hib Vaccine

Vaccine characteristics

There are currently three monovalent and one combination conjugate Hib vaccines available for use in the USA (Table 12.3). These vaccines contain Hib PRP covalently linked to a carrier protein, either tetanus toxoid (PRP-T) or the outer membrane protein complex from *Neisseria meningitidis* (PRP-OMP). The timing of

Table 12.3 Conjugate Hib vaccines available in the USA

	PedvaxHIB	ActHIB	Hiberix	Pentacel
Active ingredient	PRP-OMP[a]	PRP-T[a]	PRP-T[a]	PRP-T[a], diphtheria toxoid, tetanus toxoid, acellular pertussis antigens, inactivated poliovirus
Manufacturer	Merck & Co., Inc.	Sanofi Pasteur	GlaxoSmithKline Biologicals	Sanofi Pasteur
Primary series administration recommendation	2 months[b], 4 months	2 months[b], 4 months, 6 months	2 months[b], 4 months, 6 months	2 months[b], 4 months, 6 months
Booster dose recommendation	12–15 months	12–15 months	12–15 months	12–15 months
Vaccine components				
Adjuvant	Amorphous aluminum hydroxyphosphate			Aluminum phosphate
Stabilizers		Sucrose	Lactose	Sucrose, 2-phenoxyethanol, albumin
Emulsifier				Polysorbate 80
Antimicrobials				Streptomycin, neomycin, polymyxin B
Other	0.9% sodium chloride	Tris(hydroxymethyl) aminomethane, sodium chloride (diluent)	Residual formaldehyde	Residual formaldehyde, residual glutaraldehyde, residual bovine serum

[a]PRP-T polyribosylribitol phosphate (PRP) covalently bonded to tetanus toxoid; PRP-OMP, PRP covalently bonded to the outer membrane protein complex of *Neisseria meningitidis*

[b]Can be administered to infants as young as 6 weeks of age

administration and number of doses required to complete the primary conjugate Hib vaccine series is determined by the vaccine product used. It is important to note that immunization with a vaccine conjugated with a tetanus toxoid is not a substitute for a tetanus vaccine.

Vaccine storage, preparation, administration

PedvaxHib is provided in ready-to-use vials. There is no reconstitution required. ActHIB and Hiberix are provided as lyophilized powder which is to be reconstituted with the provided saline diluent. Pentacel consists of a liquid component (diphtheria-tetanus-acellular pertussis-inactivated polio [DTaP-IPV]) and a lyophilized powder (ActHIB). The supplied lyophilized powder is to be reconstituted with the supplied liquid component just before administration. All Hib vaccines should be maintained at refrigerator temperature (2–8 °C). When ready for use, a 0.5 mL dose of vaccine is administered intramuscularly.

Vaccine recommendations

Routine Hib immunization consists of a primary vaccine series and a subsequent booster. The primary vaccine series is typically initiated at 2 months of age but can be started as early as 6 weeks. The timing and the number of doses administered in the primary vaccine series is dependent on the vaccine product used and the age of the patient when the vaccine series is initiated (Table 12.4). The booster dose, for which any of the Hib vaccine products can be used, is administered between 12 and 15 months of age and must be given more than 8 weeks after the last dose of the primary series. Children younger than 5 years of age who have not yet been immunized against Hib should be vaccinated according to the catch-up recommendation schedule (Table 12.4).

Hib vaccination is not recommended for healthy children over 5 years old because of the low risk for acquiring invasive Hib disease in this age group. There are certain risk factors, however, that increase the risk for invasive Hib disease even among older children, adolescents, and adults. Hib vaccine recommendations for these individuals are listed in Table 12.5. In particular, vaccines administered within two weeks of starting chemotherapy are not considered to be effective. In such instances, the children should be re-immunized at least 3 months after completing chemotherapy.

Contraindications to vaccines

Hib vaccine is contraindicated in patients who have had an anaphylactic or severe allergic reaction to a prior dose of Hib vaccine or to a vaccine component. If Guillain-Barre syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the benefits and risks of giving a Hib vaccine product conjugated to a tetanus toxoid (ActHIB, Hiberix, Pentacel) should be discussed. The contraindications to the combination vaccine are similar to those of the vaccine components when separately administered.

Adverse events

Most reactions to Hib vaccine are mild and last for less than a day. Self-limiting injection site complaints such as pain, redness, and swelling are common. The

Table 12.4 Routine and catch-up immunization recommendations for Hib vaccine

Routine Hib vaccine recommendations	
Primary vaccine series	PRP-T: three doses administered at 2, 4, 6 months PRP-OMP: two doses administered at 2, 4 months If the same product cannot be used for each dose, three doses need to be administered to complete the primary vaccine series
Booster vaccine dose	Administer any Hib vaccine at 12–15 months of age
Catch-up Hib vaccine recommendations	
Younger than 7 months of age	Administer two doses of PRP-OMP or three doses of PRP-T at intervals of 2 months between doses to complete the primary vaccine series If the same vaccine product cannot be used for each dose, three doses are required to complete the primary vaccine series Administer booster dose at 12–15 months of age (and at least 2 months after the last dose in the primary vaccine series)
Received dose 1 at 7–11 months of age	Administer dose 2 at least 4 weeks after dose 1 Administer booster dose at 12–15 months of age or at least 2 months after the last dose (whichever is later)
Received dose 1 at 12–14 months of age	Administer dose 2 at least 8 weeks after dose 1 No further doses needed
Received dose 1 before 12 months of age and dose 2 before 15 months of age	Administer dose 3 at least 8 weeks after dose 2 No further doses needed
Two doses of PedvaxHIB before 12 months of age	Administer dose 3 at least 8 weeks after dose 2 No further doses needed
Unvaccinated at 15–59 months of age	Administer a single dose of Hib vaccine
Unvaccinated at 60 months of age or older	No doses of Hib vaccine recommended

adverse reactions following combination vaccines are similar to those of the vaccine components when separately administered. Severe adverse reactions to the Hib vaccine are very rare.

Immunogenicity

Antibodies to the Hib capsular polysaccharide, PRP, at a concentration of 0.15 μg/mL and 1 μg/mL confer short- and long-term protection, respectively, against invasive disease. More than 95% of infants will develop protective antibody concentrations after completion of the Hib primary vaccine series. PedvaxHib (PRP-OMP) administration results in a robust antibody response after the first dose, with a boost in titers after the second dose, thus leading to the need for only two doses of vaccine to complete the primary series with this vaccine formulation. On the other hand, ActHIB (PRP-T) requires a three-dose primary series of vaccine to achieve protective antibody concentrations. As the antibody levels decline following completion of the primary series, a booster dose administered at 12–15 months is needed to maintain protection from disease.

Table 12.5 Hib vaccine recommendations for populations at higher risk for invasive Hib disease

Special considerations	Hib vaccine recommendations
Child with invasive Hib disease, younger than 2 years old, no prior Hib vaccine	Administer Hib vaccine as per age-appropriate catch-up recommendations at least one month after disease onset
Hematopoietic stem cell transplant recipient	Re-immunize at least 3 months after transplant, regardless of age and vaccination status
Unimmunized person 5 years of age or older with HIV infection	Administer a single dose of Hib vaccine
Functional or anatomic asplenia	
Completed primary series and booster	No further vaccine doses needed
Received 0 or 1 dose of Hib vaccine between 12 and 59 months of age	Administer two doses at least 8 weeks apart
Received two doses of Hib vaccine before 12 months of age	Administer one dose at least 8 weeks after the last dose
Unvaccinated person 5 years of age or older	Administer a single dose of Hib vaccine
Unvaccinated person 15 months of age or older scheduled for elective splenectomy	Administer a single dose of Hib vaccine at least 2 weeks before the procedure
Chemotherapy, radiation treatment, 12–59 months of age	
Received 0 or 1 dose of Hib vaccine between 12 and 59 months of age	Administer two doses at least 8 weeks apart
Received two doses of Hib vaccine before 12 months of age	Administer one dose at least 8 weeks after the last dose

Impact of Vaccine on Disease Burden

The first *H. influenzae* vaccine to be developed was a monovalent polysaccharide vaccine composed of the purified PRP capsule from Hib strains that became available in the mid-1980s. As with other pure polysaccharide vaccines, this formulation of Hib vaccine was poorly immunogenic in young infants and children, failed to elicit a T-cell-dependent immune response, did not induce immune memory, and had no effect on reducing nasopharyngeal carriage [8]. Post-marketing studies in the USA found the effectiveness of this polysaccharide vaccine to range between 69% and 88% among children less than 18 months of age [9]. In addition, uptake of the polysaccharide vaccine never reached higher than 35% among US children [10]. The biochemical process of conjugating (covalently linking) the PRP polysaccharide to a protein carrier changes the manner in which the immunogen is recognized by, and processed by, the immune system. Instead of being processed in a T-cell-independent manner like pure polysaccharide antigens, conjugated PRP vaccines are processed in a T-cell-dependent manner. They are, therefore, highly immunogenic in young infants, they induce immune memory, and their use is associated with marked reductions in nasopharyngeal carriage. Monovalent conjugate Hib vaccines were first licensed by the FDA in the USA in 1987 [9] and subsequently recommended by the Advisory Committee on Immunization Practices in 1990 for use in all infants starting at 2 months of age.

Although conjugate Hib vaccines were introduced into the pediatric immunization schedule in 1990, coverage rates among infants in the USA did not reach 90% until 1995 [10]. Since then, there has been a sustained reduction in the prevalence of Hib carriage among preschool-aged children to less than 1% and a decline in disease incidence exceeding 99%. In fact, the incidence of invasive Hib infection among children younger than 5 years of age has remained below the *Healthy People 2020* goal of 0.27 per 100,000 for the past decade [11]. Currently, invasive Hib disease occurs primarily in un- or under-immunized children younger than 5 years and among children who are later found to have an inherited humoral immunodeficiency. Fully immunized individuals who develop severe Hib disease should undergo a detailed diagnostic evaluation for conditions that may have predisposed them to invasive disease.

By the year 2000, conjugate Hib vaccines were routinely used only in the Americas and European region of the WHO. While developed countries were early to incorporate conjugate Hib vaccine into their immunization programs, most underdeveloped nations were faced with insurmountable barriers to do so. Obstacles to adding Hib to existing vaccine programs included the paucity of data on country-specific disease burden, a lack of awareness of the potential for a major public health impact of vaccine, and costs associated with its routine administration [12]. Globally, the annual invasive Hib disease burden of more than eight million cases and 363,000 deaths was responsible for 3% of all-cause mortality in children under 5 years of age [13].

In this same year, the Global Alliance for Vaccines and Immunizations, or GAVI, initiated a program to provide Hib vaccines to eligible low-income countries. Despite the financial support, engagement in the program remained low, suggesting that a general lack of awareness about Hib disease was, perhaps, an even greater barrier to vaccination than vaccine costs [14]. In 2006, the WHO formally recommended that conjugate Hib vaccines be routinely administered to all infants and children of all nations. In an intensive effort to support widespread uptake of Hib vaccine, GAVI partnered with international public health organizations to support research aimed at addressing gaps in understanding disease burden; improving communication and coordination with local, regional, national, and global partners; and advocating for the adoption of Hib vaccine in countries around the world [12]. By early 2020, all but three countries, China, Russia, and Thailand, have incorporated routine Hib vaccination into their national immunization programs with ongoing efforts to optimize their rates of vaccine coverage (Fig. 12.1).

Following widespread global use of conjugate Hib vaccine, invasive Hib disease burden around the world decreased dramatically. Between 2000 and 2015, corresponding to the increasing number of countries routinely administering Hib vaccine, the number of global Hib deaths had declined by 90% (Fig. 12.2). By 2015, annual estimates of invasive Hib disease among children younger than 5 years old (excluding those with HIV) were down to 340,000 cases (from eight million) and 29,500 deaths (from 363,000) [15]. In 2015, more than 80% of all global Hib deaths were reported from four countries India, Nigeria, China, and Sudan [15].

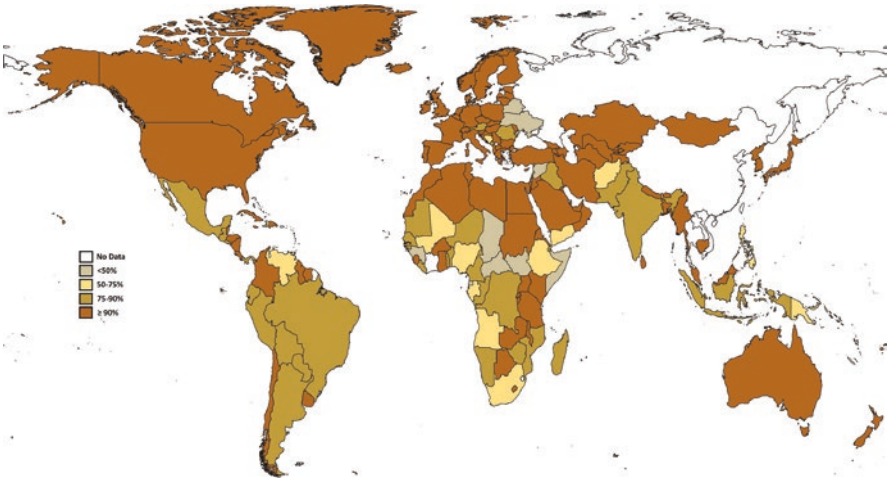

Fig. 12.1 2018 conjugate Hib vaccination rates by country

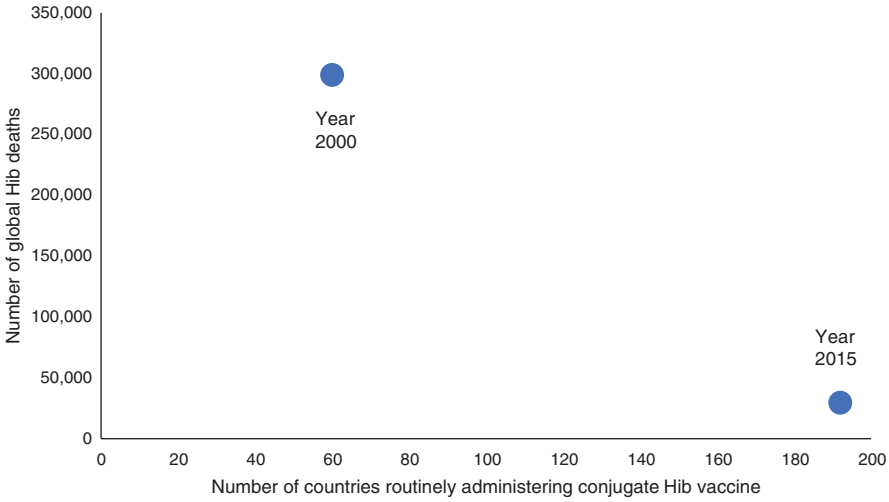

Fig. 12.2 The number of countries routinely using Hib vaccine in their pediatric immunization schedule versus the number of global Hib-related deaths among children younger than 5 years of age

India first introduced conjugate Hib vaccine in the southern state of Tamil Nadu in 2011. Within 2 years of routine vaccine use, they found a 78% decline in confirmed cases of Hib meningitis [16]. Shortly after, conjugate vaccine uptake increased nationwide. Despite an 81% decline in estimated Hib deaths in Indian children between 2000 (82,600 deaths) and 2015 (15,600 deaths), invasive Hib disease still accounted for 3% of all-cause mortality in this age group, largely because of suboptimal vaccine coverage rates in many areas. One state, Uttar Pradesh, did

not adopt Hib vaccine until the end of 2015. Of the Hib deaths in this report, 60% were reported from this region in India [17].

Conjugate Hib vaccine has proven safe and effective in preventing invasive Hib disease everywhere it is used across the globe. It is estimated that Hib vaccines prevented 1.2 million infant and childhood deaths between 2000 and 2015. The efforts and commitments of global partnerships between individual nations and GAVI, the US Centers for Disease Control and Prevention, and several agencies of the World Health Organization have been highly successful in reducing global morbidity and mortality from invasive Hib disease.

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Chapter 13
Hepatitis A

Cynthia Bonville and Joseph Domachowske

Hepatitis A Infection

Etiology

Hepatitis A infection is caused by *Hepatovirus A* (HAV), a member of the *Picornaviridae* family. The naked capsid contains a single strand of positive-sense RNA. The region of the viral genome that encodes the three major HAV capsid proteins includes highly conserved clusters of rare codons that restrict the antigenic variability expressed on the exposed surface of the virion. As such, only one serotype of HAV exists, although multiple genotypes have been identified.

Reports of epidemic jaundice presumed to have been caused by HAV date back to the time of Hippocrates in the fifth century BC. The virus remains a common cause of viral hepatitis. Infections caused by HAV are clinically indistinguishable from other types of acute viral hepatitis. Asymptomatic infection, with or without elevations in serum hepatic transaminases, is common, especially in young children. Symptomatic infection is often, but not always, associated with the development of jaundice. Serologic test results that show the presence of HAV-specific immunoglobulin M (IgM) antibody are diagnostic.

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Epidemiology of Hepatitis A

Hepatitis A infections are vastly underreported due to the very high rates of asymptomatic and minimally symptomatic disease. Globally, the geographical distribution of HAV infection is closely tied to sanitation and hygiene standards, access to clean drinking water, and crowded living conditions. Worldwide, HAV infections occur sporadically and in large-scale epidemics. Explosive eruptions of disease, like the 1988 Shanghai epidemic that affected approximately 300,000 individuals, can be quite disruptive, causing serious strain on the public health system and substantial economic loss. Cyclic recurrences of HAV outbreaks are well documented. Globally, disease burden is greatest across Central and South America, Africa, the Middle East, Asia, and the Western Pacific island groups where HAV causes an estimated 1.4 million cases with 11,000 deaths each year.

The WHO recognizes four levels of disease endemicity. Most countries and regions with poor sanitation and hygiene are highly endemic for hepatitis A infection. High endemicity indicates that more than 90% of the population becomes infected by age 10 years. Natural infection confers lifelong immunity. Epidemics across these regions are rare because the majority of older children and adults are already immune. Infections in young children are typically asymptomatic, and the few with symptoms are almost always anicteric. For these reasons, countries and regions that are highly endemic for hepatitis A infection have low symptomatic disease rates, low morbidity, and low mortality. Despite its high endemicity, HAV does not pose a public health problem, and vaccination is a very low priority. Intermediate endemicity is the classification used to describe populations where 50% or more of individuals are infected by the age of 15 years. Intermediate endemicity is typical for countries and regions with transitional economies and variable sanitary conditions. The large pool of susceptible older children and adults is associated with high rates of symptomatic disease. Large outbreaks are a common occurrence. Regions with intermediate levels of HAV endemicity have the potential to benefit most from universal childhood immunization. Low endemic regions of HAV are defined as those where 50% or more of the population is infected by age 30 years, and very low endemic regions are those where fewer than 50% of individuals are infected by age 30 years. Low and very low levels of HAV endemicity are typical for developed countries with good sanitation and hygiene. Under these conditions, the majority of infections occur in high-risk group individuals, such as injecting-drug users, men who have sex with men, and travelers to regions of high endemicity. Index cases of infection in low and very low endemic communities can lead to outbreaks. In most cases, established sanitation and hygiene practices limit person-to-person transmission, thereby restricting the extent of any outbreaks. The source of many outbreaks originates from contaminated food products that are imported from countries with high or intermediate endemicity.

Hepatitis A Infection in the United States

Prior to vaccine licensure in the mid-1990s, large, nationwide epidemics of hepatitis A were common across the United States. Hepatitis A remained the most frequent cause of viral hepatitis until 2004. Between 1987 and 1997, 17 states (AZ, AK, AR, CA, CO, ID, MO, MT, OK, OR, NV, NM, SD, TX, UT, WA, and WY) accounted for 68% of all reported US infections. The implementation of a series of hepatitis A vaccine recommendations, first targeting high-risk individuals and later targeting all children living in states with the highest rates of disease, caused a gradual shift in the epidemiology of the infection. By 2002, reports of HAV infection nationwide were down, and the state-to-state differences in rates of infection had been eliminated.

Hepatitis A Transmission

Like other non-enveloped viruses, HAV can be stable in the environment for months. Virus can be inactivated by heat, formalin, or chlorine. Humans are the only natural host.

Virus is spread person-to-person via the fecal-oral route when a susceptible individual consumes food or water that has been contaminated with feces from an infected person. The average incubation period following exposure to HAV is 28 days but can be as long as 50 days. Virus replicates in the gastrointestinal tract, reaching its highest concentration in stool 2 weeks before symptom onset. Most infected individuals excrete virus in their stool for about 3 weeks. In young children, virus replicates to higher concentrations and is shed for a longer period of time. Hepatitis A is one of most frequent causes of foodborne infection. Its long incubation period complicates trace-back when investigating foodborne outbreaks.

Clinical Presentation

Infections caused by hepatitis A are very often clinically asymptomatic or so minimally symptomatic that the infected individual does not seek medical attention. Some asymptomatic infections are clinically inapparent, but most are better categorized as subclinical since laboratory test results will most often show an elevation in serum hepatic transaminase concentrations. The likelihood of developing symptomatic disease increases with age. Symptomatic illness associated with jaundice is described as icteric, and illness without jaundice is described as anicteric infection.

Symptomatic HAV infection most typically presents abruptly with low-grade fever, myalgias, malaise, anorexia, nausea, and vomiting with associated right upper quadrant abdominal pain. When present, clinical signs that indicate the presence of hepatic inflammation and/or dysfunction such as tea- or cola-colored urine, clay-like light-colored bowel movements, jaundice, scleral icterus, and/or hepatomegaly facilitate establishing the diagnosis by immediately raising the suspicion for viral hepatitis.

On average, symptoms last 2 weeks, although some adults have recovery times with intermittent relapses for 24 weeks or longer. Complete recovery with lifelong immunity to reinfection is expected. Unlike hepatitis viruses B and C, HAV does not cause chronic infection or chronic liver disease. Very rarely, HAV can lead to life-threatening fulminant hepatitis and acute liver failure.

Between 70% and 90% of children less than 6 years of age who are infected with HAV are asymptomatic, and those with symptomatic infection only rarely develop jaundice. In contrast, 76% to 97% of infected older children and adults develop symptomatic disease.

Management

There is no specific treatment available for infection caused by HAV. Symptomatic treatment, with careful attention to avoiding medications that are metabolized by the liver, or known to be hepatotoxic, can be used for pain relief or to reduce fever.

Hepatitis A Vaccine

Globally, several formulations of HAV vaccines are used. Live oral vaccines are available for use in China and in the private sector of India, but most available formulations are formaldehyde-inactivated whole-virus vaccines. They all show similar efficacy and side effect profiles. A two-dose series is recommended, although almost all vaccine recipients develop protective antibody levels within one month of receiving their first dose. Mathematical models predict that vaccine-associated protection will last 25 years or more.

Vaccines Available in the United States

Three formulations of formalin-inactivated whole-virus vaccines are available for use in the United States:

1. Vaqta, marketed by Merck Vaccines, gained FDA licensure in 1996. It is recommended as a two-dose series. The second dose should be administered 6 to 18 months after the first. Each adult dose, used for individuals 19 years of age and older, is a 1 mL intramuscular injection containing 50 U of the immunogen.

Each pediatric dose, used for ages 12 months to 18 years, is 0.5 mL containing 25 U of the immunogen, exactly half the adult dose.

2. Havrix, marketed by GlaxoSmithKline, gained FDA licensure in 1995. It is also recommended as a two-dose series. The second dose should be administered 6 to 12 months after the first. Each adult dose, used for individuals 19 years of age and older, is a 1 mL intramuscular injection containing 1440 ELISA units of the immunogen. Each pediatric dose, used for ages 12 months to 18 years, is 0.5 mL containing 720 ELISA units, exactly half the adult dose.
3. Twinrix, marketed by GlaxoSmithKline, gained FDA licensure in 2001 as a combination vaccine comprised of the same immunogens used to manufacture Havrix (inactivated whole HAV) and Engerix-B (recombinant hepatitis B surface antigen) monovalent vaccines. Twinrix is licensed for use in adults 18 years and older who require immunization against both hepatitis A and hepatitis B infections. Unlike Havrix, Twinrix is recommended as either a three- or four-dose series. The dosing schedule recommended for the three-dose series is at 0, 1, and 6 months. The four-dose series is recommended when an accelerated schedule is necessary or desired. Doses are given at 0, 7, and 21–30 days and then followed by a booster dose 12 months after the first dose. Each 1 mL intramuscular dose contains 720 ELISA units of the HAV immunogen and 20 mcg of the hepatitis B immunogen.

Immunizing Antigens, Additives, and Excipients

Vaqta is derived from a characterized HAV strain that is cultured in MRC-5 cells, then harvested, purified, and formalin inactivated. The immunogen is then adsorbed onto an adjuvant of amorphous aluminum hydroxyphosphate sulfate.

Havrix is derived from cell culture-adapted HAV strain HM175 virus propagated in MRC-5 cells and then purified from cell lysates via ultrafiltration and gel permeation chromatography. After undergoing inactivation with formalin, the immunogen is adsorbed onto aluminum hydroxide adjuvant.

Twinrix: The HAV immunogen is manufactured as described for Havrix. The hepatitis B immunogen is recombinant hepatitis B surface antigen that is produced by the yeast, *Saccharomyces cerevisiae* and then purified using a series of physical and chemical methods. Purified immunogen is adsorbed onto aluminum hydroxide adjuvant and then combined with the HAV immunogen to produce the final combination vaccine product.

ACIP Vaccine Recommendations in the United States

In 1996, shortly after the licensure of formalin-inactivated whole-virus HAV vaccine, the ACIP recommended it be administered to individuals 2 years of age and older identified to be at risk, including those living in communities with high rates of hepatitis A infection. The advice was directed, but not exclusive, to children

residing in certain American Indian, Alaskan Native, and Hispanic communities. In 1999, ACIP expanded the recommendation for routine vaccination to children 2 years of age and older who were residing in 17 states known to have HAV infection rates exceeding the national average of 10 cases/100,000 population. The vaccine's labeling indication was lowered to 12 months in 2005. Reported rates of HAV infection from the 17 states where HAV vaccine was being administered routinely to children had dropped well below the national average. In 2006, recognizing the shifting epidemiology of HAV infection and acknowledging the FDA's expanded age indication, ACIP broadened their recommendation for HAV vaccine to a universal childhood recommendation for all children starting at age 12 months. Figure 13.1 shows the total number of hepatitis A infections reported in the United States each year between 1966 and 2016 illustrating the impressive impact of vaccinating children on the total disease burden in the US population.

Currently, ACIP also recommends HAV vaccine for individuals at high risk due to any of the following circumstances listed in Table 13.1.

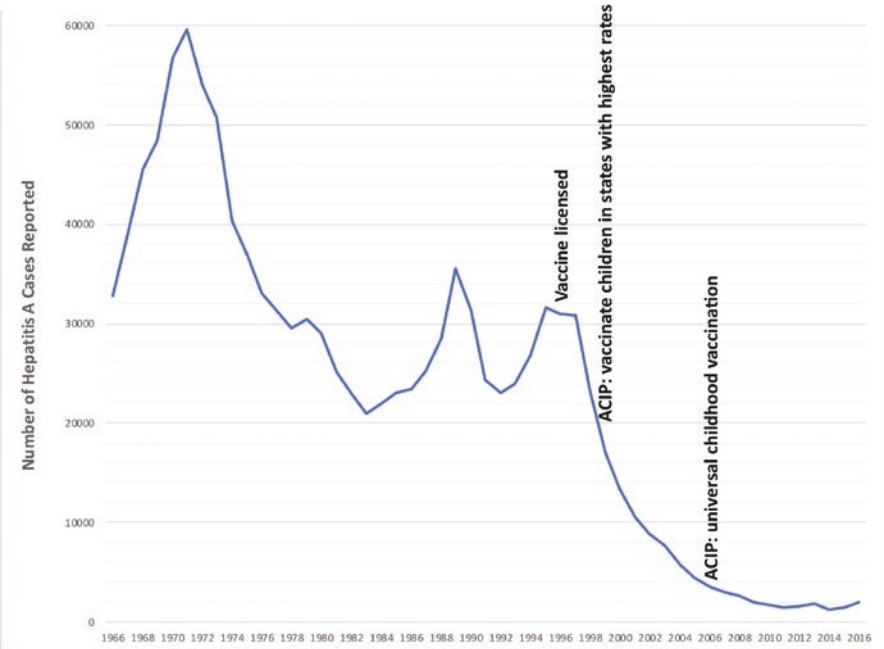

Fig. 13.1 Shown is the total number of hepatitis A cases reported in the United States each year from 1966 to 2016. Hepatitis A vaccine was approved for use by the US Food and Drug Administration in 1996. Later that year, ACIP recommended that the vaccine be given to children living in communities with high rates of infection. In 1999, ACIP expanded and clarified their recommendation to include children residing in 17 US states with high rates of infection. In 2006, ACIP recommended universal hepatitis A vaccination for all children starting at 12 months of age (see text). Source Data for graph: https://www.cdc.gov/hepatitis/statistics/SurveillanceRpts.htm

Table 13.1 Individuals and groups recommended to receive hepatitis A vaccine

Underlying medical conditions	Known or likely exposure	Social and behavioral risks
Chronic liver disease	Postexposure prophylaxis for people 12 months of age and older	Individuals who use drugs
Chronic hepatitis C infection	Household and close personal contacts of HAV-infected individuals	Men who have sex with men
Chronic hepatitis B infection	Working with HAV-infected patients or patient samples	Current or recent incarceration
Immunosuppression	Sexual partners of HAV-infected individuals	International travel to endemic areas
Individuals treated with clotting-factor concentrates	Close contact with an international adoptee from a country with high or intermediate endemicity	Individuals experiencing homelessness

Pediatric Immunization Schedule

HAV vaccine is recommended for all children 12–23 months of age as a two-dose series with catch-up recommended for children 2 years of age and older.

For those planning international travel, infants between 6 and 11 months should receive one dose prior to departure and then be revaccinated with two doses between 12 and 23 months of age as above.

Adult Immunization Schedule

Options for immunizing adults include the administration of a two-dose series of either Havrix or Vaqta using the recommended minimum dosing intervals. A three- or four-dose series of Twinrix can be considered for those who require vaccination against both hepatitis A and hepatitis B.

Global Vaccine Recommendations

The WHO recommends universal integration of HAV vaccination into national immunization schedules starting at 1 year of age. Some countries with more advanced progress in socioeconomic status and hygiene, such as Argentina, are opting for a single dose of inactivated HAV vaccine. This option provides comparable short- and intermediate-term effectiveness, is less expensive, and is easier to implement than a two-dose regimen.

Contraindications to Vaccine

Contraindications to HAV vaccine include previous life-threatening allergic reactions to prior doses or to any vaccine components. Those with an ongoing moderate or severe illness should postpone immunization until fully recovered.

Warnings and Precautions for Vaccine Use

Syncope or near-syncopal episodes can occur following the administration of any injectable vaccine.

Side Effects and Adverse Events

Self-limiting side effects may include soreness or redness at the injection site, low-grade fever, headache, and/or tiredness. Rare side effects have included dizziness, fainting, shoulder pain on the side of the injection, and allergic reactions. Serious allergic reactions that include hives, facial swelling, tachycardia, dizziness, and/or weakness are estimated to occur at less than 1 in a million doses.

The safety profile of Havrix was evaluated in clinical trials involving approximately 37,000 subjects. Localized pain at the injection site was reported by 56% of adults and 21% of children older than 2 years. The most common local reactions reported in children less than 2 years of age were injection site pain (32%) and injection site redness (29%). Systemic reactions in this age group included irritability (42%), drowsiness (28%), and loss of appetite (28%). A similar safety profile was shown in clinical trials using Vaqta. Children less than 2 years of age experienced injection site pain (37%), redness (21%), and fever (16%). The most common adverse reactions reported by adults included injection site pain (67%), injection site warmth (18%), and headache (14%).

Vaccine Efficacy and Immunogenicity from Clinical Trials

Overall, inactivated whole-virus hepatitis A vaccines result in seroconversion of more than 95% of children and adults after a single dose and 100% seroconversion after two doses. In addition, two doses of Havrix vaccine, administered 1 month apart, was shown to be 94% effective at preventing hepatitis A infection among 40,000 Thai children, aged 1–16 years, living in highly endemic villages. Seroconversion rate after the two-dose series was 99% or higher. Similarly, Vaqta vaccine was shown to be 100% effective in preventing hepatitis A infection among

1000 New York children 2 to 16 years of age who received one dose while living in a community with high rates of disease. Seroconversion following two doses was documented in 100% of two-dose vaccine recipients.

Impact of Vaccine on Disease Burden

Globally, by 2016, at least 16 countries have added universal HAV vaccine to their national pediatric immunization programs. In each case, as childhood vaccination rates increased, the national incidence of hepatitis A infection in all age groups decreased dramatically underscoring the role that young children play in the transmission of this disease. The impact of implementing universal pediatric hepatitis A vaccine programs on nationwide incidence of hepatitis A is shown in Table 13.2. For example, the Panamanian Ministry of Health added a single dose of HAV vaccine to their universal childhood immunization schedule in 2007 targeting children older than 12 months. The mean incidence of hepatitis A infection reported between 2000 and 2006 was 51 per 100,000 population. By 2010, single-dose vaccine coverage rates had reached 71% and the reported incidence of hepatitis A had dropped 93% to 3.7 per 100,000.

Similar successes have been achieved in the United States. Following the 1996 ACIP recommendations to immunize American Indian and Alaskan Native children living in communities with high rates of hepatitis A infection, the incidence of disease in those communities dropped by more than 95%, from 104 to 5 cases per 100,000 population.

Following the 1999 expanded ACIP recommendations to immunize all children in 17 states with rates of infection that exceeded the national average, there was an 88% decline in hepatitis A cases reported from the targeted states. In 2014, an all-time low of 1239 cases of hepatitis A were reported across the United States, representing a 96% decline since vaccination efforts had begun.

Table 13.2 Examples of the global impact of universal pediatric hepatitis A vaccine programs

Country	Start of vaccine	Target age	Mean vaccine coverage rates	Years compared	Incidence per 100,000 population	Decline in hepatitis A disease
Argentina	2005	1 yr	2006–2011: 96.8%	2000–2002 vs. 2006–2011	66.5 vs. 7.9	88%
Israel	1999	18 mos	2003–2010: 88%	1993–1998 vs. 2008–2012	50.4 vs. <1.0	>98%
Panama	2007	>12 mos	2010: 71% (one dose)	2000–2006 vs. 2010	51.1 vs. 3.7	93%
Uruguay	2007 2008	1–5 yrs. >12 mos	2010: 74% (one dose)	2005 vs. 2010	69.6 vs. 2.7	96%

A resurgence in disease that began in late 2016 has been more challenging to control because of the large numbers of high-risk individuals from groups that are historically harder to reach. Outbreaks continue in individuals who use drugs, in those experiencing homelessness, and among men who have sex with men. More than 15,000 cases, 8500 (57%) hospitalizations, and 140 deaths from HAV infection have been reported across these risk groups.

Inactivated whole-virus HAV vaccines are safe and highly effective. Universal vaccination programs that target young children have led to dramatic declines in disease incidence, at least in part by interrupting disease transmission from young children to other members of the community. Young children shed higher amounts of virus during infection, often lack quality hygiene practices, and are very often asymptomatic during infection. Weeks of uninterrupted transmission can occur under these conditions since the outbreak may not become evident until an adult contact develops symptomatic disease with jaundice and the incubation period for the infection can be as long as 50 days.

References and Suggested Reading

Links

World Health Organization:

https://www.who.int/news-room/fact-sheets/detail/hepatitis-a
https://www.who.int/immunization/diseases/hepatitisA/en/

U.S. Centers for Disease Control and Prevention:

https://www.cdc.gov/hepatitis/hav/index.htm

Vaccine Information Sheet

https://www.cdc.gov/vaccines/hcp/vis/vis-statements/hep-a.html

Contagion Live

https://www.contagionlive.com/outbreak-monitor?z=no&type=sub&category=Hepatitis+A

Havrix Package Insert

https://www.fda.gov/media/79349/download

Vaqta Package Insert

https://www.fda.gov/media/74519/download

Twinrix Package Insert

https://www.fda.gov/media/74182/download

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Chapter 14
Hepatitis B

Cynthia Bonville and Joseph Domachowske

Hepatitis B Infection

Etiology

Hepatitis B virus (HBV), a member of the *Hepadnaviridae* family, in the genus *Orthohepadnavirus* is the cause of hepatitis B infection, a disease primarily affecting the liver. Virions consist of partially double-stranded DNA inside an icosahedral nucleocapsid that is surrounded by an outer lipid envelope. Small, medium, and large surface proteins embedded in the outer lipid envelope are necessary for the virus to attach to and enter a target cell to initiate infection. Envelope protein lines the inner aspect of the lipid envelope, and core protein forms the viral capsid. The three proteins are more commonly referred to as hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg) because under the right circumstances, they are capable of stimulating an immune response in the infected individual. Individuals who mount an effective immune response to the virus during the acute hepatitis B disease clear the infection. Those who go on to develop chronic hepatitis B infection have a lifelong risk of developing hepatocellular carcinoma, cirrhosis, and liver failure.

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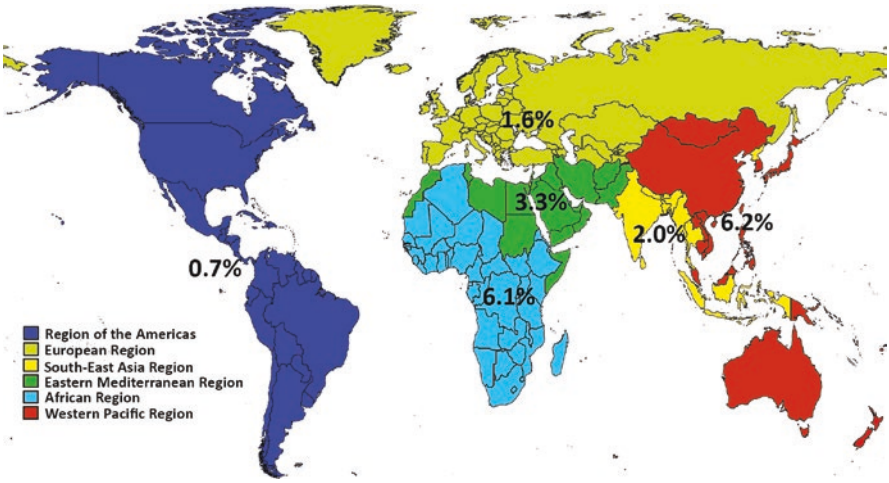

Fig. 14.1 Prevalence of hepatitis B infection in each of the six World Health Organization regions

Global Epidemiology of Hepatitis B

Hepatitis B disease is a major public health problem everywhere in the world. The burden of infection varies by country and by geographic location with the heaviest affected areas experiencing disease in 15% or more of their total population. The global distribution of disease burden can be appreciated by viewing the mean prevalence of hepatitis B infection across each of the six World Health Organization regions (Fig. 14.1). High-intermediate to high endemicity of hepatitis B, defined as a prevalence of 5% to greater than 8%, is seen across the Western Pacific (6.2%) and Africa regions (6.1%), with some countries reporting disease prevalence higher than 15%. Low to intermediate endemicity, defined as a prevalence of 2% to <5%, is seen in the Eastern Mediterranean (3.3%) and Southeast Asia regions (2.0%), while low endemicity (<2%) is seen in the regions of Europe (1.6%) and the Americas (0.7%) (Fig. 14.1).

Epidemiology of Hepatitis B in the United States

Acute hepatitis B infection rates have remained steady in the United States at 1.0 per 100,000 population since 2009. Rates among those living in nonurban areas are somewhat higher than for urban areas. Acute infection rates are highest among adult African Americans. Between 2006 and 2013, the state health departments of Kentucky, Tennessee, and West Virginia all reported steady increases in acute HBV infection among non-Hispanic Caucasians between 30 and 39 years of age. This somewhat isolated spike in acute disease activity was determined to be caused by exposures to contaminated drug paraphernalia and sharing of needles used to inject illicit substances.

Chronic hepatitis B infection also causes substantial morbidity and mortality in the United States. The 2011–2012 National Health and Nutrition Examination Survey indicated that 850,000 Americans were living with chronic hepatitis B infection at the time. By 2020, estimates of the chronic disease burden exceeded one million individuals. Non-Hispanic Asians account for nearly half of these chronic hepatitis B infections despite representing only 5% of the US population. As many as 70% of those chronically infected are foreign-born immigrants from highly endemic areas of the world. Each year, 2,000 Americans die from complications of chronic hepatitis B infection.

Transmission of Hepatitis B

Hepatitis B is transmitted from person to person via percutaneous or mucous membrane exposure to infected blood or body fluids. Possible modes of horizontal transmission include sexual contact; sharing of razors, toothbrushes, or injection drug paraphernalia; tattooing; body piercing; scarification or acupuncture using contaminated needles; and occupational exposure to blood. Perinatal transmission is very common in highly endemic regions of the world, accounting for the majority of new cases worldwide. Infants born to infected mothers who test positive for both HBsAg and HBeAg during pregnancy are at the highest risk of acquiring infection perinatally. In Asia, the risk of the infant becoming infected is close to 100%. Infants born to mothers who test positive for HBsAg and negative for HBeAg have a 5–30% risk of being infected. Young age at the time of the acute infection is an independent risk factor for developing chronic infection. Most newborns infected perinatally become chronically infected.

The average incubation period for HBV is 75 days, with a range of 30–180 days.

Clinical Presentation of Hepatitis B Infection

More than half of older children and adults infected with hepatitis B and virtually all perinatally infected newborns are asymptomatic. Others present with nonspecific signs and symptoms typical for many acute viral infections including fever, fatigue, loss of appetite, nausea, vomiting, and muscle, joint, and/or abdominal pain. The possibility of hepatitis B infection may not be considered unless or until the patient develops signs that are more specific for acute viral hepatitis, such as jaundice of the eyes or skin, tea- or cola-colored urine, right upper quadrant abdominal pain, hepatomegaly, and clay-colored stools. In those who undergo laboratory testing as part of their diagnostic evaluation early in the illness, results will be consistent with hepatic inflammation, showing elevated serum hepatic transaminases with or without hyperbilirubinemia.

Rarely, acute infection with HBV causes acute, fulminant hepatic necrosis with liver failure. Without liver transplantation, this condition is usually fatal. Overall, the mortality associated with acute HBV infection is about 1%. Laboratory evidence of acute infection includes positive tests for HBsAg and anti-HbcAg IgM. Results of HBeAg testing may also be positive. Individuals who test positive for HBeAg are highly contagious.

The likelihood that an individual will develop chronic HBV infection is age-dependent.

Most infants infected perinatally, and between 80% and 90% of children who are infected horizontally during the first year of life become chronically infected. The risk of chronic infection drops below 50% among those infected between the ages of 1 and 6 years and to less than 5% of those who acquire infection as an adult.

Chronic HBV disease is defined as the persistence of HBsAg in the blood for more than 6 months. Between 20% and 30% of individuals with chronic HBV infection develop cirrhosis, liver failure, or hepatocellular carcinoma. Patients typically remain asymptomatic until one of these complications develops. In 2015, an estimated 887,000 individuals worldwide died from complications of hepatitis B infection.

Management

Specific treatment is not available for acute HBV infection. Management includes symptomatic care, with intravenous fluid replacement, as needed.

Individuals with chronic HBV infection require lifelong medical care. Alcohol consumption and coinfection with hepatitis C and/or D negatively impact HBV morbidity and mortality. Patients should avoid medications, including those available over the counter, that are potentially hepatotoxic. Vaccination against hepatitis A should be administered to susceptible individuals. Several antiviral medications, including tenofovir and entecavir, are now available for the treatment of chronic HBV infection, with the goal of virus suppression. Curative antiviral regimens have not yet been identified. Only 10% of treatment-eligible people receive antiviral therapy.

Prevention: Hepatitis B Vaccine

Hepatitis B infection and its complications are vaccine-preventable conditions. Safe and highly effective vaccines that provide long-lasting protection have been available since 1982. Vaccine-induced immunity provides protection against infection for at least 30 years. WHO has recommended that hepatitis B vaccine be included in all national immunization schedules since 1991. Suboptimal adherence to the recommended three-dose regimen, especially in highly endemic areas and in certain high-risk populations, remains problematic.

Vaccines Available in the United States

All currently available HBV vaccines are recombinant formulations of HBsAg. The vaccine-derived HBsAg is easily detected in blood samples of individuals who have been recently vaccinated. Since serum HBsAg testing is used as a diagnostic marker for HBV infection, it is important to understand that available assays may be able to detect vaccine-derived HBsAg for as long as 28 days postvaccination.

Three monovalent formulations (Recombivax HB, Engerix-B, Heplisav-B) and three combination formulations (Pediarix, Twinrix, Vaxelis) of HBV vaccine are approved and available for use in the United States.

Available Monovalent Hepatitis B Vaccines

Recombivax HB, marketed by Merck's Vaccine Division, was FDA approved in 1986 for all ages as a three-dose series. The standard doses for children and adults are 5 mcg in 0.5 mL and 10 mcg in 1 mL, respectively. Doses are administered intramuscularly, except in patients with hemophilia where the subcutaneous route is preferred. The higher dose of 40 mcg is recommended for adults who are undergoing dialysis because of its superior immunogenicity in this high-risk population. Prefilled syringes containing single doses are available as 5 mcg/0.5 mL, 10 mcg/1 mL, and 40 mcg/1 mL.

Engerix-B, marketed by GlaxoSmithKline, was FDA approved in 1989 for all ages as a three-dose series. The standard doses for children and adults are 10 mcg in 0.5 mL and 20 mcg in 1 mL, respectively. Doses are administered intramuscularly, except in patients with bleeding disorders where the subcutaneous route may be considered. The higher dose of 40 mcg is recommended for adults who are undergoing dialysis. Prefilled syringes containing single standard doses are available as 10 mcg/0.5 mL and 20 mcg/1 mL. Adults on hemodialysis should be immunized with 2 mL of the 20 mcg/1 mL formulation for each dose.

Heplisav-B, marketed by Dynavax, was FDA approved in 2017 for use in adults as a two-dose series. The standard dose is 20 mcg in 0.5 mL. It has not been studied in adults receiving hemodialysis.

Available Combination Hepatitis B Vaccines

Twinrix, marketed by GlaxoSmithKline, was FDA approved in 2001 for use in adults. Twinrix is a bivalent combination vaccine derived from the monovalent products Engerix-B and Havrix used to immunize adults against hepatitis B and hepatitis A (see Chap. 35). The 1 mL unit dose formulation includes 20 mcg of HBsAg and 720 ELISA units of inactivated hepatitis A.

Pediarix, marketed by GlaxoSmithKline, was FDA approved in 2002 for use in children of ages 6 weeks through 6 years. Pediarix is a pentavalent combination vaccine used to immunize infants and young children against diphtheria, tetanus, pertussis, polio, and hepatitis B (see Chap. 35). Each 0.5 mL unit dose formulation contains 25 Lf units of diphtheria toxin, 10 Lf units of tetanus toxoid, 25 mcg of inactivated pertussis toxin, 25 mcg of filamentous hemagglutinin, 8 mcg of pertactin, 40 D-antigen units (DU) of type 1 poliovirus, 8 DU of type 2 poliovirus, 32 DU of type 3 poliovirus, and 10 mcg of HBsAg. A three-dose series may be given to infants born to HBsAg-negative mothers who already received a birth dose monovalent hepatitis B vaccine.

Vaxelis, co-marketed by Sanofi Pasteur and Merck's Vaccine Division, was FDA approved in 2018 for use in children of ages 6 weeks through 4 years. Vaxelis is a hexavalent combination vaccine used to immunize infants and young children against diphtheria, tetanus, pertussis, polio, hepatitis B, and *Haemophilus influenzae* type b (see Chap. 35). Each 0.5 mL unit dose formulation contains 15 Lf units of diphtheria toxin, 5 Lf units of tetanus toxoid, 20 mcg of detoxified pertussis toxin, 20 mcg of filamentous hemagglutinin, 3 mcg of pertactin, 5 mcg of fimbriae types 2 and 3, 29 DU of type 1 poliovirus, 7 DU of type 2 poliovirus, 26 DU of type 3 poliovirus, 10 of mcg HBsAg, and 3 mcg of polyribosylribitol phosphate bound to 50 mcg of the outer membrane protein complex of *Neisseria meningitidis*. A three-dose series may be given to infants born to HBsAg-negative mothers and who received a dose of any HBV vaccine prior to or at 1 month of age.

Immunizing Antigen

All available hepatitis B vaccines use recombinant HBsAg as the immunogen. The HBsAg included in Recombivax HB and Vaxelis is derived from a recombinant strain of the yeast *Saccharomyces cerevisiae* that encodes HBsAg. Yeast are grown on complex culture media containing yeast extract, soy peptone, dextrose, amino acids, and mineral salts. Recombinant HBsAg is released from the yeast cells by disruption and then purified using a series of physical and chemical methods. Purified HBsAg is treated with formaldehyde and then coprecipitated with aluminum hydroxyphosphate sulfate (alum) as the adjuvant.

Similarly, the recombinant HBsAg used in Engerix-B, Twinrix, and Pediarix is derived from genetically modified *Saccharomyces cerevisiae*. Recombinant HBsAg is purified using several physiochemical steps before being adsorbed onto aluminum hydroxide adjuvant.

The recombinant HBsAg used in Heplisav-B is expressed by a recombinant strain of *Hansenula polymorpha* yeast. The yeast are grown in a chemically defined fermentation medium containing vitamins and mineral salts. Recombinant HBsAg is released by cell disruption and purified physiochemically. Purified HBsAg is then combined with CpG 1018 adjuvant, a 22-mer phosphorothioate-linked oligodeoxynucleotide in phosphate-buffered saline.

Additives and Excipients

Recombivax HB contains less than 1% yeast protein, approximately 0.5 mg/mL of aluminum, and less than 15 mcg/mL of residual formaldehyde. The tip caps of the prefilled syringes contain natural rubber latex. Recombivax HB is preservative-free.

Engerix-B contains less than 5% yeast protein, 0.25 mg aluminum hydroxide, 9 mg/mL sodium chloride, 0.98 mg/mL disodium phosphate dihydrate, and 0.71 mg/mL sodium dihydrogen phosphate dihydrate. The tip caps of the prefilled syringes contain natural rubber latex. Engerix-B is preservative-free.

Heplisav-B contains less than 5% yeast protein, less than 20 pcg yeast DNA, less than 0.9 ppm deoxycholate, 3000 mcg CpG1018 per 20 mcg HBsAg, 9 mg/mL sodium chloride, 1.75 mg/mL sodium phosphate dibasic dodecahydrate, 0.48 mg/mL sodium phosphate monobasic dihydrate, and 0.1 mg/mL polysorbate 80. Heplisav-B is latex-free and preservative-free.

For a summary of additives and excipients included in Twinrix, Pediarix, Vaxelis, see Chaps. 4 and 35.

Vaccine Recommendations

Hepatitis B Vaccine Recommendations: Pediatrics

Guidance for the use of hepatitis B vaccine has been updated and expanded since the US Advisory Committee on Immunization Practices (ACIP) first published recommendations in 1991. Currently, a dose of monovalent hepatitis B vaccine is recommended for all infants within 24 hours of birth followed by two or three doses of monovalent or hepatitis B-containing combination vaccine to complete the series, usually by 6 months of age. The birth dose helps to ensure protection against perinatal transmission.

All newborns should receive their first dose of hepatitis B vaccine shortly after birth. Two important factors influencing the details of this recommendation are the mother's hepatitis B status and the weight of the infant. Medically stable newborns born to mothers who are known to be HBsAg negative and who weigh 2000 grams (4 lbs. 7 oz) or more should receive a dose of monovalent hepatitis B vaccine within 24 hrs of birth.

Infants born to HBsAg-negative mothers who weigh less than 2000 grams should receive their birth dose of vaccine when they reach a chronological age of 1 month or at the time of hospital discharge, whichever comes first. All infants born to HBsAg-positive mothers, regardless of weight, should receive one dose of hepatitis B vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) at different injection sites within 12 hours of birth.

Those infants weighing less than 2000 grams when they receive their first dose of the vaccine require three additional doses of vaccine (four doses total) starting when they reach a chronological age of 1 month. All infants born to mothers with unknown HBsAg status, regardless of weight, should receive one dose of vaccine within 12 hours of birth. If they weigh less than 2000 grams, they should also receive 0.5 mL of HBIG within 12 hours of birth plus three additional doses of vaccine (four total) beginning at 1 month of age. For those weighing 2000 grams or more, HBIG administration can be delayed for up to 7 days of age while awaiting test results of maternal HBsAg status.

Under most circumstances, the hepatitis B vaccine series is completed by administering a total of three doses. Dose 1 is given at birth, dose 2 is given at 1–2 months, and dose 3 is given at 6–18 months of age. If no birth dose was given, the three-dose series should be started as soon as possible. Four doses of hepatitis B-containing vaccine are permitted when a combination vaccine that includes HBV is used to complete the series following a birth dose. For subsequent doses, careful adherence to minimum age and minimum dose intervals is important. The minimum age to receive the final dose in the series is 24 weeks. The minimum interval needed between dose 1 and 2 is 4 weeks, and the minimum interval between dose 2 and 3 is 8 weeks.

ACIP also recommends catch-up vaccination for all children and adolescents under 19 years of age who have not yet completed the vaccine series. This can be accomplished with a three-dose series of the pediatric formulation of vaccine administered on a 0-, 1-, and 6-month schedule. Adolescents 11–15 years of age also have the option to be immunized with an alternative two-dose regimen using the adult formulation of Recombivax HB, with a minimum interval of 4 months between doses.

Hepatitis B Vaccine Recommendations: Adults

ACIP recommends hepatitis B vaccine for anyone who desires protection from the disease. A stated or identified risk factor is not required. In addition, vaccine is recommended for individuals and groups at high risk for infection who have not previously been immunized (Table 14.1). Identifying and vaccinating high-risk individuals before they become infected can be challenging. Available options for completing standard hepatitis B vaccination regimens in adults are shown in Table 14.2. As a group, individuals being treated with hemodialysis are at high risk for infection with hepatitis B but respond poorly to standard vaccination regimens. For these reasons, the dose and/or schedule used to vaccinate this patient population has been modified. Two options are available. Recombivax HB can be administered as a three-dose series at 0, 1, and 6 months using 40 mcg per dose. Alternatively, Engerix-B can be administered as a four-dose series at 0, 1, 2, and 6 months using 40 mcg per dose. Serologic responses should be monitored, and booster doses given as necessary.

Table 14.1 Individuals and groups recommended to receive hepatitis B vaccine

Underlying medical conditions	Known or high risk for exposure	Social and behavioral risks
Chronic liver disease	Victims of sexual assault or abuse	Individuals who inject drugs and those in drug treatment programs
Chronic hepatitis C infection	Household contacts of individuals with chronic HBV infection	Men who have sex with men, individuals with multiple sexual partners
Kidney disease including those requiring dialysis	Sexual partners of individuals with chronic HBV infection	Residents of correctional facilities
HIV infection, diabetes mellitus, need for solid organ transplantation	Healthcare and public safety workers, those working in correctional facilities	International travel to endemic areas
Individuals requiring treatment with blood products	Residents and staff of facilities for people with developmental disabilities	Individuals seeking evaluation or treatment for a sexually transmitted infection

Table 14.2 Options to complete the hepatitis B vaccination series in adults

Vaccine	Dose	Number of doses	Dosing schedule
Engerix-B	20 mcg in 1 mL	3	0, 1, and 6 mos
Recombivax HB	10 mcg in 1 mL	3	0, 1, and 6 mos
Heplisav-B	20 mcg in 0.5 ml	2	At least 4 weeks apart
Twinrix: Option 1	20 mcg in 1 mL[a]	3	0, 1, and 6 mos
Twinrix: Option 2	20 mcg in 1 mL[a]	4	0, 7 days, 21–30 days, 12 mos

[a]Also contains 720 ELISA units of inactivated hepatitis A

Contraindications to Vaccine

Contraindications to hepatitis B vaccine include a life-threatening allergic reaction following a previous dose or a known severe allergy to any vaccine component including neomycin (Twinrix, Pediarix, Vaxelis), polymyxin B (Pediarix, Vaxelis), and streptomycin sulfate (Vaxelis). Moderately to severely ill individuals should postpone immunization until they have recovered from the acute illness.

Warnings and Precautions for Vaccine Use

Careful consideration should be given to vaccinating a premature infant who has a history of apnea after receiving any vaccination. Syncope and near-syncopal episodes from vasovagal reactions are known to occur following the administration of any injectable vaccine, particularly in the adolescent population. When immunizing with Recombivax HB, Engerix-B, Twinrix, and Pediarix, caution should be used for individuals with a known hypersensitivity to latex.

Side Effects and Adverse Events of Monovalent Hepatitis B Formulations

Transient, mild-to-moderate soreness at the injection site, with or without low-grade fever, lasting up to 2 days is reported frequently. Symptoms associated with vasovagal reactions to the injection, including dizziness, ringing in the ears, and syncope, are seen regularly, particularly among adolescents. Periodic breathing and/or apnea can be seen in premature infants following vaccination. Severe allergic reactions with hives, swelling of the face and throat, and difficulty breathing are very rare occurrences, estimated at 1 per million doses.

Vaccine-Specific Safety Profiles

Mild-to-moderate injection site reactions, including pain, tenderness, pruritus, or erythema, were seen in 17% of healthy children ≤10 years old who received Recombivax HB. Overall, 10.4% experienced systemic adverse reactions. Complaints, in decreasing order of frequency, included irritability, fever >101 °F, diarrhea, fatigue, and loss of appetite. Similarly, immunized adults have reported pain, swelling, and/or bruising at the injection site. 15% experienced systemic symptoms, most commonly as fatigue, malaise, and fever >100 °C.

Engerix-B is also generally well tolerated. The most commonly reported side effects reported from adults and children enrolled across 36 clinical trials were injection site soreness (22%) and fatigue (14%). Other fairly common adverse reactions reported from 1–10% of all vaccinees included injection site erythema, induration and/or swelling, dizziness, and headaches. Fewer than 1% reported chills, influenza-like symptoms, irritability, malaise, weakness, anorexia, rash, and/or minor gastrointestinal complaints.

Local injection site reactions were also commonly reported during clinical trials with Heplisav-B. The most common local reactions included injection site pain (23–39%), redness (1–4%), and swelling (1–2%), while the most common systemic reactions reported were fatigue (11–17%), headache (8–17%), malaise (7–9%), and myalgias (6–9%).

Post-marketing safety surveillance and case-controlled studies indicate that hepatitis B vaccines are safe and well tolerated. They do not cause Guillain-Barre syndrome, chronic fatigue syndrome, rheumatoid arthritis, type 1 diabetes, or other autoimmune diseases. There is no association between HBV vaccination and the development of multiple sclerosis, and vaccination does not increase the short-term risk of relapse in multiple sclerosis. In addition, no causal relationship between hepatitis B vaccination and other neurologic disorders, including leukoencephalitis, optic neuritis, and transverse myelitis, has been identified.

Estimated Vaccine Efficacy from Clinical Vaccine Trials

During convalescence from acute hepatitis B infection, individuals who develop a robust antibody response directed against HBsAg clear the infection. Serum concentrations of anti-HBsAg antibody at or exceeding 10 mIU/mL are known to be seroprotective. Similarly, individuals who are immunized with HBV vaccine, and subsequently shown to have seroprotective concentrations of anti-HBsAg antibody, are considered to be immune to infection. This serologic correlate of immunity allows for straightforward interpretation of immunogenicity results collected during vaccine trials. Given the ongoing high prevalence of infection in many parts of the world, clinical trials to determine vaccine efficacy (i.e., the ability of vaccine to prevent infection) can also be designed.

The protective efficacy of administering both a birth dose of HBIG and a three-dose series of Recombivax to infants born to HBsAg- and HBeAg-positive mothers was shown to be 96%. Recombivax HB is highly immunogenic. Following a three-dose series of the vaccine, 100% of 92 infants, 99% of 129 children, and 99% of 112 adolescents achieved anti-HBsAg antibody concentrations exceeding 10 mIU/mL. The immunogenicity of a two-dose regimen of the adult formulation (10 mcg/1 mL) when administered to 255 adolescents between 11 and 15 years was 99%. Immunogenicity of a three-dose regimen (10 mcg/1 mL) in adults varied by age: 98% of 787 adults 20–29 years old, 94% of 249 adults 30–39 years old, and 89% of 177 adults ≥40 years old achieved protective antibody concentrations. Hemodialysis patients respond less well than healthy adults, even when using the higher 40 mcg/1 mL dose formulation. Seroprotection rates are higher in those vaccinated earlier in disease, especially those who are immunized before they begin hemodialysis.

The efficacy of Engerix-B was evaluated in infants born to mothers positive for both HBsAg and HBeAg without the coadministration of HBIG at birth ($n = 58$). Only two infants became chronic hepatitis carriers during the 12-month follow-up period, giving the vaccine series a protective efficacy rate of 95%. Vaccine efficacy was also evaluated in men who have sex with men ($n = 244$). Four subjects became infected prior to completing the three-dose series. None of those who had completed the three-dose series became infected during the 18-month follow-up period.

Neonates who received a three-dose series of vaccine (10 mcg/0.5 mL) given at 0, 1, and 6 months ($n = 52$) achieved 97% seroprotection. Children aged 6 months to 10 years ($n = 242$) achieved 98% seroprotection, and children aged 5–16 years ($n = 181$) achieved 99.5% seroprotection. Similarly, adolescents aged 11–19 years ($n = 122$) achieved 99% seroprotection, and individuals ≥40 years old ($n = 50$) achieved 88% seroprotection.

Studies of the immunogenicity of a two-dose (20 mcg/0.5 mL) series of Heplisav-B, given 4 weeks apart, showed seroprotective rates across all groups exceeding 90%. Vaccine immunogenicity was seroprotective in 100% of 18- to 29-year-olds ($n = 174$), 98.9% of 30- to 39-year-olds ($n = 632$), 97.2% of 40- to 49-year-olds ($n = 974$), 95.2% of 50- to 59-year-olds ($n = 1439$), and 91.6% of 60- to 70-year-olds.

Seroprotective rates of the hepatitis B component of Twinrix, Pediarix, and Vaxelis were noninferior to their respective monovalent hepatitis B vaccines.

Impact of Vaccine on Disease Burden

In 1990, global hepatitis B vaccine coverage rates were estimated to be 1%. In 1992, the World Health Assembly passed a resolution recommending the inclusion of HBV vaccine in the Expanded Programme on Immunization by 1997. Efforts were successful worldwide. By 2014, global coverage rates with three doses of hepatitis B vaccine had increased to an estimated 82% with regional coverage as high as 92% in the Western Pacific. Between 1992 and 2015, the number of countries in the world routinely vaccinating infants with hepatitis B vaccine increased from 31 to 185. In 2015, 84% of children had received a three-dose series, but only 39% of newborns received a birth dose. The African, Eastern Mediterranean, and European regions all remain below the global average.

Hepatitis B vaccines are safe and highly effective at preventing infection and its associated complications. Globally, vaccine uptake exceeds 80% with some regions reporting vaccination rates of 93% or more.

References and Suggested Reading

World Health Organization

https://www.who.int/news-room/fact-sheets/detail/hepatitis-b

Vaccine Information Sheets

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Recombivax HB Package Insert

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Engerix-B Package Insert

https://www.fda.gov/media/79341/download

Heplisav-B Package Insert

https://www.fda.gov/media/108745/download

Twinrix Package Insert

https://www.fda.gov/media/74182/download

Pediarix Package Insert

https://www.fda.gov/media/79830/download

Vaxelis Package Insert

https://www.fda.gov/media/119465/download

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Chapter 15
Human Papillomavirus

Manika Suryadevara

HPV Infection

Etiology

Human papillomavirus (HPV), of the *Papillomaviridae* family, is a small, non-enveloped double-stranded DNA virus whose genome encodes for early proteins (required for viral replications) and late structural proteins (L1 and L2) which form the icosahedral capsid. HPV infects and replicates in either the cutaneous or the mucosal epithelium. The HPV types which infect the cutaneous epithelium lead to plantar, flat, or filiform warts. Separately, the HPV types which infect the mucosal epithelium are stratified into low-risk or high-risk types based on their oncogenic potential. Low-risk HPV types, most commonly HPV-6 and HPV-11, cause low-grade cervical cell abnormalities, genital warts, and respiratory papillomatosis. High-risk HPV types, most commonly HPV-16 and HPV-18, lead to low-grade and/or high-grade (precancerous) cervical cell abnormalities, anogenital cancers, and oropharyngeal cancers.

The association of cervical cancer and sexual activity had been speculated long before the identification of HPV. Since it was well known that cancer was not contagious, it was theorized that this particular cancer must be caused by an infection. In the 1970s, Harald zur Hausen, a German virologist who had previously identified Epstein-Barr virus DNA from human tumors, started his work toward identifying the infectious etiology of cervical cancer. Although herpes simplex virus-2 (HSV) was initially thought to be the infecting pathogen, zur Hausen was unable to detect HSV-2 DNA from any of the cervical cancer samples. Upon further review of patient reports, he noted anecdotal data supporting the malignant transformation of

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genital warts. In 1976, he published his hypothesis that the papillomavirus that causes genital warts was potentially the same agent causing cervical cancer [3]. Just a few years later, his lab identified HPV-6 from genital warts and HPV-11 from respiratory papillomas, but, to his disappointment, these HPV types could not be identified in cervical cancer biopsies. Further investigation finally led to the discovery of HPV-16 and HPV-18 DNA in cervical cancer samples and in precancerous lesions. Subsequent international studies found that almost all cervical cancers contain HPV DNA [4, 5]. Today, we know that there are over 120 HPV types, and over 40 of these types infect the genital mucosa. In 2008, just 2 years after the first HPV vaccine was approved by the FDA for the prevention of cervical cancer, zur Hausen was awarded the Nobel Prize for Medicine or Physiology for his work leading to the development of this cancer prevention vaccine.

Pre-vaccine Epidemiology

HPV infection is the most common viral anogenital infection among men and women worldwide [6]. Globally, HPV is associated with 4.5% of all cancers [7]. Each year, over 600,000 and 300,000 new cases of HPV-attributable cancers and cancer deaths, respectively, are reported, 83% of which are cervical cancer [7]. Worldwide, cervical cancer is the third leading cause of cancer and cancer deaths among all females and the second leading cause of cancer and cancer deaths among females aged 15–44 years. In 2018, alone, 569,847 women around the world were newly diagnosed with cervical cancer, and 311,365 women died from this disease.

Similarly, HPV is the most common sexually transmitted infection in the United States, with almost all adults predicted to be infected with HPV at some point in their lifetime. It is estimated that 79 million people in the country are currently infected. Of the 14 million new infections each year, half occur in young adults between the ages of 15 and 24 years. Each year, in the United States, there are over 44,000 cases of HPV-attributable cancers, 25,000 among women and 19,000 among men. Cervical cancer alone accounts for 12,000 new cases and 4000 deaths annually. HPV is known to cause almost all of the anal and cervical cancers, 70% of oropharyngeal and vaginal/vulvar cancers, and more than 60% of penile cancers. Of note, HPV now causes more oropharyngeal cancers than alcohol and smoking combined.

Transmission

Transmission of cutaneous HPV infection occurs through casual contact, particularly if it is an area with minor skin trauma. Autoinoculation is common, leading to spread of lesions. Individuals with altered cell-mediated immunity have more severe disease and dissemination of skin lesions.

Genital HPV infection is transmitted through skin-to-skin contact, most often, though not always, through sexual intercourse. New acquisition of HPV occurs most commonly after sexual debut. Vertical transmission from mother to newborn during delivery can lead to juvenile-onset recurrent respiratory papillomatosis.

Clinical Presentation

Most HPV infections are subclinical, with 90% self-resolving within 2 years. Clinical presentation is dependent on HPV type and location of infection (Table 15.1).

Table 15.1 Clinical manifestations of HPV infection

HPV clinical manifestations	
Cutaneous infection	
Plantar warts	Warts on the feet, tend to be larger than other warts, can be painful with walking
Flat warts	Typically seen on the face and extremities, flat (not papillomatosis) in appearance, painless
Filiform warts	Seen on face and neck
Epidermodysplasia verruciformis	Rare genetic disorder, increased susceptibility to HPV infection, chronic cutaneous lesions of childhood with malignant transformation during adulthood
Mucosal infection	
Low-risk HPV types	
Juvenile-onset recurrent respiratory papillomatosis	Recurring papillomas in the upper respiratory tract, particularly the larynx, most common benign, laryngeal tumor of childhood, typically results from vertical transmission of HPV during delivery, manifestations may include hoarseness or stridor, may require intra-lesion injections or repeated debulking procedures to prevent respiratory tract obstruction
Anogenital warts	"Condyloma acuminata," skin-colored warts, cauliflower-like in appearance; painless but may be associated with itching, burning, or bleeding
Low-grade squamous intraepithelial lesions	In the cervix, these lesions are referred to as cervical intraepithelial neoplasia (CIN1)
High-risk HPV types	
Low-grade squamous intraepithelial lesions	In the cervix, these lesions are referred to as cervical intraepithelial neoplasia (CIN1)
High-grade squamous intraepithelial lesions	In the cervix, these lesions are referred to as CIN2 or CIN3
Anogenital cancers	Cervical cancer is most common HPV cancer in women
Oropharyngeal cancers	Most common HPV cancer in men

Management

There is no antiviral therapy indicated for the treatment of HPV infection. Supportive management, however, varies by the type of HPV infection.

Cutaneous Warts

One-third of cutaneous HPV warts resolve within 6 months. Those that do not resolve, cause significant pain, or are socially distressing may be managed with lesion-targeted therapy. These treatments, including cryotherapy, salicylic acid, immunomodulating agents, or laser or surgical removal, are not curative and recurrence of the lesions is common.

Respiratory Papillomatosis

Although a benign process, life-threatening complications may occur as papillomas grow in the airway. Consultation with an experienced otolaryngologist is necessary as intra-lesion therapy or surgical debulking may be required to prevent airway obstruction.

Anogenital Warts

Treatment goals of anogenital warts include wart removal, symptom improvement, and reduction of psychosocial distress. Treatment should be guided by the size, number, and anatomic site of warts, patient preference, cost, and provider experience [8]. Available treatment can be either patient-applied (imiquimod, podofilox, sinecatechins) or clinician-applied (cryotherapy, surgical removal, trichloroacetic acid, bichloroacetic acid).

Abnormal Cervical Cytology

Women with abnormal cervical cytology may require colposcopy, biopsy, excision (loop electrosurgical excisional procedure [LEEP]), or ablative treatment [9].

Prevention

HPV infection and associated complications can be prevented through (1) reducing the risk of exposure, (2) HPV screening, and (3) routine immunization. New HPV acquisition typically occurs shortly after sexual debut, with increased risk of infection with increasing number of sexual partners. Behaviors that will reduce the likelihood of being exposed to HPV include abstaining from sexual activity, correct and consistent use of physical barriers (i.e., condoms) during sex, delaying onset of sexual activity, and minimizing the number of lifetime sexual partners. Cervical cancer is the only HPV-associated cancer that can be prevented through routine screening (Table 15.2). Routine immunization against HPV among adolescents aims to prevent both HPV infection and associated complications, including cancer development.

HPV Vaccine

Vaccine Characteristics

HPV vaccines consist of L1 proteins, expressed by using recombinant DNA technology, self-assembled into noninfectious, non-oncogenic, virus-like particles that are highly immunogenic. There are three HPV vaccines used around the world (Table 15.3). The HPV types included in the nine-valent vaccine account for over 90% of all HPV-associated cancers worldwide. While the bivalent and quadrivalent HPV vaccines are still licensed for use, nine-valent HPV vaccine is the only one currently available in the United States.

Table 15.2 Cervical cancer screening recommendations as per the 2018 US Preventive Services Task Force guidline [10]

Healthy women with a cervix, no signs or symptoms of cervical cancer, and no history of high-grade precancerous cervical lesions	Cervical cancer screening recommendation
<21 years of age	No screening
21–29 years of age	Cervical cytology every 3 years
30–65 years of age	Cervical cytology every 3 years or High-risk HPV testing every 5 years or Combination of cervical cytology and high-risk HPV testing every 5 years
>65 years of age and appropriate prior screening	No screening

Table 15.3 HPV vaccines used worldwide

HPV vaccine	Manufacturer	HPV types included	FDA approval year
Bivalent	GlaxoSmithKline	16, 18	2009
Quadrivalent	Merck	6, 11, 16, 18	2006
Nine-valent	Merck	6, 11, 16, 18, 31, 33, 45, 52, 58	2014

Table 15.4 HPV vaccine recommendations

Cohort	HPV vaccine recommendations
Females and males of ages 9–12 years[a]	Routine vaccination with two-dose vaccine series[b]
Females and males of ages 13–14 years[a]	Catch-up vaccination with two-dose vaccine series[b]
Females and males of ages 15–26 years	Catch-up vaccination with a three-dose vaccine series[c]
Females and males of ages 27–45 years	Shared clinical decision-making regarding vaccination

[a]Healthy individuals without immunocompromising conditions
[b]Dose 2 given 6–12 months after dose 1 (minimum interval of 5 months)
[c]Dose 2 given 1–2 months after dose 1 (minimum interval of 4 weeks), dose 3 given 6 months after dose 1 (minimum interval of 5 months after dose 1 and 12 weeks after dose 2)

Vaccine Storage, Preparation, and Administration

HPV vaccines should be stored at refrigerator temperatures (2–8 °C). Do not freeze vaccine. Administer as soon as possible after removal from refrigeration, as a 0.5 mL dose given intramuscularly, preferably in the deltoid muscle.

Vaccine Recommendations

HPV vaccines are not therapeutic and should not be used to treat infection. Vaccination is most effective in disease prevention when administered before exposure to infection. HPV vaccination may include either a two-dose or a three-dose series, depending on age at vaccine series initiation. The Advisory Committee on Immunization Practices recommends that routine administration of the HPV vaccine series begins at 11–12 years of age (Table 15.4). Vaccinating at this medical visit allows for bundling of the HPV vaccine with the other adolescent vaccines. Further support for immunizing at the 11–12-year visit is the robust immune response to vaccination allowing a two-dose series. If the HPV vaccine series is not started until on or after the 15th birthday, a three-dose series is required to achieve the same response.

HPV vaccine doses administered earlier than the required minimum interval should be readministered after the appropriate time interval passes. If the HPV vaccine series is interrupted, it does not need to be restarted. The nine-valent vaccine can be used to complete a series that was started with either the quadrivalent or bivalent vaccine. Individuals with a prior exposure to or history of HPV infection should still be vaccinated to protect against other HPV types.

Contraindications to HPV Vaccine

Mild illness is not a contraindication to HPV vaccine receipt. If moderate or severe illness is present, vaccination should be deferred until after clinical improvement. Contraindications to the HPV vaccine include a severe allergic reaction to a vaccine component or prior dose of HPV vaccine. An anaphylactic latex allergy is a contraindication for bivalent HPV vaccination, as the prefilled syringe is capped with natural rubber latex. Severe yeast allergy is a contraindication to the nine-valent HPV vaccine, which is made in yeast. While it is not recommended that HPV vaccine be administered during pregnancy, testing for pregnancy before vaccination is not needed. If a woman is found to be pregnant after starting the HPV vaccine series, completion of the vaccine series should be delayed until after pregnancy.

Adverse Events

The most common adverse effects of the HPV vaccine are local reactions at the site of injection (pain, redness, swelling) that occurs with increasing frequency after subsequent doses. As with other vaccines administered to adolescents, syncope following vaccination has been reported. It is recommended that individuals receiving HPV vaccine be observed for 15 minutes after vaccine administration. Over 90 million doses of HPV vaccine have been administered in the United States, with no serious adverse events reported.

Immunogenicity

More than 97% of individuals develop antibodies after receiving the three-dose HPV vaccine series. Two doses of HPV vaccine administered to 9- to 14-year-olds result in similar levels of protection as the three-dose series administered to 16- to 26-year-olds. Follow-up studies a decade after initial vaccination shows persistence of protection without waning.

Impact of Vaccine on Disease Burden

In 2005, 500,000 and 260,000 cervical cancer cases and deaths, respectively, were reported worldwide. In some regions of the world, the incidence of cervical cancer was as high as 50 per 100,000 females. While screening and management of abnormal cervical cells are effective in preventing 80% of cervical cancers, implementation of screening programs in low- and middle-income countries, where rates of

cervical cancer and deaths are the highest, has proven to be difficult. Since 2009, the World Health Organization has recommended that countries introduce the HPV vaccination into their national immunization programs, with a focus on immunizing females between the ages of 9 and 13 years [6, 11, 12]. By 2018, 79 (63%) countries had implemented a national HPV vaccination program, and 44 (22%) announced plans for or piloted the use of the vaccine in their country (Fig. 15.1).

Since the introduction of HPV vaccine, more than 15 countries have shown a reduction in vaccine-type HPV detection in vaccinated females, demonstrating vaccine effectiveness, and in unvaccinated females and males, suggesting herd immunity [13]. Countries with vaccination rates of at least 50% saw reduction in HPV-16 and HPV-18 infections by 68% and a decline in anogenital warts by 61% [14]. A review of the impact of HPV vaccination in real-world settings over a decade found maximal reductions of approximately 90% for quadrivalent-vaccine-type HPV infection [15].

In the United States, the quadrivalent HPV vaccine was first approved in 2006 for females aged 9 through 26 years of age. In 2009, this recommendation was expanded to include males, 9 through 21 years of age (and high-risk males through 26 years). In 2014, the nine-valent HPV vaccine was approved and essentially now has replaced the quadrivalent HPV vaccine in this country. In 2019, the catch-up vaccine recommendation was again expanded to include all individuals through 26 years of age, regardless of gender. Most recently, in 2020, the FDA added prevention of oropharyngeal cancers to the indication for use of HPV vaccine. Still, 12 years following initial recommendation, national vaccine series completion rates

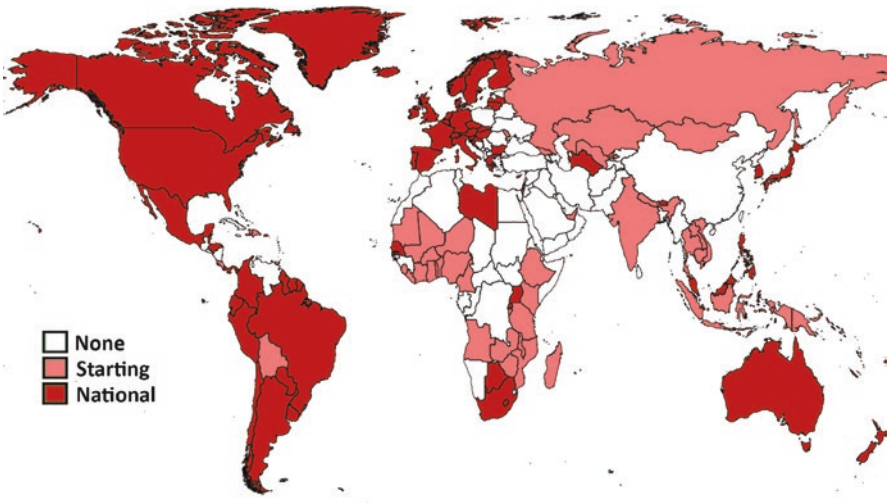

Fig. 15.1 HPV vaccine use among countries around the world, stratified by countries with no HPV vaccination program, countries that have started to implement an HPV vaccine program (announced plans, piloted, or have a partial program), and countries that have implemented a national HPV vaccination program

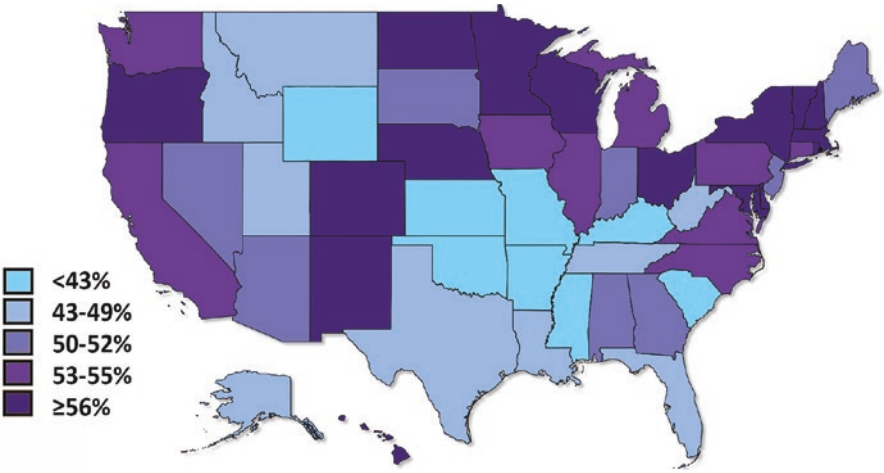

Fig. 15.2 US HPV vaccination rates by state, 2018

among 13- to 17-year-olds remain just over 50%, leaving half of US adolescents susceptible to HPV infection and HPV-associated cancer development (Fig. 15.2).

Over the course of 10 years following HPV vaccine introduction, there has been a decline in the detection of quadrivalent vaccine HPV type by 80% among vaccinated females and 40% among unvaccinated females [16, 17]. Population-based studies found significant reductions in all grades of CIN, particularly in women who were vaccinated under 20 years of age [18, 19]. In addition, Chaturvedi found that the prevalence of oral HPV-6/HPV-11/HPV-16/HPV-18 was significantly reduced among vaccinated individuals compared to the unvaccinated, with an estimated 88% reduction in prevalence of adjusting for demographics [20].

The HPV vaccine is safe and effective in the prevention of HPV infection and related complications, including oropharyngeal and genitourinary cancers. Low vaccine uptake is related to provider and parental vaccine hesitancy. Interventions geared toward emphasizing the HPV vaccine as cancer prevention are needed to improve adolescent vaccine uptake and prevent them from future development of HPV-associated cancers.

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Chapter 16
Influenza

Joseph Domachowske

Influenza Infection

Etiology

Human influenza infections are caused by influenza A and influenza B viruses. These and the two other species of influenza virus, C and D, are enveloped, segmented RNA viruses belonging to the family *Orthomyxoviridae*. Influenza A viruses are further identified according to characteristics of their two surface glycoproteins, hemagglutinin (H) and neuraminidase (N). Of the 18 different known H antigen types (H1 to H18) and the 11 different known N antigen types (N1 to N11), only a small number of HN combination viruses are capable of infecting humans. Others have evolved to infect many different avian and mammalian animal species with a fairly high level of host specificity, although some influenza viruses can infect more than one animal species. Currently, the two types of influenza A viruses that cause seasonal epidemics in humans are influenza A H1N1 and influenza H3N2. Other virus types that have been identified as causing human infection include the once widely circulating influenza A H2N2 and several others including H5N1, H7N7, and H7N9, among others that cause widespread infection in birds. To date, when these "bird flu" viruses crossed species to infected humans, they have caused either localized severe outbreaks of human infection (H5N1) or small outbreaks and clusters of infection without sustained transmission from human to human. Influenza A viruses capable of infecting both human and other animal species have the potential to develop abrupt and dramatic shifts in their genetics when infecting the nonhuman species. Antigenically shifted progeny virus generated in this manner has the potential to cause global pandemics. Each of the 11 RNA segments of the influenza virus

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genome encodes one or two viral proteins. If two different influenza A viruses infect a pig, for example, exchanges between large and entire RNA segments can occur during virus replication. Progeny virus that undergoes major antigenic changes in surface proteins causes global pandemics because the emerging virus is novel and the world's entire human population is susceptible. Only influenza A viruses are capable of antigenic shift.

Strains of influenza B viruses are further characterized as belonging to either the Victoria or the Yamagata lineage. Unlike influenza A viruses, influenza B almost exclusively infect humans (ferrets being the only known exception). This high level of host specificity does not allow the virus opportunity to undergo antigenic shifting. Influenza B viruses cause annual seasonal epidemics of widespread disease that have the potential to cause substantial morbidity and mortality, but influenza B viruses do not cause global pandemics.

In addition to influenza A's potential to undergo antigenic shifting, both influenza A and influenza B viruses are very prone to drifting mutations. These constant, gradual drifts in genetic composition occur because influenza viruses replicate under the direction of a virus-encoded RNA-dependent RNA polymerase, an enzyme that lacks the proofreading activity inherent to DNA polymerases. On average, DNA and RNA replication polymerases introduce 1 error for every 10,000 bases replicated. During replication of the ~13,500 base genome of influenza virus, any random errors made by the RNA-dependent RNA polymerase go uncorrected. Incorporated changes may be inconsequential or lethal to individual progeny virus but also cause slow, gradual, and continuous antigenic drifting in the antigenic characteristics of the virus. When the antigenic drift is sufficient to overcome a population's immunologic protection from prior infections or vaccines, the drifted virus causes new, sometimes severe, outbreaks of disease. To combat this biologic reality, influenza vaccines need to be reformulated every year, in an effort to best target the emerging infecting virus strains.

As noted, strains of influenza A viruses are further described based on specific characteristics of two surface glycoproteins, hemagglutinin (H) and neuraminidase (N). Strains of influenza A H1N1 and H3N2 viruses have co-circulated worldwide for several decades, although during most seasons, one of the two tends to predominate. Two major groups of influenza B viruses, known as the influenza B Victoria and Yamagata lineage strains, also co-circulate year to year. While uncommon, it is theoretically possible for an individual to be exposed to and infected with each of the four strains during the same season.

Epidemiology

Influenza reaches peak prevalence in winter, and because the Northern and Southern Hemispheres have winter at different times of the year, there are actually two different influenza seasons each year. Influenza seasons across tropical and subtropical areas are less predictable. The World Health Organization, in collaboration with the

National Influenza Centers, makes specific vaccine recommendations for two different vaccine formulations every year, one for the Northern Hemisphere and one for the Southern Hemisphere. The WHO Global Influenza Program recommends an evidence-based practical approach to group countries that share similar patterns of influenza seasonality and virus antigenic characteristics into influenza vaccination zones to address the country's needs. This has proven especially important when making decisions regarding the optimal influenza vaccine formulation to use in tropical nations.

Transmission

Influenza is spread from person to person via respiratory droplets. Children are more contagious than adults because they shed higher amounts of virus or longer periods of time. Young children are also less likely to practice good cough hygiene, such as coughing into their sleeves and washing their hands frequently. Respiratory droplets can spread influenza three ways. Direct transmission occurs when an infected person coughs and droplets are transferred directly into the eyes, nose, or mouth of a close contact. Airborne transmission occurs when a susceptible individual inhales the aerosols that were produced by an infected person by coughing or sneezing. Finally, hand-to-mouth, nose, or eye transmission occurs when an individual touches a contaminated surface and then touches their own mucous membranes. Influenza virus can persist on hard, nonporous surfaces such as metal or plastic countertops and door handles for 1–2 days but for only about 5 minutes on skin.

Clinical Presentation

The clinical manifestations of influenza infection vary and are influenced by both host- and virus-specific factors. Host factors that increase the risk of severe disease include extremes of age, most chronic health conditions, and pregnancy. Typical symptoms of uncomplicated influenza include the abrupt onset of fever, chills, and generalized body aches. Symptoms can be quite debilitating leaving individuals confined to bed for several days. Headache and sore throat are common. Untreated, the illness lasts for 7–10 days. A regular complication of influenza infection is the development of bacterial pneumonia. Typically, patients have already noted general improvement but then develop recurrence of fever and worsening cough. The bacterial pneumonia is often lobar and may be associated with sepsis, bacteremia, and/or the development of a parapneumonic effusion. A substantial portion of influenza-associated deaths are caused by bacterial superinfections, especially in the elderly population. The most common etiologic agents identified are *Streptococcus pneumoniae* and *Staphylococcus aureus.*

Management

The management of influenza infection is largely supportive and symptom-directed care. Maintaining adequate hydration is important. Over-the-counter pain relievers and fever reducers can offer some relief from the fevers, headache, and myalgias. Antibiotics should be reserved for the treatment of proven or suspected bacterial superinfections. Several antiviral medications with potent activity against influenza viruses are available and may be effective in shortening the illness duration if started within the first 48 hrs of the illness. Antiviral therapy should be considered in high-risk individuals such as young children, pregnant women, individuals 65 years and older, those with immunocompromising conditions, and anyone ill enough to require hospitalization.

Influenza Vaccine

Influenza vaccines are currently produced in trivalent and quadrivalent formulations. The immunogens used in quadrivalent influenza vaccines include two subtype strains of influenza A (A[H1N1] and A[H3N2]) and two lineage strains of influenza B (B[Victoria] and B[Yamagata]) viruses. Trivalent influenza vaccines include the same two subtype strains of influenza A (A[H1N1] and A[H3N2]) and one of the same two lineage strains of influenza B (B[Victoria] and B[Yamagata]) viruses. Each year, influenza vaccine formulations undergo strain modifications based on recommendations from the World Health Organization in collaboration with the US Centers for Disease Control and Prevention and other stakeholders. Until quite recently, all available inactivated influenza vaccines were produced by culturing each of the selected vaccine strains in embryonated chicken eggs. Lots of each vaccine virus were harvested, purified, and chemically inactivated and then combined to create the trivalent and quadrivalent inactivated vaccine products. By convention, inactivated influenza vaccine formulations that are produced in eggs are abbreviated as IIV. Adding the number 3 or 4 as a suffix identifies the vaccine product as either trivalent or quadrivalent. An expanding variety of available influenza vaccine formulations have become available over the last several years. Each of these new formulations was developed to fill certain unmet needs. To easily and quickly distinguish each of the newer vaccine formulations from the standard egg-derived IIVs, extended abbreviations that include an identifying prefix are used. HD-IIV4 stands for high-dose quadrivalent egg-based inactivated vaccine. Each dose of vaccine has four times more of each influenza antigen when compared to standard IIV4. HD-IIV3 and HD-IIV4 were developed in an effort to improve vaccine effectiveness among the elderly population. Clinical trials showed that HD-IIV3 was more reactogenic than IIV3 in adults 65 years and older, but it was also more immunogenic. Follow-up trials ultimately demonstrated HD-IIV to be more effective than IIV3 in preventing influenza and influenza-associated hospitalizations in elderly

adults. An adjuvanted IIV3, abbreviated aIIV3, was developed and studied for the same reason. Not surprisingly, aIIV3 was more reactogenic than IIV3 when studied in adults 65 years and older, but aIIV3 was also more immunogenic. Efforts to develop influenza vaccines that do not rely on embryonated chicken eggs have also met with success. Cell culture-based quadrivalent inactivated influenza vaccine, abbreviated ccIIV4, is manufactured by culturing the desired vaccine strains in Madin-Darby canine kidney cells, and a fully recombinant quadrivalent influenza vaccine, abbreviated RIV4, is produced in insect cells. Characteristics of each of the influenza vaccine formulations currently available in the United States are summarized in Table 16.1.

Inactivated Influenza Vaccines

Egg-based and cell culture-based technologies are used to produce inactivated influenza vaccines. The process used to generate egg-based influenza vaccines starts with inoculating embryonated chicken eggs with each of the selected strains of influenza virus. When ready for harvest, allantoic fluid containing high concentrations of the virus is collected. Next, the virus is inactivated by treatment with formaldehyde, then concentrated, and purified using gradient centrifugation. Virus is

Table 16.1 Characteristics of influenza vaccine formulations available in the United States

Brand name	Vaccine type	Manufacturer	Available formulations	Age indication	HA antigen per dose (mcg)[a]
Afluria	IIV4	Seqirus	0.25 mL dose	6–36 mos	7.5
			0.5 mL dose	≥ 3 years	15
			5 mL vial[b]	≥ 6 mos	7.5 or 15
Fluad	aIIV3	Seqirus	0.5 mL dose	≥ 65 years	15
Fluarix	IIV4	GlaxoSmithKline	0.5 mL dose	≥ 6 mos	15
Flublok	RIV4	Sanofi Pasteur	0.5 mL dose	≥ 18 years	45
Flucelvax	ccIIV4	Seqirus	0.5 mL dose	≥ 4 years	15
			5 mL vial[b]	≥ 4 years	15
FluLaval	IIV4	GlaxoSmithKline	0.5 mL dose	≥ 6 mos	15
			5 mL vial[b]	≥ 6 mos	15
FluMist	LAIV4	AstraZeneca	0.2 mL sprayer	2–49 years	NA[c]
Fluzone	IIV4	Sanofi Pasteur	0.25 mL dose	6–36 mos	7.5
			0.5 mL dose	≥ 6 mos	15
			0.5 mL vial	≥ 6 mos	15
			5 mL vial[b]	≥ 6 mos	15
Fluzone-HD	HD-IIV4	Sanofi Pasteur	0.5 mL dose	≥ 65 years	60

[a]Microgram amount of hemagglutinin per influenza vaccine strain included in each dose
[b]Thimerosal is used as a preservative in all multidose vial formulations listed
[c]Standardized to contain $10^{6.5–7.5}$ fluorescent focus units of each attenuated influenza virus strain per dose

then disrupted with a nonionic surfactant to produce a split virus preparation. The split virus is further purified and then resuspended in phosphate-buffered saline. Split virus preparations of appropriate strains are then combined to produce the final trivalent (IIV3) or quadrivalent (IIV4) vaccine products. Standard inactivated influenza vaccines contain 15 mcg of hemagglutinin from each of the virus strains included as immunogens. High-dose inactivated influenza vaccine (HD-IIV4) contains 60 mcg of hemagglutinin from each strain.

Cell culture technology has emerged as an alternative to egg-based technology for the manufacturing of inactivated influenza vaccines (cc-IIV4). The production of cell culture-based influenza vaccine starts with inoculating suspension cultures of Madin-Darby canine kidney cells with each of the selected strains of influenza virus. At harvest, cell culture supernatant containing high concentrations of the virus is collected. Next, the virus is inactivated with ß-propiolactone, disrupted using a detergent, and then purified using chemical and mechanical techniques. As with egg-based production technology, each strain is produced and purified separately before being pooled to formulate the final trivalent or quadrivalent influenza vaccine product. Like other standard inactivated influenza vaccines, cell culture-produced influenza vaccines contain 15 mcg of hemagglutinin from each of the included virus strains.

Live Attenuated Influenza Vaccine

The immunogens included in the live attenuated influenza vaccine are adapted to replicate well at 25 °C while being restricted in replication at or above human core body temperature. Each year, four reassortant influenza strains are developed for use based on vaccine strain selection for the upcoming seasonal quadrivalent influenza vaccine (LAIV4). Reassortant strain production starts with a master donor influenza virus that has already been engineered and characterized as cold adapted, temperature sensitive, and attenuated. Gene segments that encode for the hemagglutinin and neuraminidase glycoproteins are derived from the selected, antigenically relevant pool of influenza viruses. Accordingly, each of the four viruses used as immunogens in the quadrivalent live attenuated influenza vaccine maintains the replication characteristics and phenotypic properties of the master donor virus while also expressing the hemagglutinin and neuraminidase of the wild-type viruses related to strains expected to circulate during the coming influenza season. Embryonated chicken eggs are inoculated with each of the four reassortant influenza vaccine strains and then incubated to allow vaccine virus amplification. To harvest, the allantoic fluid is collected and purified using filtration. Next, the virus is concentrated using ultracentrifugation and then diluted to a working concentration with a stabilizing phosphate buffer to obtain the final sucrose and potassium phosphate concentrations. The viral harvests of each of the four reassortants are then filter sterilized. Each of the monovalent bulk preparations is tested and verified to retain cold adaptation, temperature sensitivity, and attenuating phenotypes before

being combined at the desired potency. The bulk lot of combined quadrivalent vaccines is then used to fill individual sprayers for nasal administration.

Recombinant Influenza Vaccine

The coding sequences for the hemagglutinin gene products of interest are cloned into baculovirus vectors. Each of the recombinant baculoviruses is then used to transfect Sf9 insect cells growing in a defined serum-free culture medium containing lipids, amino acids, vitamins, and mineral salts. When cultures are ready to harvest, the baculovirus-encoded hemagglutinin proteins are extracted from the insect cells with a surfactant and then further purified using column chromatography. Each of the recombinant hemagglutinins is produced and purified separately before being pooled to formulate the final trivalent (RIV3) or quadrivalent influenza vaccine product (RIV4). Recombinant influenza vaccine is formulated to contain 45 mcg of each hemagglutinin.

Influenza Vaccine Strain Selection

Annual selection of influenza strains to include in the upcoming seasonal influenza vaccine is made early in the calendar year to allow manufactures the necessary time to produce and validate the vaccine strain modifications made and to deliver vaccine for public use by late summer or early fall. Vaccine strains are chosen, in part, based on epidemiologic surveillance of circulating influenza viruses at the end of the previous season and ongoing virus activity in the opposing hemisphere. This process occurs every year. Since 1973, WHO has provided formal recommendations for the composition of influenza vaccines based on the information provided by the WHO Global Influenza Surveillance and Response System. High-yield candidate vaccine viruses are developed, and their antigenic and genetic properties characterized before being released. Reference reagents for each strain are developed in parallel. Vaccine strains and the necessary reference reagents are then made available to manufacturers worldwide upon request.

Vaccine Recommendations

Vaccination is the principal measure for preventing influenza. In the United States, the Advisory Committee on Immunization Practices recommends annual universal influenza vaccination for everyone 6 months of age and older who does not have a contraindication to the vaccine. Globally, influenza vaccine is recommended by the World Health Organization (WHO) for high-risk groups, including pregnant women,

children aged less than 5 years, the elderly, health-care workers, and people who have chronic illnesses such as HIV/AIDS, asthma, diabetes, heart disease, and immunocompromising conditions.

Vaccine Contraindications

Contraindications to receiving influenza vaccine are specific to each of the vaccine types.
IIV3 and IIV4 are contraindicated in those with a history of severe allergic reaction to any component of the vaccine or to a previous dose of any influenza vaccine. RIV4 is contraindicated in those with a history of severe allergic reaction to any component of the vaccine. LAIV4 is contraindicated in those with a history of severe allergic reaction to any component of the vaccine or to a previous dose of any influenza vaccine, children and adolescents being treated with aspirin- or salicylate-containing medications, children between 2 and 4 years of age who are diagnosed with asthma, and individuals who are immunocompromised. LAIV is also contraindicated in close contacts and caregivers of severely immunosuppressed persons who require a protected environment, such as bone marrow transplant recipients who are still hospitalized. As with other live attenuated vaccines, LAIV is contraindicated for use during pregnancy. Since replication of LAIV is required to induce the protective response of the vaccine, the vaccine is also contraindicated for those treated with influenza antiviral medications within the past 48 hours.

Warnings and Precautions

All influenza vaccines carry a warning for use during moderate or severe acute illness with or without fever. Similarly, a history of Guillain-Barré syndrome within 6 weeks after receipt of any prior influenza vaccine is a precaution for administering future doses.
Warnings and precautions that are specific for LAIV include asthma in persons aged ≥5 years and underlying medical conditions that might predispose to complications after wild-type influenza infection.

Side Effects and Adverse Events

Tables 16.2 and 16.3 list the frequency of each of the common adverse events according to each of the specific vaccine formulations. In general, the types and severity of adverse reactions are similar from one formulation to the next. Two notable exceptions include the higher reactogenicity profiles for aIIVs and HD-IIVs

Table 16.2 Adverse events reported by adults following influenza vaccination

	IIV4[a]	HDIIV4	aIIV4	RIV4	ccIIV4	LAIV4
Injection site reactions						
Pain	47%	41%	25%	37%	30%	NA
Redness	1%	6.2%	1.2%	4%	13%	NA
Swelling	0.5%	3.7%	1.3%	5%	6%	NA
Systemic reactions						
Fever	0	0.4%	3.6%	2%	1%	NR
Myalgia	24%	23%	15%	13%	12%	10%
Malaise or fatigue	11%	13%	13%	17%	12%	18%
Headache	16%	14%	13.2%	20%	15%	28%
Mucous membrane reactions						
Nasal congestion	NR	NR	NR	NR	NR	44%
Sore throat	NR	NR	NR	NR	NR	19%

[a]Similar for all formulations. Data presented are for Fluzone
NA not applicable, *NR* not reported

Table 16.3 Adverse events reported by children following influenza vaccination

	IIV4[a]	ccIIV4	LAIV4
Injection site reactions			
Pain	67%	29%	NA
Redness	34%	11%	NA
Swelling	25%	4%	NA
Systemic reactions			
Fever	7%	2%	16%
Myalgia	39%	9%	6%
Malaise	32%	7%	14%
Headache	23%	9%	9%
Mucous membrane reactions			
Nasal congestion	NR	NR	58%
Sore throat	NR	NR	11

[a]Similar for all formulations. Data presented are for Fluzone
NA not applicable, *NR* not reported

compared with standard IIVs and the LAIV-specific adverse events of nasal congestion and sore throat.

Vaccine Efficacy

Influenza remains the most commonly reported vaccine preventable illness. It is tempting to blame that observation on suboptimal vaccination rates since higher overall rates do result in less disease, but the problem is far more complex. The

efficacy of available influenza vaccines, even during particularly "good" years, doesn't come close to the efficacy rates seen with other immunizations. Available data indicate that the term "vaccine failure" might better be called "partial vaccine failure" when it comes to influenza vaccines because at the population level, immunized individuals have milder illness compared with those who were not unimmunized. Years when vaccine strains are a clear mismatch for the influenza viruses that emerge, the effectiveness of the vaccine against those strains is expected to be quite low. Overall, from year to year, influenza vaccine effectiveness is typically about 40%. Age clearly impacts vaccine effectiveness. Young children typically mount more robust protective responses than adults, while elderly adults have consistently shown reduced rates of vaccine effectiveness consistent with progressive immune senescence with each advancing decade.

Given overall influenza epidemiology, any measurable vaccine effectiveness has the potential to make a substantial impact. For example, consider an influenza season where overall vaccine effectiveness is only 20%. Despite the much lower than optimal impact, 20% effectiveness at current mean overall vaccination rates is estimated to prevent between 11,000 and 144,000 influenza-associated hospitalizations and between 300 and 4000 deaths. Obviously, more effective vaccines would be associated with a higher public health benefit, but we use the vaccines we have because they do make an impact. Efforts continue to identify strategies to improve influenza vaccine effectiveness, but even small improvements in either effectiveness or overall immunization rates can translate to fairly impressive changes in the total number of individuals affected.

References and Suggested Reading

Vaccine Information Sheets (VISs)

- VIS for IIV and RIV4: https://www.cdc.gov/vaccines/hcp/vis/vis-statements/flu.pdf
- VIS for LAIV4: https://www.cdc.gov/vaccines/hcp/vis/vis-statements/flulive.pdf

Influenza Vaccine Package Inserts

- Trivalent vaccines: https://www.fda.gov/vaccines-blood-biologics/approved-products/influenza-virus-vaccine-trivalent-types-and-b
- Quadrivalent vaccines: https://www.fda.gov/vaccinesblood-biologics/approved-products/influenza-virus-vaccine-quadrivalent-types-and-types-b

CDC Influenza Antiviral Guidance

- Influenza Antiviral Medications: Summary for Clinicians: https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

American Academy of Pediatrics (AAP) Guidance

- AAP Recommendations for Prevention and Control of Influenza in Children (Red Book Online): https://redbook.solutions.aap.org/ss/influenza-resources.aspx

Infectious Diseases Society of America (IDSA) Guidance

- 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host: https://academic.oup.com/cid/article/58/3/e44/336537

American College of Obstetricians and Gynecologists (ACOG)

- Influenza Vaccination During Pregnancy, ACOG Committee Opinion No. 732: https://www.acog.org/Clinical-GuidanceandPublications/CommitteeOpinions/Committee-on-Obstetric-Practice/Influenza-Vaccination-During-Pregnancy

Chapter 17
Japanese Encephalitis

Cynthia Bonville and Joseph Domachowske

Japanese Encephalitis Virus Infection

Etiology

Japanese encephalitis virus (JEV) is an enveloped, positive sense, single-stranded RNA member of the *Flaviviridae* family that is transmitted to humans by mosquitoes. Five genotypes, I through V, are recognized based on the nucleotide sequence of the envelope gene. Between 1870 and the mid-1990s, most infections were caused by genotype III. Infections caused by JEV genotype I have predominated during the last two decades. The recent emergence of genotype V in parts of China, Malaysia, and South Korea is an important reminder that more than one genotype can circulate simultaneously. JEV is the cause of Japanese encephalitis, a life-threatening infection of the brain parenchyma, but most human infections are mild or completely asymptomatic. Severe clinical illness is more common in children than in adults, occurring in approximately 1 of every 250 infections.

Global Epidemiology of Japanese Encephalitis Virus

The first case of Japanese encephalitis was documented in Japan in 1871. Infections caused by JEV remained largely restricted to temperate areas of Japan, Korea, Taiwan, and China during the first half of twentieth century but subsequently spread west to India, Bangladesh, Sri Lanka, and Nepal and south to most of Southeast Asia. During the 1990s, the range of infection spread deeper throughout the Western

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Pacific region to Australia and Saipan, the largest of the Northern Mariana Islands. Presently, the distribution of JEV includes 24 countries, representing approximately 60% of the world's population (Fig. 17.1). The combined number of infections from China and India alone accounts for more than 85% of all JEV infections reported. The expanding geographic distribution of JEV observed over the last 50 years is likely due to a variety of factors including population shifts and changes in ecology, agricultural practices, animal husbandry, and migratory patterns of birds.

Japanese encephalitis primarily affects children living in endemic regions where the overall mean prevalence of infection in children less than 15 years of age is estimated at 5.4 per 100,000 population. Regionally, in parts of China and North Korea, disease prevalence has been reported as high as 12.6 per 100,000 population. During the last decade, JEV is estimated to have caused approximately 65,000

Fig. 17.1 Shown is the current global distribution of Japanese encephalitis virus

symptomatic infections and more than 13,000 deaths each year. The majority of adults who reside in JEV endemic areas are naturally immune to disease from infections they had during childhood.

Disease incidence changes from year to year and varies widely both across and within endemic countries. Major outbreaks occur every 2–15 years across endemic regions, occurring primarily in rural agricultural areas, often in association with the common practice of flood irrigation used to farm rice.

The risk for JEV infection in US travelers to endemic regions of Asia is generally quite low but varies by destination, duration and season of travel, living accommodations while abroad, and the types of activities planned during the visit(s).

The overall incidence of JEV infection among travelers to Asia is less than 1 case per 1 million travelers. The incidence increases to approximately 10 cases per 100,000 people per year in those traveling to areas with active transmission who stay for prolonged periods of time. The incidence of disease further increases for those engaged in extensive outdoor activities, particularly at night. Japanese encephalitis should be suspected in any traveler returning from Asia or the Western Pacific with evidence of a central nervous system infection such as encephalitis, meningoencephalitis, aseptic meningitis, or acute flaccid paralysis.

Transmission

JEV is transmitted to humans by infected mosquitoes. The key competent vectors are *Culex* genus mosquitos, primarily *C. tritaeniorhynchus.* Female *C. tritaeniorhynchus* mosquitoes bite during the evening and nighttime, being most active just after sunset.

C. tritaeniorhynchus larva can be found in flooded rice fields, marshes, and other stagnant water sources. At least 30 other mosquito species can transmit JEV including *C. annulirostris, C. fuscocephala*, and others belonging to the genera *Culiseta, Ochlerotatus, Aedes, Anopheles*, and *Mansonia.* In temperate regions of the Northern Hemisphere, the greatest mosquito density is found between the months of June and November. Virus is maintained in an enzootic cycle between mosquitoes and principal vertebrates, amplifying in pigs and/or aquatic birds such as egrets and herons. Domestic and agricultural pigs develop high JEV titers and long-lasting viremia from natural infection.

Infected humans do not usually develop a sufficient level or duration of viremia to infect feeding mosquitoes. Humans are dead-end hosts, so infected travelers pose little or no risk of transmitting virus when they arrive at home.

Clinical Presentation

Symptomatic JEV infection most commonly presents as acute viral meningoencephalitis. The illness begins with the abrupt onset of high fever, rigors, headache, weakness, vomiting, and diarrhea. Despite the neurotropic nature of the virus,

gastrointestinal complaints are the most common presenting symptoms in children. As the illness progresses, the infected person develops mental status changes and focal neurologic deficits such as hemiplegia, tetraplegia, and/or cranial nerve palsies. Seizures are very common, especially in children. A classic presentation includes development of a parkinsonian-like syndrome with mask-like facies, tremor, cogwheel rigidity, and choreoathetoid movements. JEV can also present as a polio-like illness with acute-onset, asymmetrical flaccid paralysis.

Common complications of encephalitis include life-threatening conditions such as status epilepticus, aspiration pneumonia, increased intracranial pressure, brain hypoxia, and brainstem herniation. Between 30% and 50% of patients who survive JEV encephalitis suffer permanent neurologic, psychiatric, and/or cognitive deficits. The case-fatality rate is highest in young children where it exceeds 50%. Those who survive infection from any of the five JEV genotypes develop lifelong immunity against all genotypes.

Management

Antiviral therapy is not available. Mild to moderate infections are managed at home with supportive care to address the symptom complex. Adequate fluids to maintain hydration and over-the-counter pain relievers and fever reducers help to relieve minor symptoms. Those with signs of central nervous system involvement require hospitalization and aggressive supportive care to monitor for and treat complications.

Prevention: Japanese Encephalitis Vaccines

In areas endemic for JEV, human vaccination is prioritized over the vaccination of pigs and efforts to control mosquito populations. All 15 of the JEV vaccine formulations currently in use are based on virus genotype III. Three of these vaccines are WHO prequalified, and one is licensed in the United States. Available vaccines can be grouped into four categories (Table 17.1): inactivated whole virus derived from mouse brain, inactivated whole virus derived from cell culture, live attenuated virus, and live attenuated recombinant-chimeric vaccine. First developed in the mid-1930s, mouse brain-derived, inactivated whole virus vaccines were used exclusively until the late 1980s. In 2015, WHO recommended that mouse brain-derived vaccine be replaced by newer generation vaccines with better reactogenicity profiles, cheaper costs, and reduced dosing requirements. CD.JEVAX, the only live attenuated JEV vaccine formulation available for international use, was licensed in China in 1988. Cell culture-derived inactivated whole virus vaccine formulations (IXIARO, JESPECT, JEEV) first emerged a decade later in 1998. IXIARO was licensed in the United States and Europe in 2009, JESPECT was licensed in Australia and New

Table 17.1 Examples of available Japanese encephalitis vaccines

Vaccine type	Vaccine category	Brand name(s)	Dosing regimens for WHO prequalified formulations[a]
Inactivated whole virus	Mouse brain derived	JE-VAX	Highly reactogenic, no longer recommended
	Cell culture derived	JEEV[a] JESPECT IXIARO[b]	Two-dose series 28 days apart starting at 12 months of age
Live attenuated	Live attenuated strain SA14-14-2	CD.JEVAX[a]	Single dose at ≥8 months of age
	Recombinant-chimeric	IMOJEV[a] JE-CV ChimeriVax-JE	Single dose at ≥9 months of age Booster 1–2 years later

[a]WHO prequalified vaccine formulation
[b]See text under section "Vaccines Available in the United States"

Zealand in 2009, and JEEV was licensed in India in 2012. Live attenuated recombinant/chimeric vaccines (IMOJEV, JE-CV, ChimeriVax-JE) were first licensed in Australia in 2010.

The WHO recommends JE immunization in regions where humans live near environments that support the enzootic cycle of JEV transmission. Vaccine recommendations include one-time catch-up campaigns in target populations as defined by the local disease epidemiology, most typically in children under 15 years of age, followed by incorporation of the vaccine into the routine childhood immunization schedule.

Vaccines Available in the United States

The Vero cell culture-derived, inactivated whole virus product, IXIARO, is the only JEV vaccine formulation currently approved and available for use in the United States. IXIARO is manufactured by Valneva Scotland, Ltd. It was first licensed in the United States in 2009 for use in individuals 17 years and older based on immunogenicity trials. Licensing approval was extended to 2 months of age in 2013.

Immunizing Antigen

Genotype III, JEV strain SA_{14}-14-2 is propagated in Vero cells. Multiple harvests are pooled, clarified, and concentrated and then further purified by sucrose density gradient centrifugation following treatment with protamine sulfate. Purified virus is inactivated with formaldehyde and then adjusted to the desired concentration of 6 antigen units/0.5 mL dose. Aluminum hydroxide is added as an adjuvant.

Additives and Excipients

Vaccine additives and excipients include phosphate-buffered saline, <100 ng/mL bovine albumin, <200 pg/mL host cell DNA, <100 ng/mL host cell protein, <200 ppm sodium metabisulfite, <1 μg/mL protamine sulfate, <200 ppm formaldehyde, and 250 mcg of aluminum hydroxide. The vaccine is preservative-free and does not contain natural rubber latex.

Vaccine Recommendations

Vaccine is recommended for travelers to endemic areas after consideration of the exact travel destination, travel duration, planned activities, accommodations, and season.

Dosing recommendations for the primary vaccine series vary according to age (Table 17.2).

Travelers should plan to receive the second dose of the primary series at least 1 week before planned travel. Individuals with ongoing exposure, and those at risk for reexposure, should receive a booster dose of vaccine if a year or more has elapsed since their primary vaccine series was completed. In addition to travelers to endemic regions, JEV vaccine is recommended for laboratory workers with a high risk of exposure to JEV.

Vaccine Contraindications

Contraindications to receiving JEV vaccine include any previous life-threatening allergic reactions from a previous dose or a known severe allergy to any vaccine component, especially protamine sulfate, which is known to cause hypersensitivity reactions in some people. Moderately or severely ill individuals should postpone immunization until after they recover.

Table 17.2 Dosing recommendations for travelers receiving IXIARO vaccine

Age	Dose	Route	Dosing schedule	Booster for ongoing or recurring risk
2 months to 2 years	0.25 mL	IM	Day 0, day 28	1 year or more after completing the primary series
3–17 years	0.5 mL	IM	Day 0, day 28	
18–65 years	0.5 mL	IM	Day 0, day 7–28	
>65 years	0.5 mL	IM	Day 0, day 28	

Warnings and Precautions

Warnings and precautions for JEV vaccine include use during pregnancy where the risk of infection must outweigh the risk of immunization. Use in immunocompromised patients may result in a diminished immunological response to vaccine. The safety and efficacy have not been established in infants less than 2 months of age. Seroprotection rates following the primary series are significantly lower in adults 65 years and older compared to all other age groups.

Common Side Effects

During a clinical trial performed in the Philippines, the most common adverse events seen in infants aged 2 to 12 months were fever (>20%), injection site redness (>15%), irritability (>15%), and diarrhea (>10%). Children between 1 and 3 years of age had similar rates of fever (13–20%) but lower rates of injection site redness (3–6%). Other adverse events included diarrhea (5–7%), influenza-like symptoms (4–8%), irritability (3–8%), loss of appetite (3–6%), vomiting (3–4%), rash (1–4%), excessive fatigue (1–3%), and headache (1%). Similar adverse reactions were experienced by children 3–12 years of age with lower frequency. Adolescents 12 to <18 years old experienced pain (7–15%), tenderness (5–10%), redness (1–4%), or swelling (<1%) at the injection site. Between 3% and 5% developed fever or headache. Serious adverse reactions were rare across all groups. Approximately 1% of children less than 3 years of age experienced a febrile seizure ranging from 2 days to >5 months after receiving a dose of IXIARO. No temporal clustering related to the timing of vaccination was observed.

Estimated Effectiveness or Efficacy from Clinical Vaccine Trials

Vaccine efficacy data are not available from clinical trials. IXIARO vaccine was licensed in the United States based on immunogenicity studies demonstrating development of protective neutralizing antibody. For clinical trial purposes, a 50% plaque-reduction neutralization antibody test (PRNT50) result showing a titer of ≥1:10 was used as the surrogate for protective immunity. Titers measured 28 days after completing the primary series showed 100% seroprotection in children 2 months to 17 years old and 96% seroprotection in adults. In adults ≥65 years, titers measured 42 days after completing the primary series showed 65% seroprotection.

Japanese encephalitis causes substantial morbidity and mortality across endemic regions of the world, disproportionately affecting children. Survivors of the infection are often left with serious lifelong neurologic and cognitive deficits. The infection is vaccine-preventable starting as early as 2 months of age. Vaccine should also be considered for those who plan to travel to endemic regions, particularly during the known seasonal periods of disease transmission.

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https://www.who.int/immunization/diseases/japanese_encephalitis/en/

U.S. Centers for Disease Control and Prevention

https://www.cdc.gov/japaneseencephalitis/index.html

Vaccine Information Sheet

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Chapter 18
Measles

Manika Suryadevara

Measles Infection

Etiology

Measles morbillivirus (formerly measles virus) is a single-stranded, enveloped RNA virus in the family Paramyxoviridae that is only pathogenic to humans. Infection of respiratory epithelial cells is mediated by two viral envelope glycoproteins, hemagglutinin (attachment to the target cell) and fusion protein (virus entry). Neutralizing antibodies to the hemagglutinin protein confer immunity to infection.

Pre-vaccine Epidemiology

Prior to the development of the measles vaccine in the 1960s, measles caused an estimated 30 million infections and 2.6 million deaths worldwide each year [2]. In the United States, specifically, there were 3–4 million measles cases, 48,000 hospitalizations, and 500 deaths annually [3]. The highest incidence of infection was seen in children younger than 5 years of age. By the age of 15 years, most children already had evidence of prior measles infection. Measles outbreaks were cyclical, occurring every 2–4 years, typically during the late winter and early spring in temperate climates and during the dry season (with low-level transmission throughout the year) in tropical climates. The timing of these increased infections coincided with periods of close contacts (schools) and high population density. The mortality rate from measles infection was high, particularly in settings with high rates of

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malnutrition. Improved nutritional status, supportive care, and availability antibiotic therapy for secondary bacterial infections led to an initial decline in measles mortality rate in developed countries, even prior to vaccination.

Transmission

Measles is transmitted from person to person via respiratory droplets, airborne nuclei, and direct contact. After viral replication is established in the nasopharynx, virus enters the bloodstream and spreads to the reticuloendothelial system. A second period of viremia occurs during the peak of viral replication in the lymph nodes and spleen. Individuals with measles infection are considered contagious from 4 days prior to onset of rash to 4 days after the rash appears. With an attack rate in susceptible individuals as high as 90%, measles is considered to be one of the most highly contagious infectious diseases. Ninety-five percent of the population needs to be immune to measles to stop community transmission.

Clinical Presentation

Measles infection starts as an acute respiratory illness with fever, cough, coryza, and conjunctivitis. The pathognomonic finding on physical examination is Koplik spots. These small white or bluish-white lesions appear transiently on the buccal mucosa for a day or so just before the eruption of a skin rash. Erythematous macules, discrete at first and then coalescing, appear on the head, face, and neck before spreading to the trunk and extremities. Individuals appear ill. Common associated symptoms include fatigue, loss of appetite, headache, and photophobia. Approximately 30% of those infected with measles develop complications such as otitis media, laryngotracheobronchitis, pneumonia, diarrhea, and dehydration. Measles encephalitis is uncommon, occurring in approximately 1 case per 1000. Young infants, pregnant women, and immunocompromised and malnourished individuals are at the highest risk for development of complications or death from measles infection. Vitamin A deficiency has been identified as an independent risk factor for developing life-threatening disease when infected with measles. Mortality rates during outbreaks have been reported as high as 30% among malnourished children living under conditions of extreme poverty and between 0.1% and 0.3% among previously healthy children and adults.

A rare but devastating long-term complication, known as subacute sclerosing panencephalitis (SSPE), occurs in up to 10 per million people previously infected with measles. SSPE is a rare degenerative central nervous system disease that causes progressive neurologic deterioration about a decade after the initial infection. The group at highest risk for developing SSPE is individuals who acquired measles infection prior to the age of 2 years. The incidence of SSPE has decreased dramatically since the widespread use of the measles vaccine. Live attenuated measles strains used in vaccines are not associated with the development of SSPE.

Management

There is no antiviral therapy available for the treatment of measles infection. In addition to supportive care, the World Health Organization (WHO) recommends that all children with measles be treated with supplemental vitamin A. For children living in countries where severe measles is uncommon, those who are known or suspected to be vitamin A deficient and those ill enough to require hospitalization for measles should receive supplemental vitamin A.

Prevention

The primary approach to community-wide measles prevention includes the routine, universal use of live attenuated measles vaccine as a two-dose series starting at age 1 year. If a susceptible (under- or unimmunized) individual is exposed to measles, the measles vaccine may be administered within 72 hours of exposure if there are no contraindications to vaccination. For susceptible individuals exposed to measles who cannot receive immunization, for reasons including but not limited to young age, severe immunosuppression, and pregnancy, intravenous or intramuscular immunoglobulin should be administered within 6 days of exposure to prevent infection and potential complications. In the event of an outbreak, the measles vaccine, not immunoglobulin, should be used unless contraindicated.

Live Attenuated Measles Vaccine

Vaccine Characteristics

The currently used measles-containing vaccine is a live attenuated Edmonston-Enders strain of measles virus prepared in cultures of chick embryo fibroblasts. In the United States, measles-containing vaccines are available only in combination with other viral vaccines (mumps and rubella, with or without varicella) (Table 18.1). Monovalent measles vaccine is not available for use in this country.

Vaccine Storage, Preparation, and Administration

MMR and MMRV are supplied as lyophilized powder to be stored between −50 °C and 8 °C, protected from light at all times. Improperly stored vaccine may lose potency. Sterile, preservative-free water is provided as the diluent to be stored in the refrigerator (2–8 °C) or at room temperature. Prior to reconstitution, the vial containing the lyophilized vaccine should be stored at 2–8 °C. Once reconstituted, the

Table 18.1 Measles vaccines available in the United States

	MMR[a] vaccine	MMRV[a] vaccine
Brand name (manufacturer)	MMR II (Merck)	ProQuad (Merck)
Age of administration	12 months of age and older[b]	12 months to 12 years
Vaccine ingredients		
Active ingredients	Attenuated measles, mumps, rubella viruses	Attenuated measles, mumps, rubella, varicella viruses[c]
Stabilizer	Sorbitol, sucrose, gelatin, human albumin	Sorbitol, sucrose, gelatin, human albumin
Acidity regulators	Sodium phosphate, sodium chloride	Sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, sodium bicarbonate, potassium phosphate monobasic, potassium chloride, potassium dibasic, potassium phosphate monobasic
Cell culture growth	Fetal bovine serum	Bovine calf serum
Antibiotics	Neomycin	Neomycin
Preservative	None	None
Others		Residual MRC-5 cells

[a]*MMR* measles-mumps-rubella, *MMRV* measles-mumps-rubella-varicella
[b]MMR vaccine may be given to infants 6–11 months if living in an area of epidemic or traveling to endemic region
[c]Measles, mumps, rubella components similar between MMR and MMRV, but MMRV achieves higher measles geometric mean titers than MMR; varicella component in MMRV has higher potency than monovalent varicella vaccine, but varicella geometric mean titers similar between the two vaccines

vaccine should be administered immediately. After reconstitution, MMR vaccine can be refrigerated for up to 8 hours prior to use. MMRV must be administered within 30 minutes. The 0.5 mL dose of vaccine is given by subcutaneous injection.

Vaccine Recommendations

Recommendations regarding the timing of vaccination and the number of doses needed to complete the measles immunization series are dependent on four factors: prior vaccination history, age, risks for exposure to measles from local outbreaks, occupation or planned travel, and evidence for existing immunity. The criteria used to establish the presence of existing immunity are summarized in Table 18.2. The standard recommendation for measles vaccination under most circumstances is two doses separated by 28 days or longer. Either combination vaccine may be used to prevent measles infection. However, the CDC recommends using separate MMR

Table 18.2 Evidence of immunity to measles infection

Fulfilling any one of the following bullets is evidence of immunity to measles infection
Written, dated documentation of age-appropriate measles vaccine dose(s) Healthcare providers should only document doses of vaccines they administer Self- or parent-reported doses are not valid
Laboratory evidence of immunity
Laboratory confirmation of disease
Born before 1957

and varicella vaccines for the first dose at age 1 year (unless the parents state a specific preference for MMRV) and using MMRV for the second dose. The first dose of MMRV vaccination is associated with higher risks of fever and febrile seizures for children 12–23 months of age than the first dose of MMR vaccination. However, since this difference is not seen with subsequent doses and in older age groups, the use of MMRV vaccine is recommended for the second dose to reduce the number of injections at that visit.

Measles-containing vaccines are routinely recommended for all individuals 12 months of age and older unless contraindicated. These vaccines are not administered earlier than 1 year of age because residual circulating maternal antibody will neutralize the vaccine and impair the developing antibody response. Children vaccinated between 6 and 12 months of age may be vaccinated if they are living in an area of measles epidemic or are traveling to a measles endemic country. However, vaccine doses administered prior to 12 months of age are not considered valid for completion of the two-dose recommendation. Under such circumstances, two additional doses should be administered at least 28 days apart beginning as early as 12 months of age. Table 18.3 details the current recommendations for measles vaccination.

Contraindications to Measles Vaccine

Contraindications to receiving measles vaccine are shown in Table 18.4. Precautions and other considerations regarding measles vaccination are listed separately in Table 18.5.

Adverse Events

Reactions to measles vaccine typically occur 7–10 days following vaccination in nonimmune individuals. Therefore, these effects are more likely to occur after the first rather than subsequent doses of measles-containing vaccine. A list of possible adverse events following measles vaccination can be found in Table 18.7.

Table 18.3 Recommendations for measles vaccination

Measles vaccine recommendations	
Routine pediatric immunization	Dose 1 administered at 12–15 months Dose 2 administered at 4–6 years
Un- or underimmunized school children (kindergarten through postsecondary school)	
No evidence of immunity to measles[a]	Administer two-dose vaccine series, at least 28 days apart Children may attend school after the first dose has been given
Receipt of one dose of measles vaccine after first birthday	Administer second dose of vaccine series, at least 28 days after the first
Infants 6–11 months of age Living in epidemic area Traveling to endemic area	Administer one dose of vaccine. This dose is not counted as part of the series. Complete the immunization series with two doses, starting at age 12 months
Adults	
Born during or after 1957, no evidence of immunity to measles[a]	Should receive at least one dose of vaccine
Healthcare providers, no evidence of immunity to measles[a]	Administer two-dose vaccine series, at least 28 days apart
International travelers, no evidence of immunity to measles[a]	Administer two-dose vaccine series, at least 28 days apart

[a]Evidence of immunity as defined in Table 18.2

Table 18.4 Contraindications to measles vaccination

Conditions	Notes
Anaphylaxis to neomycin or gelatin	Vaccine is contraindicated
Severe allergy to vaccine components	Patients with known egg allergy can receive vaccine as recommended
Pregnancy	Pregnancy is a contraindication to vaccine Pregnancy should be avoided for 4 weeks after receipt of vaccine Breastfeeding is not a contraindication for vaccination Household contacts of pregnant women should be immunized as recommended
Severe immunosuppression	Severe immunosuppression from primary or acquired immunodeficiency or medications is a contraindication to vaccine Specific recommendations for vaccinating HIV[a]-infected individuals are summarized in Table 18.5 For individuals treated with systemic corticosteroids at or exceeding doses of 2 mg/kg/day of prednisone (or its equivalent) for 14 days or longer, vaccine should be deferred for 1 mos after the discontinuation of steroids Household contacts of severely immunocompromised individuals should be immunized as recommended

[a]HIV human immunodeficiency virus

Table 18.5 Precautions and considerations for measles vaccination under special circumstances

Conditions	Notes
Moderate to severe acute illness	Delay vaccination until illness resolved
Personal or family history of seizures	Increased risk of febrile seizures following MMRV vaccine Consider using MMR and varicella vaccines separately
Thrombocytopenia	Increased risk of vaccine-associated thrombocytopenia
Tuberculosis	If TST[a] is indicated, it should be performed before or on the same day as measles vaccination or be delayed for 4 weeks after receiving measles vaccine. Antituberculosis treatment should be initiated in patients with active tuberculosis prior to measles vaccination
Receipt of antibody-containing blood product	Includes immunoglobulin therapy, whole and packed red blood cells Vaccination should be delayed for a duration determined by the type and quantity of the blood product received (see Table 18.6)
Human immunodeficiency virus (HIV) infection	May receive measles vaccine if: Children 1–13 years old with CD4+ count ≥15% Adolescents 14 years and older with CD4+ count <200 lymphocytes/mm^3 Children perinatally infected with HIV infection who received measles vaccine before starting treatment with combination antiretroviral therapy should be considered unvaccinated Household contacts should be immunized as recommended MMR vaccine should be used when vaccinating individuals who are infected with HIV as MMRV vaccine has not been studied in this population

[a]*TST* tuberculin skin test

Table 18.6 Recommended minimum interval between receipt of antibody-containing blood product and the administration of measles vaccine

Product and indication	Dose and route of administration	Recommended interval (months)
Blood transfusion		
Washed red blood cells (RBCs)	10 ml/kg IV	0
Adenine-saline added RBCs	10 ml/kg IV	3
Packed RBCs	10 ml/kg IV	6
Whole blood	10 ml/kg IV	6
Plasma, platelets	10 ml/kg IV	7
Infection prophylaxis		
Botulinum immune globulin (Baby BIG)	1 ml/kg IV	6
Cytomegalovirus immune globulin	Max 150 mg/kg IV	6
Hepatitis A immune globulin		
Contact; international travel <2 months	0.1 ml/kg IM	3
International travel >2 months	0.2 ml/kg IM	3
Hepatitis B immune globulin (HBIG)	0.06 ml/kg IM	3

(continued)

Table 18.6 (continued)

Product and indication	Dose and route of administration	Recommended interval (months)
Measles prophylaxis		
Standard, non-immunocompromised	0.5 ml/kg IM	6
Pregnancy, immunocompromised	400 mg/kg IV	8
Rabies immune globulin (RIG)	20 IU/kg	4
Tetanus immune globulin (TIG)	250 U	3
Varicella prophylaxis		
VariZIG	125 units/kg IM (max 625 units)	5
Immune globulin	400 mg/kg IV	8
Immunoglobulin therapy		
Replacement for immunodeficiency	400 mg/kg IV	8
Idiopathic thrombocytopenic purpura (ITP)	400 mg/kg IV	8
ITP	1000 mg/kg IV	10
Kawasaki disease	2000 mg/kg IV	11

Immunogenicity

More than 95% of 12-month-olds and 98% of 15-month-olds develop a sustained protective immune response to their first dose of measles-containing vaccine. Vaccine efficacy following a two-dose series of measles vaccine exceeds 99%.

Impact of Vaccine on Disease Burden

The widespread use of the measles vaccine, developed in the 1960s, resulted in a decline in measles infections and measles-related complications, both nation- and worldwide (Figs. 18.1 and 18.2). Yet, in 2000, measles still infected 31–40 million people around the world and was the fifth most common cause of death in children younger than 5 years of age. While measles vaccination prevented an estimated 23 million deaths globally between 2000 and 2018, the recent rise in vaccine hesitancy, the ease of international travel, and the persistence of weak immunization programs have led to an increase in measles infection in many areas of the world [2]. The number of measles cases reported globally in 2018 was 167% higher than just 2 years prior, with increases in infection seen in five of the six WHO regions [4]. This trend has continued as more than 500,000 cases of measles were reported from 180 countries in 2019, the highest number of measles cases in any year since 2006 [5].

Table 18.7 Adverse reactions following receipt of measles-containing vaccines

Adverse reaction	Notes
Allergic reaction	Hypersensitivity reactions are likely due to trace amounts of neomycin and/or gelatin in the vaccine Anaphylactic reactions are rare
Fever	14% of vaccinated children when MMR and varicella vaccines are administered at 12–23 months at same visit 20% of vaccinated children when first dose of MMRV vaccine is administered at 12–23 months Temperatures can be 39.4 °C or higher Often otherwise asymptomatic, may also have rash Not contagious
Rash	4% of vaccinated children when MMR and varicella vaccines are administered at 12–23 months at same visit 5% of vaccinated children when first dose of MMRV administered at 12–23 months Transient
Febrile seizure	3–4 per 10,000 vaccinated children when MMR and varicella vaccines are administered at 12–23 months at same visit 7–9 per 10,000 vaccinated children when first dose of MMRV administered at 12–23 months Because of this modest increase risk of febrile seizures, ACIP states a preference for separate MMR and varicella vaccines over MMRV combination vaccine for children 12–23 months of age receiving their first dose of measles-containing vaccine Higher risk with personal or family history of seizures Consider using MMR and varicella vaccines separately if there is a personal or family history of seizures
Thrombocytopenia	1 in 30,000–40,000 vaccinated individuals Typically seen 2–3 weeks after vaccination but may occur as late as 2 months after vaccination Risk of thrombocytopenia is higher with disease than vaccination Most episodes associated with few, if any, symptoms Higher risk seen with personal history of thrombocytopenia
Arthralgia	Uncommon in young children Seen in up to 25% of nonimmune adult women who are vaccinated Associated with the rubella component of vaccine

WHO African Region

In the pre-vaccine era, each year, there were over one million measles infections reported in the WHO African Region [6]. In 1965, the initiation of first major measles control program in Africa, involving 20 countries in the region, ultimately led to the country-level interruption of measles transmission in the Republic of Gambia [6]. In the 1980s, following routine administration of measles vaccinations in all African countries, there was a decline in measles cases across the region (Fig. 18.3).

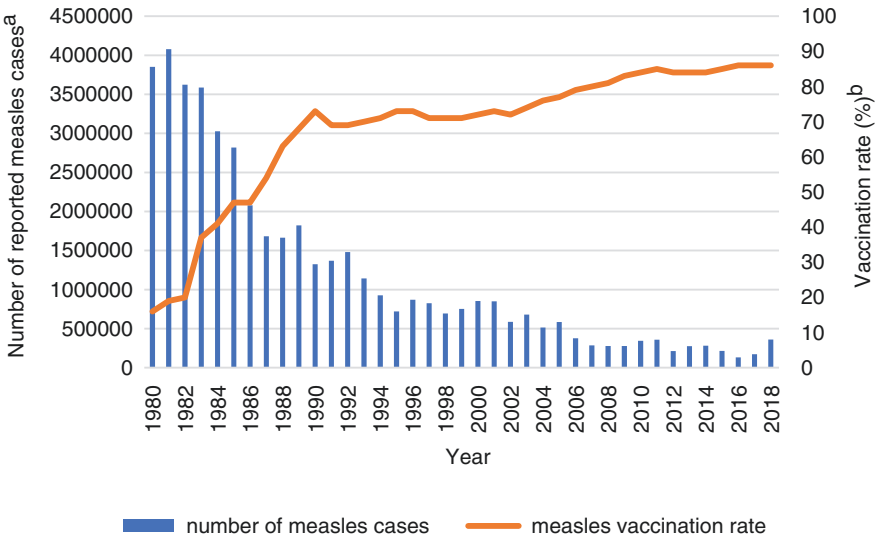

Fig. 18.1 Number of reported measles cases and first dose of measles vaccination rate by year, 1980–2018, worldwide. ([a]Adapted from the World Health Organization data. [b]Adapted from UNICEF-reported immunization data)

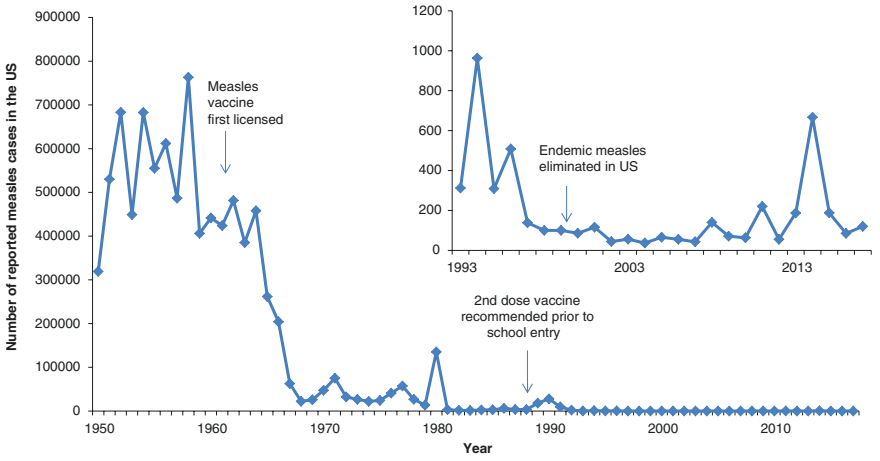

Fig. 18.2 Number of measles cases in the United States reported by year

In 2011, the WHO African Region members established a goal of measles elimination by 2020, defined as the absence of endemic measles virus transmission in a geographic area for at least 12 months. While it is estimated that measles vaccination in Africa prevented over 12 million deaths between 2000 and 2018, as of this writing, no country in the WHO African Region has yet to be verified to have eliminated measles (Fig. 18.4).

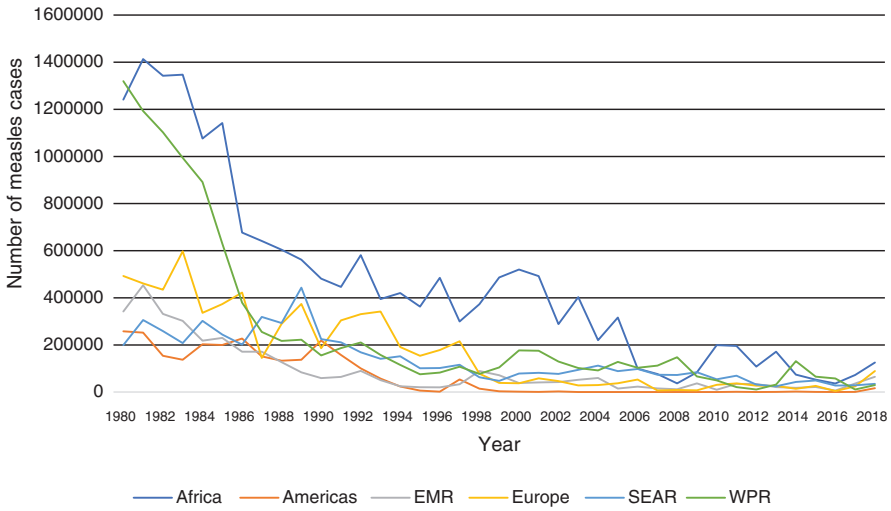

Fig. 18.3 Number of reported measles cases following introduction of measles vaccine per year, 1980–2018, by the World Health Organization region: EMR Eastern Mediterranean Region, SEAR Southeast Asian Region, WPR Western Pacific Region

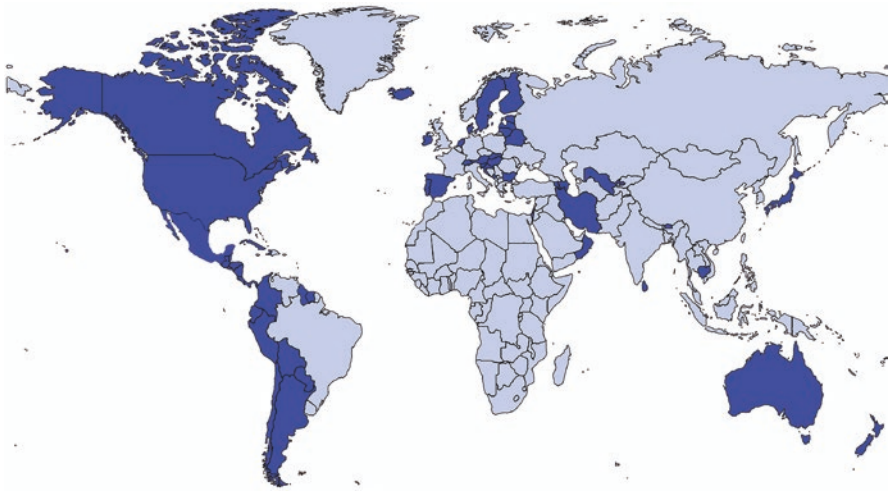

Fig. 18.4 Map depicting countries where measles has been verified to be eliminated (dark blue) as of 2019

WHO Eastern Mediterranean Region

Before implementation of the vaccination program, there were an estimated 200,000 measles cases reported in this region each year. The measles vaccine was routinely used in this region starting in the early 1980s, corresponding with a decline in new infections (Fig. 18.3). In 1977, the countries in the region established a goal of eliminating

measles by 2010. As of the current writing, three EMR have achieved measles elimination (Bahrain, Iran, and Oman) (Fig. 18.4) [7]. Persistent transmission and intermittent outbreaks of measles in this region have been attributed to civil unrest and mass population displacement, both of which are obstacles to successful immunization programs.

WHO European Region

Most countries in this region have had measles control programs, including vaccination, since the 1980s. With first dose measles vaccination rates of 79%, there were still over 185,000 measles cases reported in 1990 [8]. Over the next 7 years, vaccination rates increased to 87% by 1997. In 1998, the members of this region established a goal of eliminating measles by 2007. By 2017, 37 countries were declared to be measles-free (Fig. 18.4). However, due to increases in vaccine hesitancy, the number of reported measles cases in the WHO European Region has significantly increased over the past few years (from 5,273 cases in 2016 to 82,596 cases in 2018) [9]. The majority of these cases were reported in eight countries (Ukraine, Serbia, France, Israel, Georgia, Greece, Italy, and Russia). The increases in cases in the European region resulted in imported infections in other areas of the world, including the United States.

WHO Western Pacific Region

Despite the use of measles vaccine for decades, in the 1980s, measles vaccination rates in this region remained less than 90%, allowing for ongoing community-wide transmission. While these countries did not meet their goal of measles elimination by 2012, the members of this region were successful in increasing first dose measles vaccination rates to 98% by this year and recorded the lowest number of measles cases ever at just under 11,000 cases. However, between 2013 and 2016, there was a surge in measles cases in this region due to an increase in imported infections, weakened immunization programs, and insufficient capacity for testing during outbreaks. Infections repeatedly imported into countries which had already achieved measles elimination resulted in re-establishment of ongoing endemic measles transmission [10]. Currently, nine countries and areas within this region have been verified to have eliminated measles (Fig. 18.4).

WHO Southeast Asian Region

Between 1985 and 1990, the first dose of measles vaccination rate increased dramatically in this region from 10% to over 80%, leading to a substantial decline in measles cases (Fig. 18.3). Since then, however, measles vaccination rates have stayed stable between 85% and 89%. By 2018, two (India and Indonesia) of the six countries with

most unvaccinated infants were in the Southeast Asian Region [4]. Regional implementation of measles control programs, including the use of measles vaccination, has led to measles elimination in five countries (Fig. 18.4). Currently, the WHO SEAR members have established a goal to eliminate measles from the region by 2023.

WHO Americas Region

During the 1970s, it was estimated that measles infection in the Americas resulted in almost 102,000 deaths. By the 1980s, the measles vaccine was routinely used throughout the area. In the 1990s, the members of this region established a goal to eliminate measles by 2000. The Americas, the first of the WHO regions to be declared measles-free, had successfully achieved measles elimination in 2016. However, endemic transmission of measles has since re-established in Venezuela (2018) and Brazil (2019) (Fig. 18.4) [4].

In the United States, specifically, the introduction of the measles vaccine into the pediatric immunization schedule led to a greater than 99% decrease in the reported incidence of measles (Fig. 18.2). Subsequent measles outbreaks were mainly associated with gaps in immunity, either due to primary vaccine failure (leading to the recommendation for a second dose of vaccine) or low vaccine uptake (due to limited medical access or vaccine hesitancy). Through implementation of an intensive immunization program nationwide, measles was declared to be eliminated from the country in 2000. The following decade saw a rise in vaccine hesitancy, leading to a reduction in measles vaccine uptake in select subpopulations throughout the country. As the number of cases of measles infections increased worldwide, unimmunized travelers imported infection into the United States. Measles infections in under- or unimmunized communities result in transmission of infection within the country. This combination of international travel and increasing vaccine hesitancy has accounted for the majority of recent US measles outbreaks (see Chap. 36, for more details on measles outbreaks in the United States). In fact, a recent measles outbreak in an Orthodox Jewish community in New York City was so persistent and difficult to control that it threatened the measles elimination status of the country [11].

Despite such setbacks in public health efforts to curb measles outbreaks both in the United States and across the globe, measles vaccine has led to substantial progress in the prevention and control of the disease. The realization that disease elimination is possible across large geographic areas has led to preliminary discussions about the feasibility of one day achieving global eradication.

Is Global Eradication of Measles Feasible?

The 2002 Institute of Medicine Report from the Forum on Emerging Infections includes a section on “Considerations for Viral Disease Eradication: Lessons Learned and Future Struggles.” In that report, the six preconditions required to

successfully eradicate a human viral infection, such as measles, are discussed. Careful consideration of each of these criteria and the proof of concept that viral infections can be eradicated provide convincing evidence that, if targeted, measles will one day be eradicated.

The first criterion to be met is the absence of a known or suspected animal reservoir for the virus. Measles virus belongs to the genus *Morbillivirus*. Viruses from this genus are highly host-specific. A related *Morbillivirus*, rinderpest, once caused large-scale epidemics in cattle and related animal species resulting in catastrophic agricultural losses. Vaccination programs and international efforts led to rinderpest eradication, with the formal declaration announced in 2011. Measles infects humans. No known animal or environmental reservoir is recognized. A related morbillivirus infection has already been eradicated globally. The potential for measles eradication is real.

The second criterion to meet is the availability of sensitive and specific tools for diagnosis and surveillance. Testing for the presence of early (IgM) antibody in the serum from suspected cases is highly sensitive and specific for measles infection. It is simple to perform and has a rapid turnaround time. Classic measles infection can almost always be diagnosed on clinical grounds. Serologic testing is done to confirm the clinical suspicion.

Measles meets the third criterion for potential eradication because transmission can be interrupted from person to person. Like smallpox infection, measles is highly contagious because it is transmitted via the airborne route. Interruption of transmission depends on immediate airborne isolation (quarantine) of the index case(s). Close contacts that are known to be susceptible, such as those in the same household, should be given passive prophylaxis and active vaccine (if 6 months or older). Passive prophylaxis, in the form of human immunoglobulin, provides immediate protection. Active vaccination provides long-term protection. An ongoing challenge includes pockets of underimmunization. The infection is so contagious, and the incubation period is 2 weeks or less, allowing little time to curb an outbreak in a highly susceptible population.

Natural infection from measles confers lifelong protection from reinfection. Current measles vaccine formulations are 96% effective at inducing lifelong immunity when administered as a single dose at or around 1 year of age. To reduce further the 4% primary vaccine failure rate, a second dose is recommended at least 4 weeks after the first, especially during an outbreak. A two-dose series of measles vaccine is 99% effective at inducing lifelong protective immunity. Lifelong immunity following infection or vaccination meets criterion number four. An ongoing challenge is delivery of two (or one!) doses of vaccine to all areas of the world. Measles vaccine requires an intact cold chain or it loses effectiveness. Many areas of the world with ongoing measles transmission lack reliable electricity and refrigeration.

The fifth criterion that identifies measles as a potential target for eradication is that the international public health community recognizes the burden of the disease and its sequelae. The known morbidity and mortality associated with measles, particularly among young children, has made measles control and elimination a major international priority. A combined decision by all stakeholders to move from

measles control and elimination to an effort for measles eradication is the logical next step.

Finally, for a successful eradication program to move forward, political commitment to the effort is required. Once the commitment is in place, allocation of resources and standard operating procedures for containment of any and all outbreaks can be launched. The investment is high cost up front. A remaining obstacle is to convince policy makers that, ultimately, this will be a highly cost-effective program. Models show, not unexpectedly, that an eradication effort is economically sound.

Four viral infections have been globally eradicated using vaccines, smallpox (1980), rinderpest (2011), poliovirus type 2 (2015), and poliovirus type 3 (2019), providing proof of concept that global eradication is feasible. In the last 35 years, the global measles burden has been reduced by more than 96%, from 4.5 million to an average of 200,000 cases annually. Progress is stunning. Eradication is feasible.

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Suggested Reading

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Chapter 19
Meningococcus

Manika Suryadevara

Etiology

Neisseria meningitidis, also known as meningococcus, is a gram-negative diplococcus. Bacterial virulence is determined by the lipooligosaccharide (LOS), factor H binding protein (FHbp), and the polysaccharide capsule. LOS releases endotoxins that trigger the inflammation cascade that leads to shock. FHbp, a surface lipoprotein, binds to human factor H, downregulating the complement pathway and allowing the bacteria to avoid host defenses. Similarly, the polysaccharide capsule resists complement-mediated and phagocytic responses, further evading host defenses. There are 13 distinct meningococcal capsular polysaccharides that have been identified, of which six (A, B, C, W, X, Y) have been described to cause invasive disease.

Pre-vaccine Epidemiology

Invasive meningococcal disease occurs worldwide, with a peak incidence in the first year of life and again in adolescence. Serogroup distribution varies by age and geographic location. The majority of cases in Europe, the Americas, and Australia are caused by serogroups B, C, and Y, with an increasing number of cases caused by serogroup W reported in recent years. In Asia, serogroup A disease is more prevalent in lower income countries, including India and Philippines, while the majority of disease in Taiwan, Japan, and Korea are caused by serogroups C and W [3]. In Africa, meningococcal disease is highly endemic with incidence of >10 cases per 100,000 population in almost all countries. Further, of all the regions in the world,

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the highest incidence of meningococcal disease is found in the meningitis belt of sub-Saharan Africa, spanning from Senegal to Ethiopia, where, prior to vaccine introduction, the majority of infections were caused by serogroup A (Fig. 19.1).

Cyclical epidemics have been reported in Europe, Asia, and the Americas over the past 50 years, but none have been as large as those described in the African meningitis belt. During these large outbreaks, incidence rates can be as high as 500–1000 cases per 100,000 population in some areas of this region [4, 5]. The largest meningococcal epidemic in history occurred in these sub-Saharan African

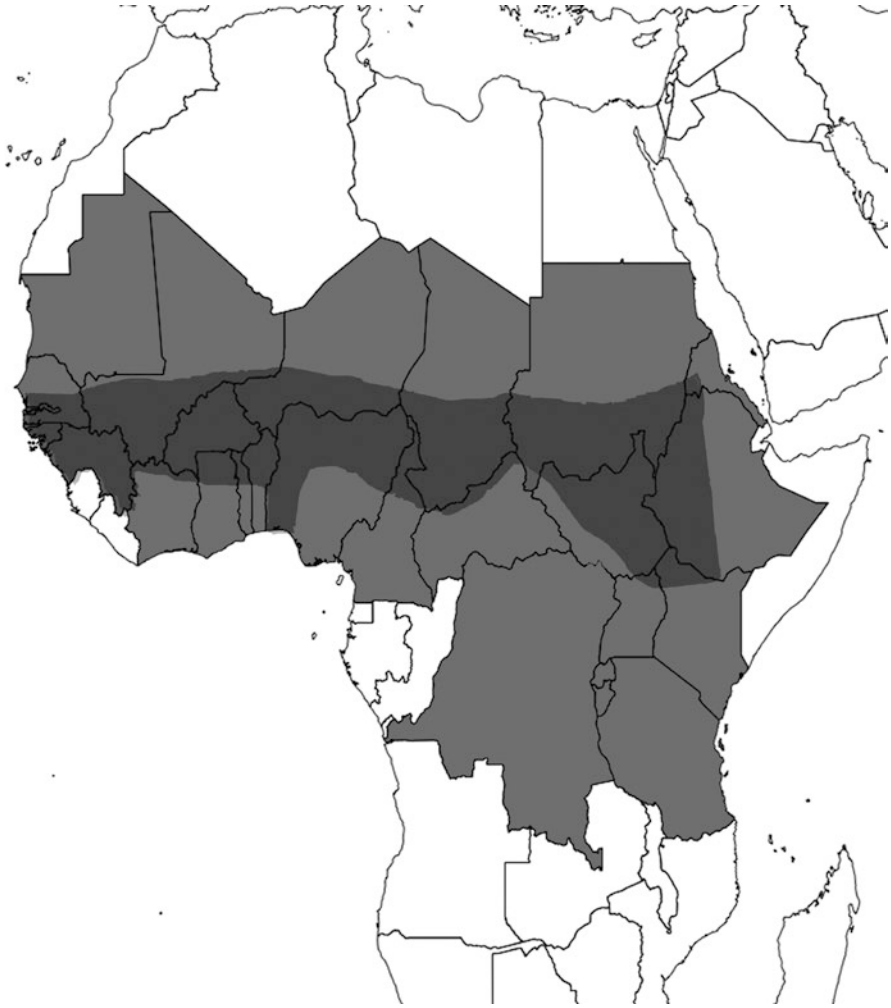

Fig. 19.1 Map depicting the African "meningitis belt" which has the highest incidence of meningococcal disease worldwide

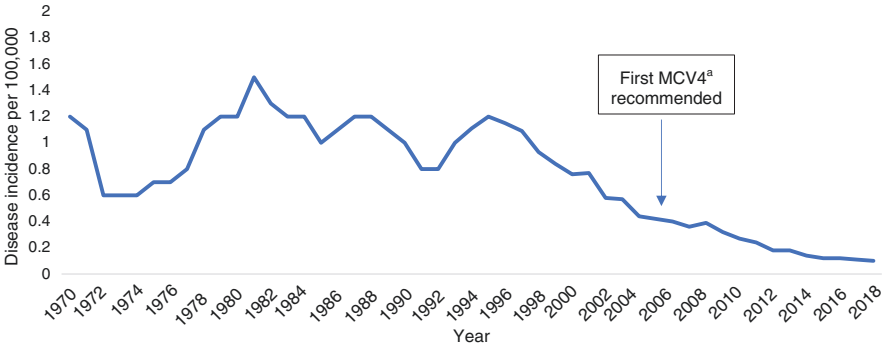

Fig. 19.2 Incidence of invasive meningococcal disease in the United States, 1970–2018. [a]MCV4 quadrivalent meningococcal conjugate vaccine

Table 19.1 Medical conditions that increase the risk of invasive or recurrent meningococcal disease

Medical risk factors for invasive or recurrent meningococcal disease
Complement deficiency: primary or acquired (autoimmune disease or eculizumab receipt)
Functional or anatomic asplenia
Human immunodeficiency virus
Underlying chronic disease

countries in 1996–1997, during which time there were at least 250,000 and 25,000 meningococcal cases and deaths, respectively.

In the United States, meningococcal disease is the leading cause of meningitis in adolescents. Interestingly, disease incidence in this country has been on the decline even prior to widespread use of vaccine (Fig. 19.2). By the time quadrivalent meningococcal conjugate vaccine was approved in 2005, disease incidence was down to 0.42 per 100,000 population, from a peak incidence of 1.2 in 1988. The majority of meningococcal cases in the United States are caused by serogroup B, with the remainder caused by serogroups C, W, and Y.

Certain medical conditions increase an individual's risk for developing invasive meningococcal disease (Table 19.1). In particular, the complement pathway plays a significant role in host response to infection. Conditions that impair the complement pathway, including complement deficiency, autoimmune diseases, and receipt of eculizumab (which inhibits terminal complement), increase host susceptibility of invasive and recurrent meningococcal disease. There are also sociodemographic factors that contribute to disease risk. Household contacts of an individual with invasive meningococcal disease, for instance, have at least 500 times the rate of meningococcal disease than the general population. Also, household crowding, college students living in residence halls, active or passive smoking, poor nutrition, and travel to an endemic region are all risk factors for acquiring invasive meningococcal disease.

Transmission

Meningococcus is transmitted through close contact to contaminated respiratory droplet or secretions. Upon acquisition, the bacteria attach to nasopharyngeal mucosal cells, leading to colonization. Invasive disease occurs when colonized bacteria enters into the bloodstream, often following an antecedent viral upper respiratory infection. Following bacteremia, the bacteria can disseminate to distal sites, including the cerebrospinal fluid.

Clinical Presentation

Invasive meningococcal disease most commonly causes meningitis or sepsis (with or without meningitis) manifesting as fever, petechial rash, shock, and multiorgan dysfunction. Less common presentations include pneumonia, arthritis, otitis media, epiglottitis, myocarditis, pericarditis, and endophthalmitis. Even with appropriate antibiotic management, the mortality rate for invasive meningococcal disease is 10–15%. Among the survivors of infection, 20% still have permanent sequelae, including hearing loss, neurologic deficits, limb amputation, impaired school performance, behavioral problems, or attention deficit hyperactivity disorder.

Management

The treatment for invasive meningococcal disease includes intravenous administration of a third-generation cephalosporin (either ceftriaxone or cefotaxime) while bacterial cultures are pending. De-escalation to penicillin is recommended after pathogen confirmed.

Prevention

There are four strategies for prevention of invasive meningococcal disease.

Community-wide prevention: Routine vaccination using quadrivalent meningococcal vaccine and meningococcal B vaccine should be administered to the targeted populations to prevent disease in the case of future exposure. *Individual exposure:* Individuals who have had direct contact with infected respiratory droplets or secretions (Table 19.2) should receive chemoprophylaxis as soon as possible, preferably within 24 hours of identification of index case, regardless of vaccination status. Potential chemoprophylaxis agents include rifampin, ceftriaxone, ciprofloxacin, or azithromycin. One dose of ceftriaxone eradicates nasopharyngeal carriage. Index

Table 19.2 Recommendations for who should receive chemoprophylaxis following contact with a person with invasive meningococcal disease

Chemoprophylaxis recommended for the following if contact with index case occurred within 7 days prior to symptom onset or within 24 hours of initiating antibiotics
Household contacts
Childcare or preschool contact
Direct exposure to respiratory secretions (kissing, sharing utensils or toothbrushes, endotracheal intubation)
Slept in same dwelling
Passengers seated directly next to index case during airline flight over 8 hours
Index case if at least one dose of ceftriaxone or cefotaxime was not received during treatment course

cases who do not receive at least one dose of ceftriaxone or cefotaxime as part of their management should also receive chemoprophylaxis after completing treatment course. Chemoprophylaxis is not indicated for exposures that occurred more than 2 weeks prior. *Community outbreak:* Community-wide vaccination is recommended during outbreaks caused by a vaccine-preventable serogroup. *Recipients of eculizumab*: Eculizumab, a monoclonal antibody used to treat atypical hemolytic uremic syndrome, is associated with a 1000- to 2000-fold increased incidence of invasive meningococcal disease [6]. Between 2008 and 2016, 16 recipients of eculizumab developed meningococcal disease, 14 of whom were vaccinated [6]. In addition to quadrivalent meningococcal vaccine and meningococcal B vaccine, providers should consider penicillin prophylaxis for the duration of the treatment course, which is lifelong for many recipients.

Meningococcal Vaccine

Vaccine Characteristics

In the United States, there are two quadrivalent meningococcal conjugate vaccines licensed and approved for use to prevent invasive meningococcal infection from serogroups A, C, W, and Y. There are also two recombinant meningococcal vaccines to prevent against infection with serogroup B (Table 19.3).

Vaccine Storage, Preparation, and Administration

Menactra is supplied as a single-dose vial which should be stored refrigerated (2–8 °C). 0.5 mL dose of vaccine should be administered intramuscularly.

Menveo is supplied as a lyophilized MenA component and a liquid MenCWY component which should both be stored refrigerated (2–8 °C). The liquid vaccine

Table 19.3 Available vaccines to prevent against invasive meningococcal disease in the United States

Meningococcal vaccines	Ingredients	Year licensed	Age group Approved
Quadrivalent conjugate vaccines			
MenACWY-D; Menactra (Sanofi Pasteur)	MenA, C, W, Y polysaccharides conjugated to diphtheria toxoid; residual formaldehyde, sodium phosphate-buffered isotonic sodium chloride solution, no preservative or adjuvant	2005	9 months to 55 years[a]
MenACWY-CRM; Menveo (Novartis)	MenA, C, W, Y polysaccharides conjugated to CRM_{197}, phosphate-buffered saline, residual formaldehyde, no preservative or adjuvant	2010	2 months to 55 years
Meningococcal B vaccines			
MenBFHbp; Trumenba (Pfizer)	Two *Neisseria meningitidis* serogroup B recombinant factor H binding protein variants (A and B), polysorbate 80, aluminum phosphate, histidine buffered saline	2014	10–25 years
MenB-4C; Bexsero (Novartis)	Four recombinant proteins (factor H binding protein, neisserial adhesin, neisserial heparin binding antigen, outer membrane vesicle, aluminum hydroxide, sodium chloride, histidine, sucrose	2015	10–25 years

[a]Menactra is not recommended for use under 2 years of age because it can interfere with infant immunologic response to pneumococcal conjugate vaccine. When Menactra and Daptacel are given to 4- to 6-year-olds, Menactra should be administered prior to or at the same visit as Daptacel to avoid interference with the immunological response to Menactra

component should be used to reconstitute the lyophilized vaccine component. 0.5 mL dose of vaccine should be administered intramuscularly immediately after reconstitution.

Trumenba is supplied as a prefilled syringe which should be stored refrigerated (2–8 °C). Shake syringe to ensure homogenous white suspension. Do not use vaccine if it cannot be resuspended. 0.5 mL dose of vaccine should be administered intramuscularly.

Bexsero is supplied in single-dose prefilled syringes which should be stored refrigerated (2–8 °C). Shake syringe to ensure homogenous white suspension. Do not use vaccine if it cannot be resuspended. 0.5 mL dose of vaccine should be administered intramuscularly.

Vaccine Recommendations

Quadrivalent meningococcal conjugate vaccine should be administered routinely to all eligible adolescents at their 11 to 12 years, with a booster dose given at 16 years of age. There is a category B recommendation to offer meningococcal B vaccine to

previously unimmunized adolescents between the ages of 16 and 23 years. Catch-up vaccinations and vaccine recommendations for individuals at high risk for invasive meningococcal disease are listed in Tables 19.4 and 19.5.

Table 19.4 Meningococcal vaccine recommendations for adolescents

Age group	Recommendations
11–12 years	Routine administration of single dose of quadrivalent meningococcal vaccine, followed by a booster dose at 16 years of age
Previously unimmunized, 13–15 years	Catch-up administration of a single dose of quadrivalent meningococcal vaccine, followed by a booster dose at 16–18 years of age
Previously unimmunized, 16–18 years	Catch-up administration of a single dose of quadrivalent meningococcal vaccine; booster doses are not needed unless high-risk conditions exist (see Table 19.5)
Previously unimmunized, 16–23 years	Category B recommendation to offer two doses of meningococcal B vaccine, 6 months apart

Table 19.5 Meningococcal vaccine recommendations for individuals at high risk of invasive disease, including those with persistent complement deficiencies (primary or acquired), functional or anatomic asplenia, HIV infection, travel to endemic region, community outbreak with vaccine-preventable serogroup, microbiologists routinely exposed to *Neisseria meningitidis*

Age	Primary vaccine series	Booster vaccine[a]	Notes
2–23 months			
First dose at 2 months	Four doses of Menveo (2, 4, 6, 12 months)	Administer booster vaccine 3 years after primary series. Repeat boosters every 5 years	Menactra is not recommended for use in this age group as it interferes with infant immunologic response to pneumococcal conjugate vaccine
First dose at 7 months	Two doses of Menveo (dose 2 to be given in second year of life, at least 3 months after dose 1)		
Previously unimmunized 2–6 years	Two doses of either quadrivalent meningococcal vaccine, 2 months apart	Administer booster vaccine 3 years after primary series. Repeat boosters every 5 years	Menactra may be used at least 4 weeks after completion of pneumococcal conjugate vaccine series When both Menactra and Daptacel[b] are to be administered to children aged 4–6 years, Menactra should be given prior to or at the same visit as Daptacel to avoid interference with immunologic response to meningococcal vaccine

(continued)

Table 19.5 (continued)

Age	Primary vaccine series	Booster vaccine[a]	Notes
Previously unimmunized 7–55 years	Two doses of either quadrivalent meningococcal vaccine, 2 months apart	Administer booster vaccine 5 years after primary series. Repeat boosters every 5 years	
10 years and older at high risk of invasive meningococcal disease or in a community with meningococcal B outbreak	Two doses of Bexsero, 1 month apart or three doses of Trumenba (dose 2 at 1–2 months, dose 3 at 6 months after initiation)		

[a]Continue booster doses as long as individual remains at high risk of invasive meningococcal disease
[b]Daptacel, diphtheria, and tetanus toxoids and acellular pertussis vaccine

Contraindications and Precautions to Meningococcal Vaccine

Contraindications to meningococcal vaccines include a severe anaphylactic reaction to a previous dose of meningococcal vaccine or to any vaccine component. The caps of the prefilled syringes of Bexsero are composed of natural rubber latex and may cause an allergic reaction. As a precaution, Guillain-Barre syndrome has been reported following quadrivalent meningococcal conjugate vaccines. Benefits and risks should be considered prior to administering quadrivalent meningococcal conjugate vaccine to individuals with a known history of Guillain-Barre syndrome.

Adverse Events

Adverse reactions to meningococcal vaccines include redness, tenderness, and swelling at the site of injection, headaches, irritability, and malaise. As with other vaccines administered to adolescents, syncope following vaccination has been reported. It is recommended that adolescents receiving a meningococcal vaccine be observed for 15 minutes after vaccine administration.

Immunogenicity

While the conjugate vaccines are immunogenic, circulating antibodies decline 3–5 years after a single dose of quadrivalent meningococcal conjugate vaccine. A booster dose at 16 years of age and every 5 years for individuals at high risk of invasive disease is recommended to maintain protective levels of circulating antibodies.

Impact of Vaccine on Disease Burden

The first vaccine developed to protect against invasive meningococcal disease was a polysaccharide vaccine licensed in the 1970s. Similar to other polysaccharide vaccines, there was poor immunogenicity in young infants, a lack of boosted response with repeated doses, and no reported effect on nasopharyngeal carriage. Conjugating the polysaccharide vaccine to a protein carrier elicits a T-cell-dependent immune response, resulting in increasing immunogenicity in infants, boosted response with subsequent doses, and eradication of nasopharyngeal carriage. Quadrivalent meningococcal conjugate vaccine protecting against serogroups A, C, W, and Y was first approved and recommended in the United States in 2005.

Following widespread use of quadrivalent meningococcal conjugate vaccine, disease incidence in the United States continues to be low, with even further reductions in serogroup C and Y infections (Figs. 19.3 and 19.4). While outbreaks continue to occur, they account for only 5% of all meningococcal disease. Between

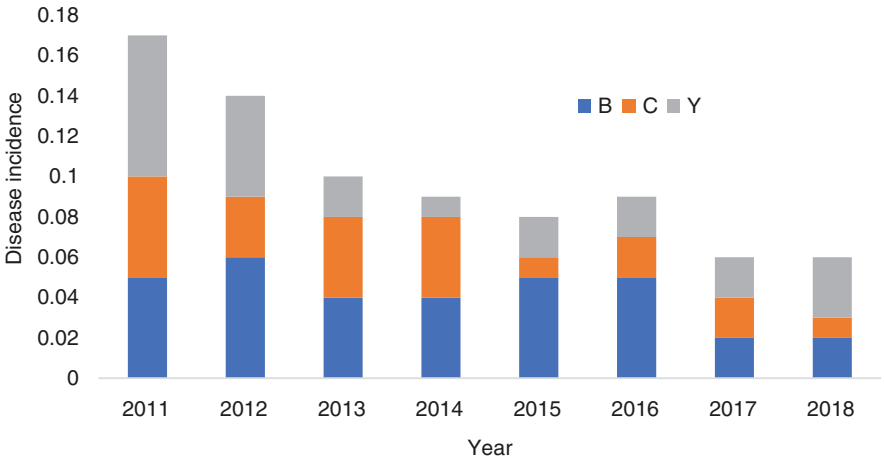

Fig. 19.3 Incidence, per 100,000 population of invasive meningococcal disease by serogroup, 2011–2018

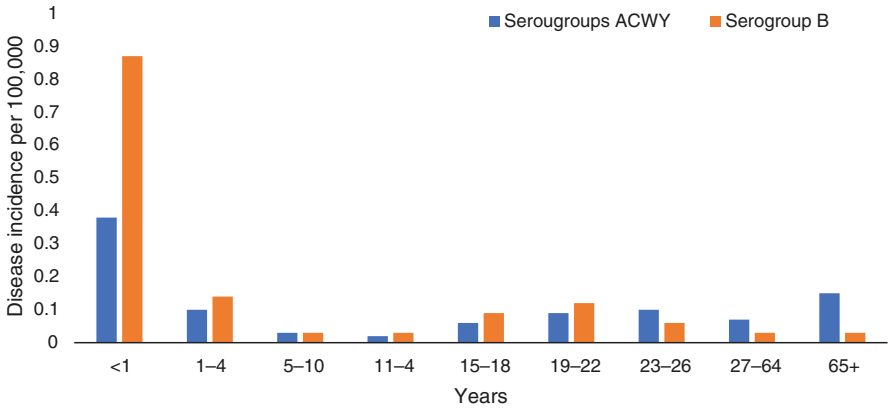

Fig. 19.4 Meningococcal disease incidence in the United States, by age, 2009–2018

2009 and 2013, there were 180 cases associated with 36 meningococcal outbreaks across the country [7]. During this time, there were eight university outbreaks (serogroup B accounting for six, serogroup C accounting for two) and two large outbreaks of serogroup C infection among men who have sex with men [7].

Meningococcal outbreaks have been known to occur in the university settings. Students attending a university experiencing a meningococcal outbreak have a 200- to 1400-fold increased risk of acquiring disease than the general population [8]. Administration of meningococcal B vaccines has been used in response to university outbreaks, with variable vaccine uptake. During a 2013–2014 meningococcal B outbreak at a university in New Jersey, a mass vaccination campaign, using what was at the time an investigational vaccine, was initiated. They were able to achieve two-dose series vaccination coverage of 89.1% and had no new meningococcal B cases reported among university students after the start of the immunization program [9]. Interestingly, later studies have found that meningococcal B vaccination may not reduce nasopharyngeal carriage, emphasizing the need for high vaccination rates for individual protection, as herd immunity cannot be assured [10, 11].

Globally, the introduction of meningococcal vaccine in Africa has led to dramatic results. In 2010, MenAfriVac, a monovalent meningococcal A conjugate vaccine manufactured by the Serum Institute of India, Ltd., was introduced in Burkina Faso, Mali, and Niger. As of June 2015, over 220 million under 30 years of age in 15 African countries have been immunized against meningococcal A disease. By 2015, the number of confirmed meningococcal A disease cases declined by over 99% in countries with a national meningococcal vaccination program [12]. Between 2015 and 2017, the average annual disease incidence in five countries (Burkina Faso, Chad, Mali, Niger, Togo) of the meningitis belt, where vaccine coverage rates exceeded 90%, was down to 7.5 (ranging from 0.4 in Mali to 14.7 in Niger) per 100,000 population [13]. The incidence of meningococcal A disease during this time was low, with most of the cases caused by serogroups C and W. Of interest, the proportion of cases caused by serogroup X increased from 0.6% in 2015 to 27% in

2017 [13]. Fall et al. found that since 2010, there were no cases of meningococcal A disease reported among vaccinated individuals in this region [14]. As meningococcal A disease is nearly eliminated in the countries which have implemented a national meningococcal immunization program, outbreaks due to other serogroups continue to be on the rise [12]. The use of multivalent meningococcal conjugate vaccines may be required to maintain control of this disease in this high-risk region.

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Chapter 20
Mumps

Manika Suryadevara

Mumps Infection

Etiology

Mumps virus, an enveloped, single-stranded RNA virus, is in the genus *Rubulavirus,* in the Paramyxoviridae family. The surface glycoproteins, hemagglutinin-neuraminidase and fusion protein, are responsible for mediating virus-host cell attachment and fusion.

Pre-vaccine Epidemiology

Historical records dating back to the eighteenth century describe the occurrence of mumps epidemics, particularly in crowded settings [2]. Prior to use of vaccine, passive surveillance found annual incidence of mumps infections to be greater than 100 cases per 100,000 population in many areas around the world [2]. In the United States, mumps infected most children by 14 years of age, with peak incidence occurring seasonally between January and May. While the majority of children with mumps infection developed parotitis, up to one-third of infections were asymptomatic. Mumps was reported to cause 10% and 36% of aseptic meningitis and encephalitis cases, respectively, although deaths from this infection were

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uncommon [3]. In 1967, the year the mumps vaccine was licensed in the United States, there were over 186,000 mumps cases reported across the country.

Transmission

Mumps is transmitted from person to person through direct contact, respiratory droplets, and contaminated fomites. The highest amount of virus shedding occurs 1–2 days prior to symptom onset. People infected with mumps remain contagious through 5 days after symptoms began. After acquisition of infection, the virus replicates in the nasopharynx prior to invasion of the bloodstream. The transient viremia allows for spread of virus to distal sites.

Clinical Presentation

When symptomatic, mumps infections typically start with a prodrome of fevers, headache, and myalgias, prior to the development of swelling of at least one salivary gland, most commonly the parotid. Over 90% of symptomatic persons with mumps will develop parotitis. While the parotid swelling can be unilateral, it is common for the contralateral parotid to be affected after several days. Symptoms usually self-resolve over the course of 7–10 days.

Complications of mumps infection typically involve the testes, ovaries, and meninges. Orchitis, the most common mumps complication in postpubertal men, is most often unilateral and is rarely associated with sterility. Oophoritis and/or mastitis may develop in postpubertal women. Of the central nervous system complications, aseptic meningitis is the most common. Aseptic meningitis due to mumps can occur before, during, or after the parotid swelling. In some cases, the meningitis may manifest without any evidence of parotitis. Mumps meningitis is a benign process and self-resolves without any sequelae. Sensorineural hearing loss, mostly unilateral, has been reported. This complication, while most often transient, rarely leads to permanent deafness. Encephalitis is the most severe of the mumps complications, with manifestations of altered level of consciousness and seizures with or without parotitis. Still, most people with mumps encephalitis experience a full recovery with minimal ongoing neurologic deficits. Other rare complications associated with mumps infection include pancreatitis, glomerulonephritis, transverse myelitis, thrombocytopenia, and thyroiditis.

Management

There is no antiviral therapy available for the treatment of mumps infection. Management of infection is supportive care.

Prevention

The primary approach to community-wide mumps prevention includes the routine, universal use of live attenuated mumps vaccine as a two-dose series starting at age 1 year. Neither vaccination nor immune globulin is recommended for prevention of infection following exposure to mumps. However, it is recommended that susceptible individuals be vaccinated against mumps after an exposure not to prevent disease from the current exposure but to provide immunity for future exposures.

Live Attenuated Mumps Vaccine

Vaccine Characteristics

There are many different strains used globally to prevent mumps infection, including but not limited to Jeryl-Lynn, Urabe, Rubini, Leningrad-3, and L-Zagreb mumps virus strains. The mumps-containing vaccine currently used in the United States is a live attenuated Jeryl-Lynn strain of mumps virus prepared in cultures of chick embryo fibroblasts. In the United States, mumps-containing vaccines are available only in combination with other viral vaccines (measles and rubella, with or without varicella) (Table 20.1). Monovalent mumps vaccine is not available for use in this country.

Vaccine Storage, Preparation, and Administration

MMR and MMRV are supplied as lyophilized powder to be stored between −50 °C and 8 °C, protected from light at all times. Improperly stored vaccine may lose potency. Sterile, preservative-free water is provided as the diluent to be stored in the refrigerator (2°C to 8°C) or at room temperature. Prior to reconstitution, the vial containing the lyophilized vaccine should be stored at 2°C to 8°C. Once reconstituted, the vaccine should be administered immediately. After reconstitution, MMR vaccine can be refrigerated for up to 8 hours prior to use. MMRV must be administered within 30 minutes. The 0.5 mL dose of vaccine is given by subcutaneous injection.

Vaccine Recommendations

The mumps vaccine series requires two doses of vaccines administered at least 28 days apart. In the United States, routine administration of mumps vaccine begins at 12–15 months of age, with the second dose of vaccine given at age 4–6 years (Table 20.2). Refer to Chap. 18 (“Measles”) for information regarding the use of

Table 20.1 Mumps-containing vaccine products available in the United States

	MMR[a] vaccine	MMRV[a] vaccine
Brand name (manufacturer)	MMR II (Merck)	Proquad (Merck)
Age of administration	12 months of age and older[b]	12 months to 12 years
Vaccine ingredients		
Active ingredients	Attenuated measles, mumps, rubella viruses	Attenuated measles, mumps, rubella, varicella viruses[c]
Stabilizer	Sorbitol, sucrose, gelatin, human albumin	Sorbitol, sucrose, gelatin, human albumin
Acidity regulators	Sodium phosphate, sodium chloride	Sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, sodium bicarbonate, potassium phosphate monobasic, potassium chloride, potassium dibasic, potassium phosphate monobasic
Cell culture growth	Fetal bovine serum	Bovine calf serum
Antibiotics	Neomycin	Neomycin
Preservative	None	None
Others		Residual MRC-5 cells

[a]MMR measles-mumps-rubella; MMRV measles-mumps-rubella-varicella
[b]MMR vaccine may be given to infants 6–11 months if living in an area of epidemic or traveling to endemic region
[c]Measles, mumps, rubella components similar between MMR and MMRV, but MMRV achieves higher measles geometric mean titers than MMR; varicella component in MMRV has higher potency than monovalent varicella vaccine, but varicella geometric mean titers similar between the two vaccines

Table 20.2 Recommendations for mumps vaccination

Mumps vaccine recommendations	
Routine pediatric immunization	Dose 1 administered at 12–15 months Dose 2 administered at 4–6 years (or at least 28 days after dose 1)
No evidence of immunity to mumps[a]	Administer two-dose vaccine series, at least 28 days apart
Infants 6–11 months of age traveling internationally	Do not need to administer vaccine unless measles vaccine is indicated If vaccine is administered, it does not count as a valid dose; two-dose vaccine series needs to be initiated after 12 months of age
High-risk adults without evidence of immunity to mumps[a] Healthcare personnel (even those born before 1957) Students in postsecondary educational institutions International travelers	Administer two-dose vaccine series, at least 28 days apart

[a]Evidence of immunity as defined in Table 20.3

Table 20.3 Evidence of immunity to mumps infection

Fulfilling any one of the following bullets is evidence of immunity to mumps infection
Written, dated documentation of age-appropriate mumps vaccine dose(s) Healthcare providers should only document doses of vaccines they administer Self- or parent-reported doses are not valid
Laboratory evidence of immunity
Laboratory confirmation of disease
Born before 1957

MMR and MMRV in children. Adults with high risk of mumps exposure and no documented evidence of immunity should also receive the two-dose vaccine series. Table 20.3 lists the criteria used to establish immunity to mumps.

Contraindications to Mumps Vaccine

Refer to Tables 18.4, 18.5, and 18.6 in Chap. 18 ("Measles") for contraindications, precautions, and considerations for MMR vaccine administration.

Adverse Events

Reactions to mumps vaccine typically occur 7–10 days following vaccination in non-immune individuals. Therefore, these effects are more likely to occur after the first rather than subsequent doses of mumps-containing vaccine. Refer to Table 18.7 in Chap. 18 ("Measles") for adverse reactions following receipt of MMR vaccination.

Immunogenicity

A single dose of mumps vaccine induces production of mumps antibody in 94% of individuals. The administration of a second dose of MMR vaccine targets vaccine nonresponders and increases mumps antibody titers, at least fourfold, in many of those who did mount a response to the first dose [3].

Impact of Vaccine on Disease Burden

In the 1960s, Maurice Hilleman isolated the mumps virus infecting his 5-year-old daughter, Jeryl-Lynn. He then passed the virus in chicken egg fibroblasts to develop the first live attenuated mumps vaccine. This Jeryl-Lynn mumps virus strain

vaccine, initially licensed in 1967, remains the only mumps vaccine routinely used in the United States today. In 1977, the Advisory Committee on Immunization Practices (ACIP) recommended that all infants receive a dose of mumps-containing vaccine after 1 year of age. Shortly after, in an effort to reduce the number of vaccines administered at a single visit, the mumps vaccine was combined with measles and rubella vaccines to become the MMR vaccine.

During the mid-1980s, there was a resurgence in mumps cases in the United States [Fig. 20.1], with 12,848 cases reported in 1987 (incidence of 5.2 cases per 100,000 population) [4]. Most of these cases still occurred in school-age children, with outbreaks occurring in high schools and college campuses. Interestingly, in contrast with pre-vaccine epidemiology, over one-third of the infections are reported in adolescents 15 years of age and older, the cohort of children born before the recommendation for routine MMR vaccination. Based on this information, this resurgence was attributed to low adolescent vaccine coverage.

By this time, some states were starting to require immunity to vaccine-preventable diseases for school entry. During this resurgence, it was noted that the incidence rate of mumps infection in states requiring proof of mumps immunity for school attendance was 1.1 mumps cases per 100,000 population, compared to 11.5 cases per 100,000 population in states with no mumps vaccine law [4]. As the number of states with comprehensive immunization laws increased, the incidence of mumps across the country decreased [5]. Following significant increases in measles outbreaks over the next decade, in 1989, the ACIP recommended a second dose of MMR vaccine to be given at 4–6 years of age [3]. As a result, both measles and mumps cases were on the decline.

Following introduction of mumps vaccine, global disease burden has been reduced by 88% and by 97% in areas which have implemented a single vaccine dose or two vaccine doses, respectively (Fig. 20.2). In the United States, following national use of two doses of MMR vaccine, there was a reduction in annual mumps disease burden, which was no longer seasonal, to under 300 cases, with an incidence of 0.1 per 100,000 population. Reductions in mumps-associated pancreatitis, meningitis, and encephalitis to less than 1% of cases were also reported. Furthermore,

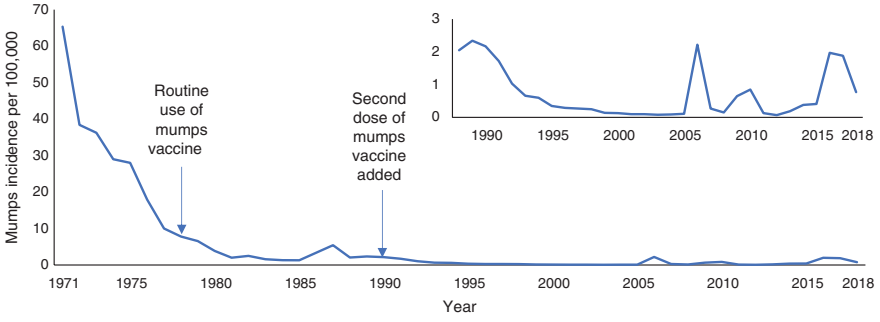

Fig. 20.1 Incidence of mumps infections per 100,000 population in the United States between 1971 and 2018

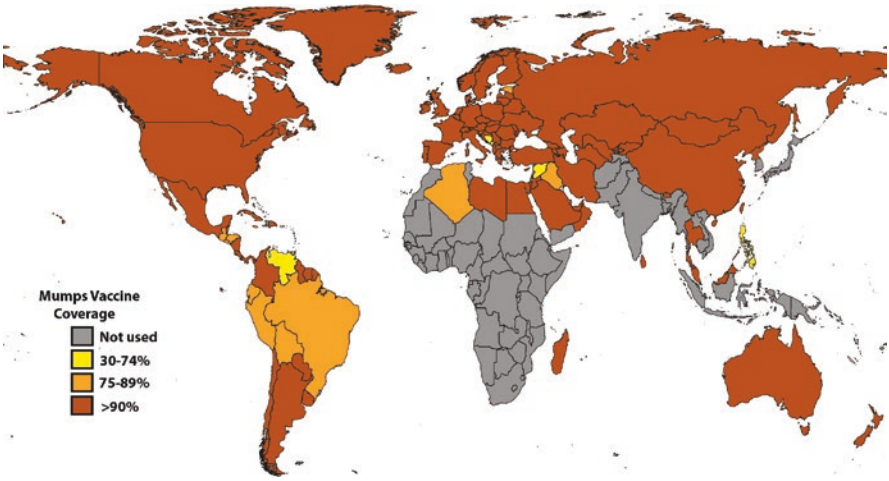

Fig. 20.2 Mumps-containing vaccine coverage rates by country in 2018

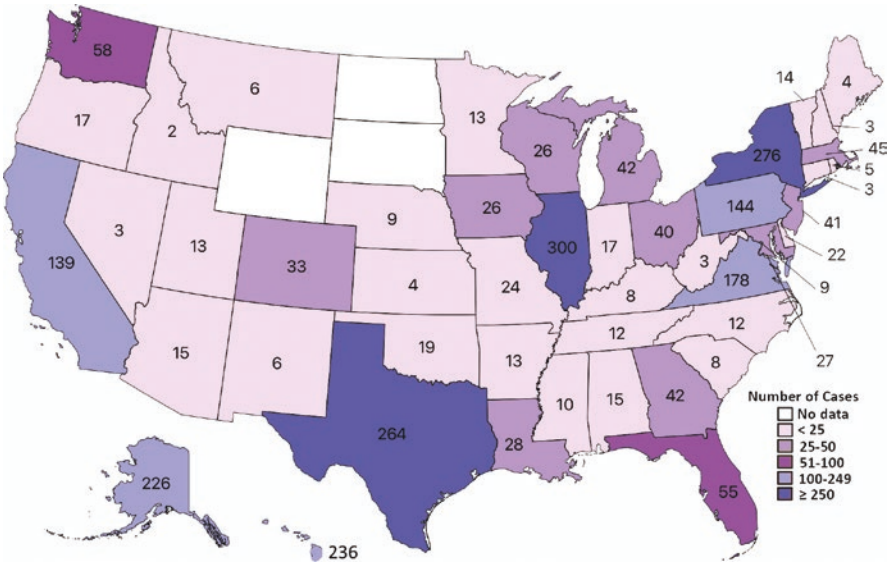

Fig. 20.3 Number of reported mumps cases in the United States in 2018, by state

with most of the infants and young children immunized against mumps, there was a shift in outbreak cases to the adolescent and young adult cohorts. By the early 2000s, the incidence of mumps infections in the United States was down to less than or equal to 0.1 cases per 100,000 population. However, since then, there have been an increase in mumps cases and multiple mumps outbreaks that have been reported both throughout the country and worldwide (Figs. 20.3 and 20.4).

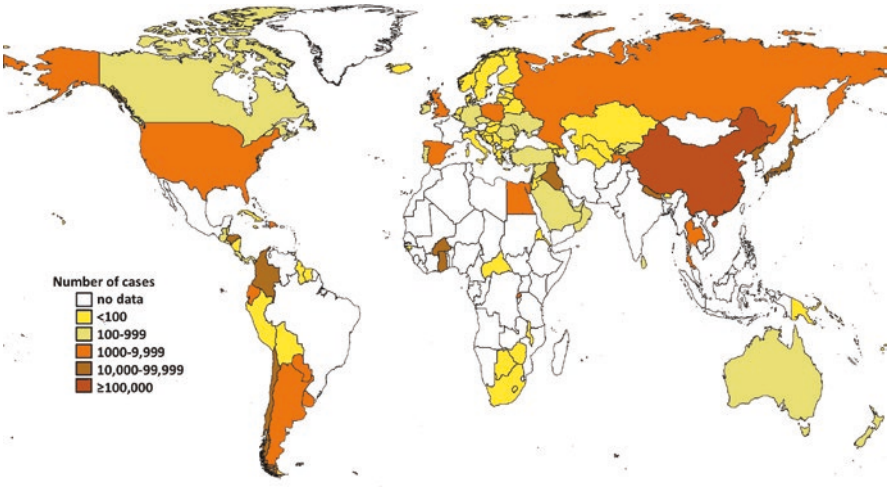

Fig. 20.4 Number of reported mumps cases worldwide in 2018, by country

There are several factors which contribute to outbreaks of vaccine-preventable diseases [6]. The increase in vaccine hesitancy and resulting reduction in vaccination rates have led to a rise in vaccine-preventable diseases worldwide. While this holds especially true for measles and pertussis, where disease clusters are associated with under-immunized communities, mumps outbreaks can be seen in highly vaccinated communities. For example, a mumps outbreak occurred at the University of Iowa in 2015, where 98% of the students had already received two doses of MMR vaccine [7].

Another possible reason for vaccine-preventable disease persistence is primary vaccine failure. Post-licensure studies found vaccine efficacy of one or two doses of mumps-containing vaccine to be 78% and 88%, respectively. There are other mumps virus strains used for vaccination around the world, but these strains are associated with higher rates of adverse events, particularly vaccine-associated aseptic meningitis, when compared to the Jeryl-Lynn strain, making them less appealing for routine use. There is also antigenic variation between vaccine-strain mumps virus (genotype A) and wild-type mumps virus circulating in North America and Europe (genotype G). However, there is enough to cross-neutralizing immunity induced to protect from infection with either genotype [6].

The factor most likely contributing to the persistence of mumps outbreaks is secondary vaccine failure or waning immunity [6]. During the University of Iowa mumps outbreak in 2015, mentioned above, students were greater than nine times more likely to acquire mumps infection if they had received the second dose of MMR vaccine more than 13 years prior to the outbreak [7]. Ultimately, mumps outbreaks occur in settings of close contact, particularly schools and universities, among persons who had received two doses of vaccine in the past. While two doses are effective in disease prevention in the general population, this schedule seems less effective in reducing disease incidence during an outbreak. At the October 2017

meeting, the ACIP recommended a third dose of mumps-containing vaccine to individuals who have previously received two doses of vaccine and who are at an increased risk for acquiring mumps due to a local outbreak [8].

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Chapter 21
Pertussis

Joseph Domachowske

Pertussis Infection

Etiology

Pertussis is caused by the Gram-negative bacterium *Bordetella pertussis*. Humans are the only known reservoir for the pathogen. The related bacterial species *B. parapertussis* and *B. bronchiseptica* can cause an identical clinical illness. *B. bronchiseptica* is the cause of kennel cough in dogs.

Epidemiology

Worldwide, whooping cough affects around 16 million people and leads to an estimated 50,000 to 200,000 deaths each year. The majority of pertussis-related deaths occur during the first year of life. Pertussis continues as a global public health problem despite generally high childhood coverage with the DTP and DTaP vaccines. About 90% of all cases occur in developing countries. In the United States, prior to vaccine availability, an average of 178,171 cases were recognized annually with peaks of disease cycling every 2–5 years. After pertussis vaccines were introduced in the 1940s, the incidence of infection declined dramatically. By 1976, average annual cases had been reduced to approximately 1000. This decline, however, was not sustained. Since 1980, cases of pertussis have slowly increased, and by 2015, the number of reported cases had reached 20,762. The global burden of pertussis cases in 2018 is shown in Fig. 21.1.

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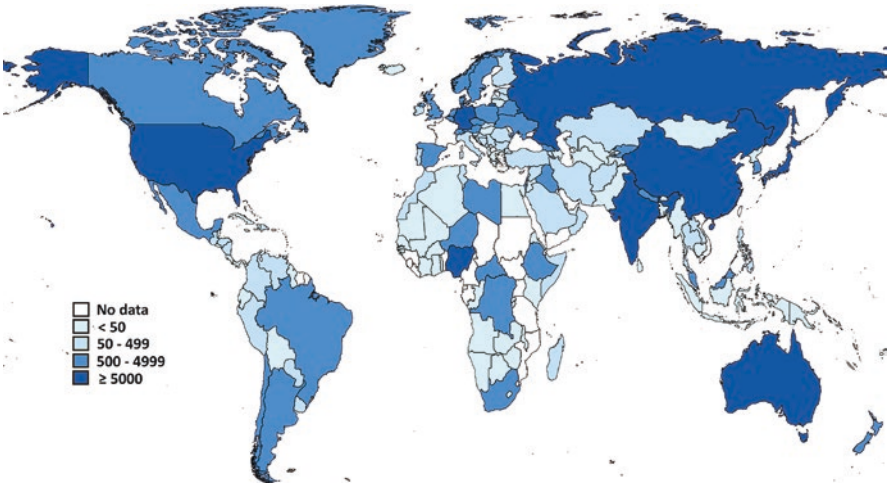

Fig. 21.1 Shown is the number of pertussis cases reported, by country, in 2018. (Source of data used to generate the figure: https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/pertussis/en/)

Transmission

Humans are the only known source of pertussis disease. Transmission occurs when a susceptible individual inhales respiratory droplets containing the pathogen, almost always during close contact with an infected individual who is coughing. The incubation period is typically 7–10 days prior to the onset of symptoms.

Clinical Presentation

The classic clinical illness has three phases. Initially, during the catarrhal phase, the infection is associated with nasal congestion and discharge, low-grade fever, and cough. After 7–10 days, the characteristics of the cough change abruptly. The frequent, uncontrollable coughing fits begin to interrupt routine activities heralding the paroxysmal phase of the illness. During cough paroxysms, the individual may develop cyanosis. Sustained hypoxemia can lead to syncope or seizure activity. The coughing spells become more frequent and increasingly severe. After each prolonged coughing fit, in an effort to recover, the individual inhales deeply and forcefully creating the unmistakable whooping sound that gives pertussis its more familiar name, whooping cough. The violent coughing triggered by pertussis has been documented to cause subconjunctival hemorrhages, rib fractures, urinary incontinence, hernias, vertebral artery dissection, and pneumothorax from pleural rupture. Frequent posttussive emesis can lead to dehydration and electrolyte disturbances. It is not uncommon for infants with protracted illness to develop weight loss and malnutrition. In

young infants, an identical pertussis syndrome has also been associated with infections caused by *B. parapertussis, B. bronchiseptica*, respiratory syncytial virus, adenoviruses, and *Chlamydia trachomatis*. After 2–3 weeks, the coughing fits begin to change again in quality, first becoming less severe and then less frequent. Pertussis is a prolonged cough illness, known in some cultures as "100 days of cough." The protracted convalescent phase of the illness is characterized by gradual improvement over the next 10 weeks or so. Cough illnesses lasting 3 weeks or longer not caused by asthma, sinusitis, or chronic bronchitis from smoking cigarettes are likely pertussis infections that have reached the convalescent phase. Symptoms of classic whooping cough are less common among very young infants who become infected and among older children and adults who become infected despite partial, preexisting immunity. Very young infants may not appear to cough at all but instead present with periodic breathing or apnea with periods of cyanosis from hypoxemia. Pertussis infection should be considered in all infants that present with apnea, brief resolved unexplained events, and sudden infant death. Older children and adults with incomplete protection from prior immunization often present with milder symptoms of infection such as prolonged cough illness with few paroxysms that are only occasionally associated with a deep inspiratory whoop. The astute clinician may recognize a history of frequent post-tussive vomiting as suspicious for pertussis illness. Although children and adults with waning immunity to pertussis may present with milder forms of disease, they represent a substantial reservoir of the infection and can easily spread the infection to other susceptible individuals.

Management of Pertussis

Providers should have a very low threshold for hospitalizing infants younger than 6 months of age who are diagnosed with pertussis so that they can be observed for possible signs of hypoxemia during paroxysms of cough and monitored for the development of dehydration. All individuals who are diagnosed with pertussis during their first 3 weeks of symptoms should be treated with antibiotics that are effective against *B. pertussis*. The antibiotic of choice is azithromycin for all age groups. All individuals who have been in close contact with the index case of pertussis should also receive a course of appropriate antibiotics. Alternatives to azithromycin include erythromycin or clarithromycin. Trimethoprim-sulfamethoxazole may also be considered for those with allergies to the first-line agents. The goal of antibiotic treatment is to render the patient noncontagious so the infection cannot spread further. Unfortunately, antibiotic treatment does not alter the natural course of the illness for those who have already entered the paroxysmal phase of infection. Patients should be aware that the antibiotics will not shorten their illness, and they will continue to cough for as long as 100 days. Individuals with pertussis are most contagious during their first 2 weeks of symptoms. Those who have already been coughing for longer than 3 weeks are no longer contagious and do not require antibiotic treatment.

Pertussis Vaccine

The first pertussis vaccine was developed by pediatrician Leila Denmark in the 1930s in collaboration with Emory University and Eli Lilly and Company using inactivated whole bacterial cells (whole-cell pertussis vaccine). In 1942, whole-cell pertussis vaccine was combined with diphtheria and tetanus toxoids to generate the first DTwP combination vaccine. The "w" is used to indicate that the vaccine immunogens are derived from whole bacterial cells. *B. pertussis* is a Gram-negative organism and, as such, contains lipopolysaccharide (endotoxin) as a component of its cell wall. Traces of endotoxin are present in whole-cell pertussis vaccines, causing them to be quite reactogenic. Most immunized infants develop fever and irritability during the first 48 hours following vaccination, some excessively so. In efforts to reduce the reactogenicity of pertussis vaccine, Japanese scientists developed an acellular vaccine that consisted of highly purified *B. pertussis* proteins. Later formulations of acellular pertussis vaccines were subsequently developed. All formulations included inactivated pertussis toxin in combination with 1, 2, 3, or 4 other purified proteins. All were shown to be effective and less reactogenic than whole-cell formulations. Worldwide, whole-cell pertussis vaccines are still widely used because they are much less expensive than acellular vaccines and provide protection against disease for approximately 10 years. While some acellular vaccines are 85% protective against any cough illness from pertussis infection, the protective efficacy wanes quickly with time. Post-licensure studies indicate that 3 years after completing an acellular pertussis vaccine series, the vaccine's effectiveness declines to less than 75%.

The once taught adage that pertussis vaccination affords 10 years of protection against pertussis infection while natural disease confers lifelong immunity has been disproven because it does not apply to acellular vaccines, and experience has shown that infants who develop natural infection early in life can develop pertussis again as adults.

Vaccines Available in the United States

Monovalent vaccines for pertussis are no longer available for use in the United States. Pertussis vaccination is, therefore, accomplished with combination vaccine formulations that include pertussis immunogens. All of the available formulations of pertussis-containing vaccines also include tetanus and diphtheria toxoids, and some also contain polio, *Haemophilus influenzae* type B, and/or hepatitis B antigens. Table 21.1 includes each of these combinations identified by brand name and manufacturer. In the United States, DTaP acellular pertussis-containing vaccines are recommended as a five-dose series during childhood at 2 months, 4 months, 6 months, 15–18 months, and 4–6 years of age. A dose of TdaP is then recommended at age 11 or 12 years. All adults should receive a single dose of TdaP as part

Table 21.1 Pertussis vaccines currently available in the United States

Combination vaccine	Brand name	Manufacturer	Diseases targeted for prevention
DTaP	Daptacel Infanrix	Sanofi Pasteur GlaxoSmithKline	Diphtheria Tetanus Pertussis
Tdap	Adacel Boostrix	Sanofi Pasteur GlaxoSmithKline	Tetanus Diphtheria Pertussis
DTaP, hepB, IPV	Pediarix	GlaxoSmithKline	Diphtheria Tetanus Pertussis Hepatitis B Polio
DTaP, IPV	Kinrix Quadracel	GlaxoSmithKline Sanofi Pasteur	Diphtheria Tetanus Pertussis Polio
DTaP, IPV, Hib	Pentacel	Sanofi Pasteur	Diphtheria Tetanus Pertussis Polio *Haemophilus influenzae* type b
DTaP, IPV, hepB, Hib	Vaxelis	MSP Vaccine Company	Diphtheria Tetanus Pertussis Polio Hepatitis B *Haemophilus influenzae* type b

of keeping their tetanus vaccination status current. After one dose as an adult, additional doses are recommended for pregnant women during each pregnancy. Beyond that, TdaP or Td can be used every 10 years to maintain immunity against tetanus.

Vaccine Characteristics

Whole-cell inactivated pertussis vaccines were introduced in the 1930s and are still used throughout the developing world today. Acellular pertussis vaccine formulations became widely available in the early 1990s, gradually replacing the use of whole-cell inactivated vaccines in most developed countries. The manufacturing of whole-cell inactivated pertussis vaccine begins with growing a characterized strain of *Bordetella pertussis* in defined bacterial culture medium. Bacteria are killed and detoxified using heat inactivation or chemical treatment. Whole-cell pertussis vaccines are estimated to contain approximately 3000 different antigens. The number of these antigens that serve as immunogens when the vaccine is administered is unknown but likely number in the hundreds.

Table 21.2 Pertussis antigens included in available diphtheria, tetanus, and pertussis combination vaccines in the United States

	Inactivated pertussis toxin	Filamentous hemagglutinin	Pertactin	Fimbrial agglutinins 2 and 3
Daptacel	10 mcg	5 mcg	3 mcg	5 mcg
Pentacel[a]	20 mcg	20 mcg	3mcg	5mcg
Infanrix[b]	25 mcg	25 mcg	8 mcg	NA
Adacel	2.5 mcg	5 mcg	3 mcg	5 mcg
Boostrix	8 mcg	8mcg	2.5 mcg	NA

[a]The pertussis antigenic components are identical in Quadracel and Vaxelis
[b]The pertussis antigenic components are identical in Kinrix and Pediarix

Acellular pertussis vaccines used throughout the world have included between 1 and 5 of the following immunogens: pertussis toxin (inactivated), filamentous hemagglutinin, pertactin, fimbria type 2, and fimbria type 3 (see Table 21.2). The manufacturing process starts with growing a characterized strain of *Bordetella pertussis* in defined bacterial culture media. Subsequent steps are carried out, as needed, depending on which of the five immunogens are to be included in the final vaccine product. Pertussis toxin (inactivated) and filamentous hemagglutinin are produced and released by the bacterium into the culture supernatant. Supernatant is collected and processed to concentrate them. Fimbrial agglutinogens and pertactin are extracted directly from the bacterial cells using heat and flocculation. Each of the pertussis antigens is then precipitated using ammonium chloride and ultrafilter purified. Filamentous hemagglutinin is treated with formaldehyde, and pertussis toxin is inactivated with glutaraldehyde. Residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed separately onto aluminum phosphate as an adjuvant and then combined for use as a bulk stock for the production of acellular pertussis-containing combinations vaccines (e.g., DTaP-HepB-IPV, DTaP-HIB-IPV). Monovalent pertussis vaccine is no longer available for use in the United States.

Additives and Excipients

Acellular pertussis vaccines contain culture medium residuals such as mineral salts, casamino acids and dimethyl-beta-cyclodextrin. Residual amounts of formaldehyde, glutaraldehyde, and/or 2-phenoxyethanol may be detected in the final product as they are used during the manufacturing process prior to a number of purification steps. All acellular pertussis vaccines include an aluminum phosphate salt as an additive at the end of the manufacturing process to serve as the adjuvant.

Contraindications to Vaccine

There are three contraindications to using pertussis-containing vaccines. First, as with all other immunizations, pertussis-containing vaccines are absolutely contraindicated in anyone who has experienced a severe allergic reaction after receiving a previous dose or is known to have a severe allergy to any ingredient in the vaccine. Two other contraindications are unique to pertussis-containing vaccines, including anyone who develops encephalopathy within 7 days of a prior dose of a pertussis-containing vaccine unless another cause (i.e., genetic predisposition) is identified and the presence of any progressive neurologic disorder. Progressive neurologic disorders are those that are continuing to change with time such as infants diagnosed with infantile spasms, uncontrolled epilepsy, or an evolving encephalopathy. Infants and children with neurologic problems that are clearly identified, where treatment regimens have been successful in stabilizing the condition, can be immunized.

Warnings and Precautions for Vaccine Use

Precautions weighing the potential risks and benefits of completing a pertussis vaccine series should be considered in children who developed any of the following conditions within 48 hours of receiving a previous dose: fever of ≥40.5 °C that is not attributable to another cause, a collapse or shock-like condition referred to as a hypotonic-hyporesponsive episode, or persistent and inconsolable crying lasting more than 3 hours. In addition, precautions should be taken when administering vaccine to any child who experienced seizures within 3 days of being vaccinated, whether accompanied by fever or not.

Side Effects and Adverse Events

Vaccine-associated adverse events have already been described for tetanus and diphtheria toxoid-containing vaccines. Please refer to either Chap. 10 or Chap. 29 for a review of the most common adverse events. Moderate- to severe-grade side effects are uncommon. The vast majority are mild, transient, and self-limiting. As with other vaccines given by injection, local injection site reactions are common. Systemic adverse effects are also typically mild and include headache, muscle pain, and fever, all of which can be treated symptomatically with over-the-counter pain relievers and fever reducers.

Vaccine Efficacy

Newer clinical vaccine trials have relied on the immunogenicity profiles for each of the pertussis antigens included in a given vaccine. While immunogenicity is reassuring that the patient's immune system recognized and responded to the vaccine immunogens, the serologic correlate(s) of immunity to pertussis are unknown. Most experts agree that robust responses to pertussis toxin are necessary but perhaps insufficient for complete protection. Clinical vaccine trials that were performed during outbreaks of pertussis infection indicated some differences in vaccine efficacy based on the formulation of the vaccine used with overall rates of protection of between 75% and 85%. Clinical trial results and real-world experience indicate that current acellular pertussis vaccines are highly immunogenic and quite effective in preventing disease following exposure. This protective efficacy, however, declines much more rapidly than seen with other vaccines. Efforts to maintain a robust initial immune response but to provide a more durable protective response are ongoing in clinical trials using new formulations and novel adjuvants.

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U.S. Centers for Disease Control and Prevention:

Vaccine Information Sheet

World Health Organization

https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/pertussis/en/

U.S. Centers for Disease Control and Prevention

https://www.cdc.gov/tetanus/index.htm

Vaccine Information Sheets

https://www.cdc.gov/vaccines/hcp/vis/visstatements/dtap.html
https://www.cdc.gov/vaccines/hcp/vis/vis-statements/tdap.html
https://www.cdc.gov/vaccines/hcp/vis/vis-statements/td.html

FDA Approved Package Inserts

Daptacel

https://www.fda.gov/vaccines-blood-biologics/vaccines/daptacel

DT Vaccine

https://www.fda.gov/media/119411/download

Infanrix

https://www.fda.gov/vaccines-blood-biologics/vaccines/infanrix

Kinrix

https://www.fda.gov/vaccines-blood-biologics/vaccines/kinrix

Pediarix

https://www.fda.gov/media/79830/download

Pentacel

https://www.fda.gov/media/74385/download

Quadracel

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Tenivac

https://www.fda.gov/media/76610/download

Vaxelis

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Adacel

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Chapter 22
Plague

Cynthia Bonville and Joseph Domachowske

Plague

Etiology

Historically, plague is a well-known cause of pandemics associated with high rates of mortality. The infection is caused by the Gram-negative bacterium *Yersinia pestis*. Three main forms of the disease are recognized, bubonic, septicemic, and pneumonic plague. The incubation period is typically 2–4 days with a range of 1–7 days.

Epidemiology

Y. pestis is naturally distributed worldwide due to its presence in enzootic cycles between fleas and rodents. When human living conditions inadvertently encourage closer interactions between rodents and humans, outbreaks of infection can be seen. Across urban settings, this occurs with overcrowding, especially in impoverished settings. In poor rural areas, the practices of clearing land and storing crops in or near living quarters encourage rodents to move closer to human dwellings. The World Health Organization identifies plague as an internationally notifiable disease. Since the 1990s, epidemics of plague have been described in Asia, South America, and Africa. The most highly endemic region of the world between 2013 and 2018 was the island country of Madagascar where more than 2300 cases and hundreds of deaths from plague were reported. Other areas of the world reporting significant

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numbers of cases during this period included the African nations of the Democratic Republic of Congo (n = 410), Tanzania (n = 36) and Uganda (n = 22), the South American country of Peru (n = 40), and the United States (n = 40) (Fig. 22.1).

The region of the world identified as having the greatest enzootic presence of *Y. pestis* is the Western United States where the pathogen cycles between fleas and most species of wild rodents across a large geographical area. Other animals native to this area that are known to harbor *Y. pestis* include black bears, mountain lions, coyotes, foxes, raccoons, skunks, wolves, mule deer, pronghorn antelope, and domestic dogs, cats, and pigs. Epizootics are seasonal, occurring during cooler summers preceded by wet winters. The highest endemicity is found throughout the Colorado Plateau, a mostly rural, semiarid upland forest and grasslands region roughly centered at the point where Arizona, New Mexico, Utah, and Colorado meet to form the Four Corners. The Colorado Plateau is home to nine national parks, including the Grand Canyon, Zion, Mesa Verde, and Petrified Forest. From the Colorado Plateau, the endemicity of *Y. pestis* extends into Southern California, Oregon, and Western Nevada. A less dense enzootic presence continues into Western Texas, Western Oklahoma, Wyoming, Idaho, Montana, and Washington. Despite this widespread, naturally occurring distribution of *Y. pestis,* relatively few human cases are reported (Fig. 22.2)**.** Taken together, California and the Four Corner states of New Mexico, Arizona, Colorado, and Utah account for 93% of all reported cases of human plague.

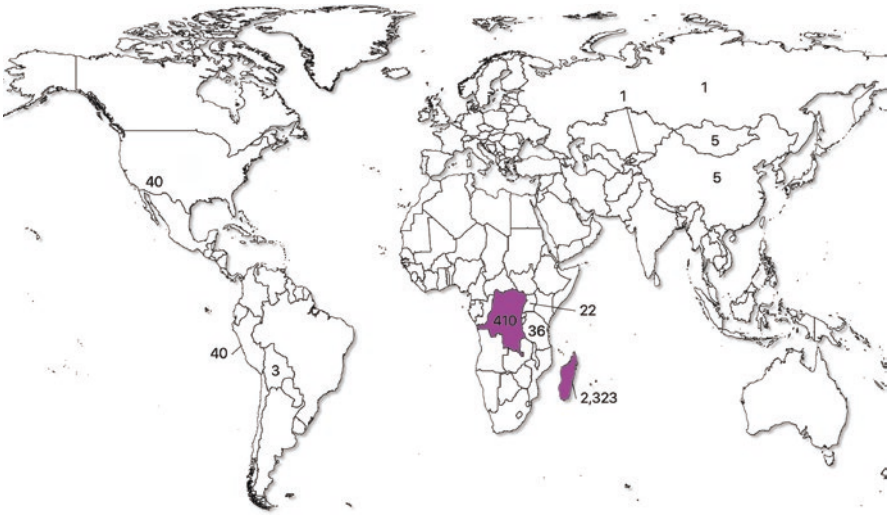

Fig. 22.1 This world map shows the total number of human plague cases reported by each country to the World Health Organization between 2013 and 2018. The Democratic Republic of the Congo and the island nation of Madagascar are highlighted. Together they accounted for 95% of all reported cases during this period of time. (Source: https://www.who.int/health-topics/plague#tab=tab_1)

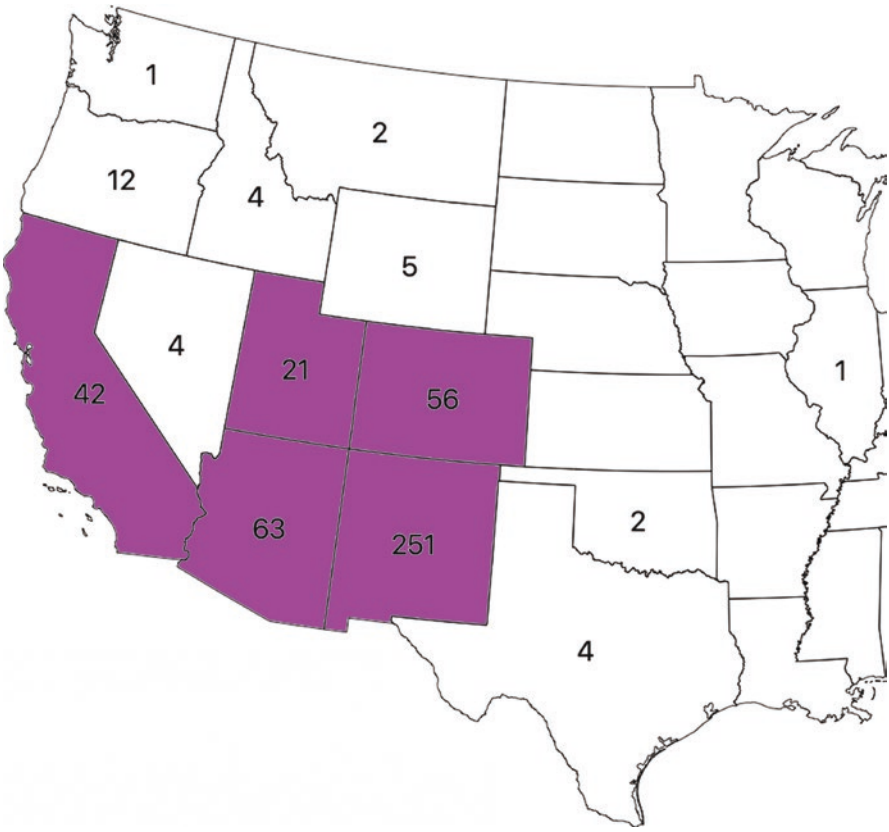

Fig. 22.2 This map of the Western United States shows the number of human cases of plague reported by each state to the US Centers for Disease Control and Prevention between 1965 and 2012. New Mexico, Arizona, Colorado, California, and Utah are highlighted. Together they accounted for 93% of all reported cases during this period of time. The single case from Illinois was laboratory transmitted. (Source of data used to generate the original figure: Centers for Disease Control and Prevention https://www.cdc.gov/plague/maps/index.html)

Transmission

Plague is a zoonotic disease that is only occasionally transmitted to humans. Paul-Louis Simond first linked the transmission of infection to fleas in 1898. The understanding that *Y. pestis* was maintained in a reservoir by cycling between wild rodents and their fleas was first appreciated circa 1914. Natural enzootic cycles occur in areas with low annual precipitation, such as deserts, semideserts, savannas, prairies, and pampas. The enzootic cycle is maintained across relatively resistant rodent host populations where *Y. pestis* circulates at low rates with minimal rodent morbidity or mortality. The fleas and their rodent hosts function as long-term bacterial reservoirs. In contrast, epizootic cycles represent periods of bacterial amplification. *Y. pestis* circulates at high rates causing extensive rodent

mortality. Disease in larger wild mammals, humans, and their pets typically follow epizootics with significant rodent deaths as infected fleas seek out blood meals from alternate hosts.

The symbiotic relationship between the flea and *Y. pestis* is parasitic rather than commensal like most arthropod vector pathogens. As bacteria replicate in the midgut of the flea, they produce a biofilm across the proventriculus separating the flea's esophagus and stomach. Blood meals taken by the flea are restricted from entering the stomach. Starvation triggers increased biting behavior by the flea. During attempts to feed, blood mixes with bacteria in the flea's esophagus and is regurgitated into the bite wound, thereby transmitting the infection.

The oriental rat flea, *Xenopsylla cheopis*, is the principal vector for transmitting *Y. pestis*. It is very common in the environments and habitats of rodent hosts but not specific for them. Larger wild and domestic animals and humans are accidental hosts. At least 30 other species of flea are also capable of transmitting plague including the human flea, *Pulex irritans*, and the cat flea, *Ctenocephalides felis*.

When *Y. pestis* is transmitted to humans by the bite of an infected flea, bacteria enter at the site of the bite and migrate via lymphatic vessels to the regional lymph nodes (bubonic plague). Transmission also occurs following direct contact with infected animals or contaminated tissues or fluid. Bacteria enter through breaks in the skin and migrate to the bloodstream (septicemic plague). Human-to-human and animal-to-human transmission can also occur by inhaling aerosolized droplets generated by a person or animal with pneumonic plague.

Clinical Presentation

The sequence of clinical manifestations from plague depends on its route of transmission. The bubonic, septicemic, and pneumonic forms of plague each have defining characteristics, with substantial overlap in presenting features. Bubonic plague is the most common form, accounting for 80–85% of all cases. Following the bite of an infected flea, the patient develops abrupt onset of fever, chills, headache, body aches, and extreme fatigue. Swollen, painful lymph nodes called buboes appear proximal to the inoculation site, often in the groin, axillae, or neck. Infected lymph nodes may drain purulent material. Failure to recognize and treat early in the course of the disease can result in hematogenous spread and development of septicemic plague. Septicemic plague also occurs following the bite of an infected flea. High fever and extreme fatigue progress rapidly to the signs and symptoms of septic shock. Bacterial endotoxins trigger disseminated intravascular coagulation which can lead to life-threatening bleeding and/or gangrenous necrosis of end perfusion sites such as fingers, toes, nose, and ears. This complication is the origin of the term "Black Death" used to describe epidemic plague during the fourteenth century. Pneumonic plague accounts for 3% of cases. It occurs following the inhalation of infectious droplets generated by infected individuals or animals. Symptoms include high fever, chills, and asthenia with rapidly progressing pneumonia. Patients develop

cough, hemoptysis, and difficulty breathing that leads rapidly to respiratory failure. If not recognized and treated quickly, pneumonic plague is nearly 100% fatal.

Management

Early recognition and the prompt initiation of antibiotic treatment are the two most essential components in the management of plague. Close attention to antibiotic susceptibility test results is very important as multidrug-resistant strains of *Y. pestis* are being reported from large outbreak areas. Short incubation periods and rapid progression to respiratory failure and sepsis are poor prognostic indicators. Infected patients remain contagious for up to 72 hours after starting appropriate antibiotic treatment.

Antibiotic treatment regimens that are currently recommended by the US Centers for Disease Control and Prevention include intravenous gentamicin or fluoroquinolone for 10–14 days or until 2 days after the fever breaks. Oral antibiotics can be used to complete the 10- to 14-day course in patients well enough to be discharged from the hospital. Pneumonic plague is highly contagious. Individuals who have had close contact with a person diagnosed with pneumonic plague in the last 7 days should be treated with postexposure antibiotic prophylaxis for 1 week. Options include doxycycline, ciprofloxacin, and levofloxacin. After completing 7 days of antibiotic prophylaxis, exposed individuals should undergo twice daily temperature monitoring for another 7 days and seek medical care if fever develops.

The management of plague outbreaks is especially challenging. Flea vector control is a critical component of the early response. The source of the outbreak needs to be identified and eliminated by searching for clusters of small mammal deaths and instituting small mammal control. The order of action is critical, since rapid and aggressive rodent control will drive fleas to alternate hosts including humans and domestic animals.

Plague Prevention

Throughout endemic regions, individuals and communities need to pay close attention to ensuring that their homes, buildings, and surrounding areas are rodent-free. A sustained effort to eliminate potential rodent nesting places by removing brush, rock piles, trash, and excess firewood can be remarkably successful. Hunters, trappers, butchers, and taxidermists should avoid touching or handling the skins, hides, or flesh of dead or ill animals without wearing gloves. Sick or dead animals should be reported to local health departments or law enforcement so they can be removed safely and tested if necessary. Squirrels, chipmunks, and other rodents should not be fed. Those who work or enjoy recreational activities outdoors should use a DEET (N,N-diethyl-meta-toluamide)-containing insect repellent to avoid flea bites. Pet

dogs and cats should routinely be treated for fleas and be seen by a veterinarian when sick. Pet food should be kept in rodent-proof containers. Allowing pets to sleep in the same bed with a family member is a known risk factor for contracting plague, so it should be avoided.

Individuals planning travel to plague endemic regions should be aware of the risks, potential outcome of infection, and lack of a commercially available vaccine. Travelers should use insect repellent during outdoor activities and seek prompt medical advice if symptoms develop. Up-to-date information, including current travel alerts, can be found on the International Association for Medical Assistance to Travelers (IAMAT) website at https://www.iamat.org/risks/plague.

Plague Vaccine

Historically, several formulations of live attenuated whole cell vaccines were once available in different parts of the world. Inactivated whole cell vaccines emerged later, including one derived from formaldehyde inactivated *Y. pestis* strain 195/P that was approved for use in the United States between 1946 and 1999. It was used to immunize more than a million US servicemen being deployed to Vietnam but was discontinued in 1999 due to diminished interest, high reactogenicity, and suboptimal immunogenicity of short duration. A similar vaccine formulation, using heat-killed *Y. pestis* 195/P strain, was licensed for use in Australia until 2005.

Currently, the WHO does not recommend immunization with any of the old-generation vaccines and does not recognize any formulation to be prequalified. Recent disease activity, including the ongoing plague outbreak in Madagascar where multidrug-resistant infections have emerged, and the potential for using *Y. pestis* as an agent of bioterrorism have renewed interest in developing safe and effective plague vaccines. In 2019, the WHO registered 17 different vaccine candidates under development.

Types of Vaccines Available in United States

Currently, no licensed vaccines against plague are available for human use in the United States; however, on March 8, 2017, the US Food and Drug Administration granted DynPort Vaccine Company LLC “Orphan Drug Designation” for its recombinant rF1V vaccine formulation. Orphan Drug Designation provides important incentives to support the development of products for rare diseases. The vaccine is being developed as part of the US Department of Defense’s countermeasure armamentarium against agents of bioterrorism. The vaccine is intended to be administered to individuals considered to be at high risk for exposure to aerosolized *Y. pestis*. The rF1V vaccine was originally developed by scientists at the US Army Medical Research Institute of Infectious Diseases (USAMRIID).

Immunizing Antigen

The antigen used in the vaccine is a fused recombinant protein referred to as rF1V. The coding sequences for *Y. pestis* F1 capsular and virulence (V) proteins were cloned into *E. coli*. Recombinant *E. coli,* expressing the fused rF1V protein, are grown in a defined bacterial liquid culture medium. rF1V that is isolated and purified from cultures is formulated with a 2% aluminum hydroxide wet gel suspension as an adjuvant to produce the immunogen for the final vaccine product. Labeling information for the rF1V vaccine describing its safety and immunogenicity profile is not yet available.

Plague is an uncommon life-threatening infection in humans. Existing prevention measures include avoiding flea bites and reducing the potential for exposure to rodents. The epidemiology is well described, and individuals at increased risk are easily identified. The emergence of multidrug resistance in *Y. pestis* and concerns regarding its potential use as an agent of bioterrorism have reinvigorated efforts to develop safe and effective vaccines.

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Chapter 23
Pneumococcus

Cynthia Bonville and Joseph Domachowske

Streptococcus pneumoniae Infection

Etiology

Pathogenic strains of *Streptococcus pneumoniae* are encapsulated Gram-positive bacteria that grow in laboratory cultures in short chains and lancet-shaped diplococci. The organism's polysaccharide capsule is its single most important virulence factor due to its ability to evade innate host defense mechanisms by preventing mucociliary trapping, facilitating adherence to and colonization of the nasopharynx, and blocking antibody bonding, thereby preventing opsonization and phagocytosis. At least 98 capsular serotypes have been recognized, each one independently recognized by the host immune system. All pneumococcal serotypes are capable of causing invasive disease, but the ten most commonly isolated from individuals with serious infections account for more than 60% of invasive infections worldwide. Nasopharyngeal colonization with one or more strains of *S. pneumoniae* can be detected in approximately 25% of healthy individuals at any given time.

Global Epidemiology

Invasive pneumococcal infections occur worldwide. Disease prevalence and the distribution of the infecting serotypes differ across populations and geographical areas. Globally, among children less than 5 years of age, there are an estimated 14.5 million cases and 1 million deaths from invasive pneumococcal disease (IPD) each

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year. Case fatality rates are highest in low-income countries. The disease burden is especially high across much of Africa where conditions of poverty, malnutrition, and lack of access to healthcare contribute to all causes of morbidity and mortality. Pneumococcal disease is especially common in populations with high rates of infection with human immunodeficiency virus. In 2015, mortality rates from invasive pneumococcal infection in children less than 5 years of age exceeded 200 per 100,000 in the African nations of Chad, Somalia, and Angola. The six countries reporting mortality rates between 100 and <200 per 100,000 included Afghanistan, Central African Republic, the Democratic Republic of the Congo, Guinea, Niger, and Nigeria. *S. pneumoniae* is classified by the World Health Organization as one of the top 12 bacterial pathogens in need of prioritized research.

Epidemiology in the United States

S. pneumoniae is responsible for causing an estimated 4 million infections and 22,000 deaths each year in the United States. Mild to moderate middle ear and sinus infections are especially common in children. Outpatient visits for acute otitis media alone account for more than 18 million pediatric medical visits each year. *S. pneumoniae* remains a leading cause of bacterial pneumonia, bacteremia, and meningitis across all age groups. Each year, an estimated 1.2 million antibiotic-resistant infections result in 19,000 excess hospitalizations and 7000 deaths. Invasive pneumococcal disease is a nationally notifiable disease.

Transmission

Humans are the only known reservoir for *S. pneumoniae.* The organism resides on the mucosal surfaces of the nasopharynx as part of the normal human microbiome. Nasopharyngeal colonization rates as high as 85% are seen among preschool-aged children and then slowly decline with age until reaching a nadir of ~20% in older adults. Human-to-human transmission occurs through direct contact and via large droplets. The majority of exposures result in transient asymptomatic nasopharyngeal carriage of the newly acquired serotype. A minority result in more sustained colonization, and even fewer go on to cause a local upper respiratory infection. More serious illnesses develop when a combination of host factors and bacterial virulence factors merges to create conditions favorable for the bacteria to invade. Since preschool-aged children have the highest rates of nasopharyngeal colonization with pneumococcus, they represent the primary vectors of transmitting new bacterial serotypes to their close contacts at home and in their communities.

Host factors that increase susceptibility to invasive disease include underlying disorders of immune function and any conditions that disrupt the integrity or

function of the mucociliary escalator. Such conditions include a current or recent viral respiratory tract infection, especially from influenza, preexisting chronic lung disease, and exposure to irritants or pollutants like cigarette smoke or oils used for vaping. Recent nasopharyngeal acquisition is a prerequisite for invasive disease since colonization lasting more than 3 weeks is sufficient for the development of local immunity, including protection from serotype-specific immunoglobulin A. When host defenses are down, newly acquired bacterial serotypes can either invade the bloodstream directly across injured respiratory epithelium or disseminate to the lower respiratory tract to cause pneumonia. Invasive disease is most common among children <2 yrs of age (underdeveloped, naïve immune system), adults >65 years of age (immune senescence, comorbidities), and individuals who are immunocompromised.

Clinical Presentation

S. pneumoniae is a common cause of bacterial conjunctivitis, otitis media, mastoiditis, sinusitis, pneumonia, pleural empyema, bacteremia, and meningitis across all age groups and in all areas of the world. Less common serious disease manifestations include osteoarticular infections, purulent pericarditis, spontaneous bacterial peritonitis, and deep tissue or organ abscess. Invasive infection is also an uncommon trigger for the development of hemolytic uremic syndrome. Hemolytic uremic syndrome is a life-threatening illness characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and uremia that is epidemiologically more closely tied to recent infections from Shiga-like toxin producing strains of *Escherichia coli*.

Community-Acquired Bacterial Pneumonia

S. pneumoniae is the most common cause of community-acquired bacterial pneumonia in all groups beyond the newborn period. The disease burden is greatest among those aged ≥65 years. Following a 2- to 3-day incubation period, symptom onset is abrupt starting with fever and chills. Sudden, often intense, pleuritic chest pain that worsens with deep inhalation or coughing may have a sharp, stabbing, or burning quality. The cough is productive of rust-colored sputum except in young children. As the illness progresses, patients become tachypneic and may complain of shortness of breath. Serious infections can lead to hypoxemia and respiratory failure. Complications include the development of parapneumonic effusions or empyema, necrotizing pneumonia, respiratory failure, and death. Approximately 25% of infected patients become bacteremic. Pneumococcal pneumonia has an overall mean case fatality rate of 5–7%. The risk of death is highest at the extremes of age.

Pneumococcal Bacteremia

The majority of adults who are found to have pneumococcal bacteremia have an obvious sinopulmonary source of infection with the expected associated symptoms. In contrast, most young children with pneumococcal bacteremia present with fever but no obvious anatomic focus of infection. Worldwide, pneumococcal sepsis with bacteremia accounts for 1 in every 100 childhood deaths under 5 years of age. At any age, without prompt treatment, pneumococcal bacteremia has the potential to seed distant sites such as the meninges, bones, joints, and peritoneum.

Pneumococcal Meningitis

Pneumococcal meningitis can develop as a complication of bacteremia with hematogenous spread to the meninges, from contiguous spread of a nearby infection or by invasion via a congenital or acquired anatomic defect. Patients develop fever in association with headaches, neck stiffness, irritability, lethargy, photophobia, and/or vomiting. Acute complications include seizures, focal neurologic deficits, and coma. Permanent neurologic sequelae including sensorineural hearing loss, cognitive deficits, chronic seizure disorder, and global developmental delay occur in up to 58% of survivors. The case fatality rates are approximately 8% in children and 22% in adults. Factors known to increase the risk of invasive pneumococcal infection are shown in Table 23.1.

Management

Infections caused by *S. pneumoniae* require treatment with antibiotics. Appropriate initial empiric treatment options depend on the location and severity of the infection. When culture and susceptibility results are available from the microbiology laboratory, therapy can be adjusted accordingly. Prior to 1990, nearly all *S. pneumoniae* isolates from human infections were susceptible to penicillin. Penicillin and

Table 23.1 Factors associated with an increased risk for invasive pneumococcal disease

Intrinsic	Medical conditions	Behavioral and environmental
African American	HIV infection[a]	Daycare attendance
Alaskan Native	Asplenia[a]	Excessive alcohol use
Native American White Mountain Apache	Chronic heart, lung, liver, or kidney disease, diabetes	Cigarette smoking, exposure to second-hand smoke
Native American Navajo	Recent influenza infection	Incarceration
Age < 5 yrs old	Hypogammaglobulinemia	Homelessness, homeless shelter
Age ≥ 65 yrs old	CSF fluid leaks, cochlear implants	Unvaccinated

CSF cerebrospinal fluid
[a]In children, risk increases 50-fold

multiple drug resistance emerged during the 1990s, spreading rapidly across the United States and other parts of the world. By 2000, 40% of *S. pneumoniae* identified in clinical microbiology laboratories demonstrated resistance to one or more antibiotic class, most notably including penicillins and/or macrolides. Rates of antibiotic resistance stabilized and then began to decline following the introduction of conjugate pneumococcal vaccine to the universal childhood immunization schedule beginning in 2000. Subsequent changes to the definition of and interpretation guidelines for penicillin non-susceptibility in 2008 also influenced overall rates of reported resistance, which have declined from 40% to less than 30% in most parts of the United States. Antibiotic resistance is associated with increased healthcare costs due to persistent or recurrent disease from treatment failures, increased hospitalizations for the treatment of stubborn infections and their complications, the necessity to use more expensive antibiotics, and the need to develop and maintain surveillance systems to track resistance patterns. Additional time and resources are also needed to inform and educate patients, providers, microbiologists, and pharmacists on important aspects of judicious and appropriate antibiotic use.

Pneumococcal Vaccines

In the United States, efforts to refine the effectiveness of heat-killed whole cell bacterial vaccines used between 1909 and the mid-1930s and the first polysaccharide vaccines used during the 1930s and 1940s were halted as newly discovered, highly effective antibiotics became widely available. By the early 1950s, due to the lack of demand for vaccine, the manufacturer had ceased production and then subsequently withdrew their license voluntarily. By the early 1970s, interest in pneumococcal vaccines for the prevention of pneumococcal pneumonia in adults was reinvigorated, ultimately leading to the licensure of Pneumovax in November 1977. Pneumovax was Merck Sharp & Dohme's original 14-valent pneumococcal polysaccharide vaccine (PPSV) that included capsular serotypes 1, 2, 3, 4, 6A, 7F, 8, 9 N, 12F, 14, 18C, 19F, 23F, and 25F. It was introduced in the United States and Europe for use in adults aged ≥50 years and those aged ≥2 years with high-risk underlying chronic medical conditions. In July 1983, the manufacturer of Pneumovax gained licensure for their expanded 23-valent formulation of PPSV under the new brand name, Pneumovax 23 (Table 23.2). While the new formulation included capsular antigens directed against more serotypes, the pure polysaccharide nature of the antigens continued to offer the same limitations of the 14-valent PPSV. First, all pure polysaccharide vaccines are processed in a T-cell-independent manner. The vaccine-induced B-cell response results in short-term (2–5 years) production of antibody without the usual T-cell help to undergo affinity maturation or to develop long-term immune memory. Subsequent doses of pure polysaccharide vaccine do not, therefore, offer any boosting of preexisting immunity. Additional disadvantages of pure polysaccharide vaccines are their inability to induce protective immune responses in children less than 2 yrs of age and their lack of effect on

Table 23.2 Pneumococcal vaccines used in the United States, 1977–2020

Vaccine type	Brand name	Dates used	Number of serotypes	Serotypes included
PPSV	Pneumovax	1977–1983	14	1, 2, 3, 4, 6A, 7F, 8, 9N, 12F, 14, 18C, 19F, 23F, 25F
	Pneumovax 23	1983–today	23	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F
PCV	Prevnar	2000–2010	7	4, 6B, 9V, 14, 18C, 19F, 23F
	Prevnar 13	2010–today	13	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F

[a]*PPSV* pneumococcal polysaccharide vaccine, *PCV* pneumococcal conjugate vaccine

nasopharyngeal carriage in all age groups due to the lack of immunoglobulin class switching to produce secretory IgA.

A safe and effective multivalent pneumococcal vaccine for use in children starting as young as 6 weeks of age first became available in February 2000 with the FDA approval of Wyeth Laboratories 7-valent product marketed under the brand name Prevnar. The immunizing antigens in Prevnar included capsular polysaccharides from pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F (Table 23.2), but instead of using them as pure polysaccharide antigens, they were each covalently linked to a protein. The process, called conjugation, changes the manner in which the polysaccharide antigen is presented to the immune system from a T-cell-independent pathway to a T-cell-dependent pathway. The result is a conjugate vaccine with the full advantages of T-helper cell engagement. The protein conjugate used to manufacture Prevnar is CRM_{197}, so named because it was number 197 among many other "*c*ross-*r*eacting *m*aterials" that were identified during a search for nontoxigenic variants of diphtheria toxin. The CRM_{197}-conjugated polysaccharide antigens in Prevnar, like the antigens in other conjugated polysaccharide vaccines, induce robust T-cell-dependent immune responses in infants as young as 6 weeks of age, with development of immune memory, the ability to boost with subsequent doses, and high-level affinity maturation of IgG with ability to class switch to IgA. The ability to begin immunizing at a much younger age is critically important since invasive infections from *S. pneumoniae* are so common among children less than 2 yrs of age. In 2000, when Prevnar first became available, the seven antigens included covered up to 80% of the pneumococcal serotypes responsible for invasive infections in US children and more than 90% of serotypes that had already developed resistance to penicillin. The vaccine was recommended by the ACIP as a four-dose series for universal use starting at 2 mos of age the same year. Within 1 year, the incidence of all-cause IPD in children less than 5 yrs of age declined by 48% (Fig. 23.1). Early on, vaccine shortages restricted vaccine availability, yet by 2005 the incidence of IPD had gone from 79 to 22 cases per 100,000, a decline of 72%. Despite the impressive decline in disease burden, the emergence of highly virulent infections caused by non-vaccine serotypes 6A, 15, and 19A raised concerns about the growing impact of "replacement disease." Infections caused by

serotype 19A were of special concern due to the stain's development of high-level, multidrug antibiotic resistance. In 2010, the FDA approved Wyeth Laboratories Prevnar 13 vaccine, an expanded formulation of Prevnar that included six additional conjugated polysaccharides including 6A and 19A (Table 23.2). Children who began their PCV series with Prevnar were recommended to complete their series with Prevnar 13, and all children under age 5 yrs who had completed the Prevnar vaccine series were recommended to receive a single booster dose of Prevnar 13. From the year that Prevnar was approved (2000) to 2016, the overall incidence of IPD declined from 79 to 9 cases per 100,000, an overall reduction of 89%. Over the same period of time, IPD caused by serotypes included in the vaccine declined by 97%, from 72 to 2 cases per 100,000 (Fig. 23.1). The public health benefits of routinely vaccinating young children against IPD extended to adults between the ages of 19 and 64 (Fig. 23.2) and among those 65 yrs and older (Fig. 23.3). In the prevaccination era, nasopharyngeal colonization with pneumococcus was detected in up to 85% of preschool-aged children. Routine childhood vaccination has nearly eliminated nasopharyngeal colonization with vaccine serotypes, thereby removing a major reservoir of the pathogen resulting in a herd immunity effect.

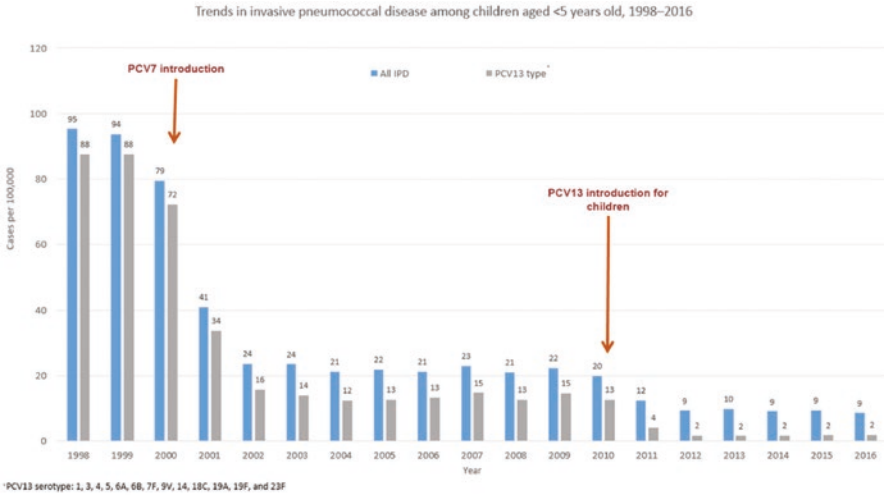

Fig. 23.1 Shown are changes in the incidence of invasive pneumococcal disease (IPD) among children <5 years old from 1998 to 2016 in the United States. Blue bars represent overall IPD incidence, while the gray bars represent IPD incidence caused by serotypes included in the 13-valent pneumococcal conjugate vaccine (PCV13). Pneumococcal 7-valent conjugate vaccine (PCV7) was introduced for use among children <5 years old in 2000. PCV13 was introduced for use among children <5 years old in 2010. The overall IPD incidence declined from 95 cases per 100,000 in 1998 to 9 cases per 100,000 in 2016; IPD caused by PCV13 serotypes declined from 88 cases per 100,000 in 1998 to 2 cases per 100,000 in 2016. (Source: Centers for Disease Control and Prevention. The data are available on the agency website at no charge: https://www.cdc.gov/pneumococcal/surveillance.html. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the US Government, Department of Health and Human Services, or Centers for Disease Control and Prevention)

Since the introduction of Prevnar 13, challenges with infections caused by replacement pneumococcal serotypes have become less problematic; however, increased rates of colonization and recent reports of invasive infections caused by the non-vaccine serotype 35B are being monitored carefully.

The availability of two formulations of pneumococcal vaccines for use in older children and adults has led to a series of recommendations from ACIP on how to best use them, especially since they differ in the number of serotypes included and the manner by which they are processed by the immune system. A summary of these recommendations is shown in Table 23.3**.** Current, detailed recommendations can be found at https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html. When both vaccines are recommended to be given in series, the PCV-13 dose or series of doses should be administered first. When more than one dose of PCV-13 is recommended, doses should be separated by at least 4 weeks. When PPSV is recommended to be given following PCV-13, the minimum dose interval is 8 weeks.

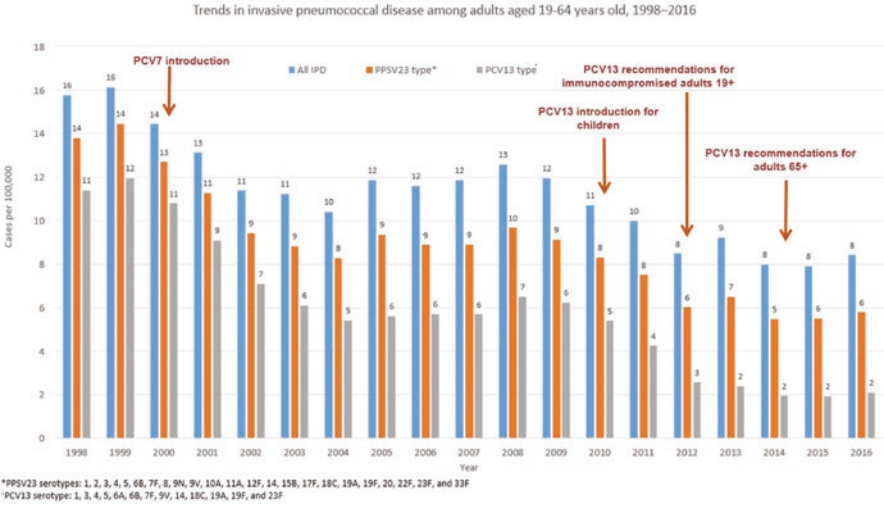

Fig. 23.2 Shown are changes in the incidence of invasive pneumococcal disease (IPD) among adults 19 through 64 years of age from 1998 to 2016 in the Unites States. Blue bars represent overall IPD incidence, orange bars represent IPD incidence caused by serotypes included in the 23-valent pneumococcal polysaccharide vaccine (PPSV23), and gray bars represent IPD incidence caused by serotypes included in the 13-valent pneumococcal conjugate vaccine. PPSV23 has been available since 1984 and recommended for all adults 65 years or older and for people 2 years or older with chronic medical conditions. Pneumococcal 7-valent conjugate vaccine (PCV7) was introduced for use among children <5 years old in 2000. Pneumococcal 13-valent conjugate vaccine (PCV13) was introduced for use among children <5 years old in 2010, for adults 19 years or older with immunocompromising conditions in 2012, and for all adults 65 years or older in 2014. (Source: Centers for Disease Control and Prevention. The data are available on the agency website at no charge: https://www.cdc.gov/pneumococcal/surveillance.html. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the US Government, Department of Health and Human Services, or Centers for Disease Control and Prevention)

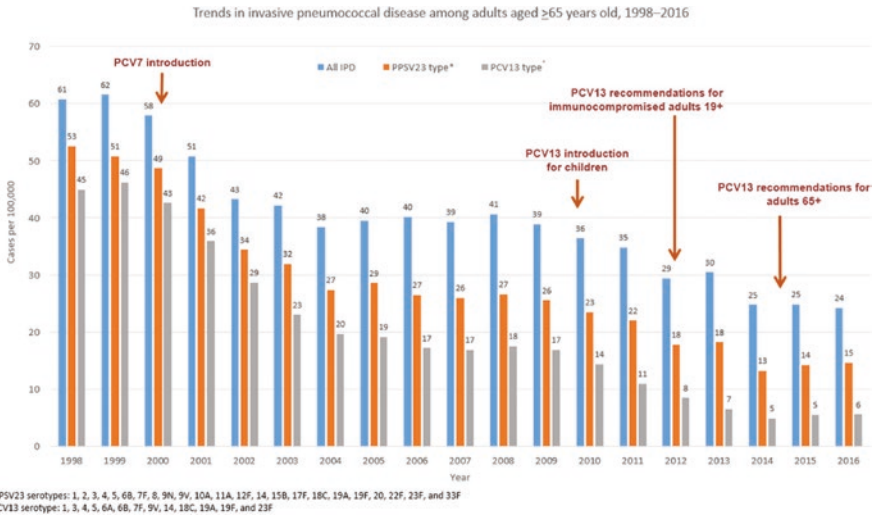

Fig. 23.3 Shown are changes in the incidence of invasive pneumococcal disease (IPD) among adults 65 years or older from 1998 to 2016 in the United States. Blue bars represent overall IPD incidence, orange bars represent IPD incidence caused by serotypes included in 23-valent pneumococcal polysaccharide vaccine (PPSV23), and gray bars represent IPD incidence caused by serotypes included in the 13-valent pneumococcal conjugate vaccine (PCV13). (Source: Centers for Disease Control and Prevention. The data are available on the agency website at no charge: https://www.cdc.gov/pneumococcal/surveillance.html. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the US Government, Department of Health and Human Services, or Centers for Disease Control and Prevention)

When more than one dose of PPSV is recommended, doses should be separated by 5 years or longer.

US Pediatric Immunizations

The 13-valent pneumococcal conjugate vaccine, PCV-13, is marketed in the United States by Pfizer Incorporated under the brand name Prevnar 13. Each 0.5 mL dose contains 2.2 μg of serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F saccharides and 4.4 μg of serotype 6B saccharide each individually conjugated to the CRM_{197} carrier protein. The vaccine is administered as a 0.5 mL dose via the intramuscular route. It is available in single-dose prefilled syringes. No dilution of reconstitution is needed. The vaccine should be stored between 2°C and 8°C. A summary of current ACIP recommendations for its use can be found in Table 23.3. The recommended universal pediatric vaccine series includes four doses given at 2, 4, 6, and 12 to 15 months of age.

Table 23.3 A summary of current recommendations for using pneumococcal vaccines

Age	Year[a]	Vaccine(s)	Indication(s)
≥ 65 yrs	1983	PPSV	Universal
2–64 yrs	1997		Chronic heart, lung, liver, kidney disease
			Alcoholism
			Diabetes
			CSF leaks
			Sickle cell disease, hemoglobinopathies
			Asplenia
			Malignancy
			HIV infection
			Solid organ transplantation
			Alaskan Natives
			Native Americans
19–64 yrs	2010	PPSV-23	All of the above *and*
			Cigarette smoking
			Cochlear implant
			Inherited or acquired immunodeficiencies
≤ 5 yrs	2010	PCV-13	Universal
2–18 yrs		PCV-13 and then PPSV-23	Asplenia
			Inherited or acquired immunodeficiencies
			CSF leaks
			Cochlear implant
			Chronic heart or lung disease
			Diabetes
≥ 19 yrs	2012	PCV-13 and then PPSV-23	CSF leaks
			Cochlear implant
			Sickle cell disease, hemoglobinopathies
			Asplenia
			Inherited or acquired immunodeficiencies
			Chronic renal disease, nephrotic syndrome
			Malignancy
			Solid organ transplantation
		PPSV only	Chronic heart or lung disease
			Diabetes
			Chronic liver disease, alcoholism
			Cigarette smoking
6–18 yrs	2013	PCV-13 and then PPSV-23	Same indications recommended in 2012 for individuals ≥19 yrs listed above
		PPSV only	
≥ 65 yrs	2014	PCV-13 and then PPSV-23	Universal category A recommendation
	2019	PCV-13 and then PPSV	Universal use for healthy people ≥65 yrs changed to category B recommendation[b]; use in immunocompromised unchanged

[a]Year of most recent ACIP recommendations

[b]Category B recommendation indicates shared clinical decision-making in lieu of universal vaccination

US Adult Immunizations

The 23-valent pneumococcal polysaccharide vaccine, PPSV-23, is marketed in the United States by Merck Sharp & Dohme Corporation under the brand name Pneumovax 23. The 0.5 mL dose of Pneumovax 23 contains 25 mcg of each polysaccharide antigen (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F) in an isotonic saline solution. A summary of current ACIP recommendations for its use can be found in Table 23.3. The vaccine is administered as a 0.5 mL dose via the subcutaneous or intramuscular route. It is available in single-dose prefilled syringes, single-dose vials, and multidose (five-dose) vials ready for use. No dilution of reconstitution is needed. The vaccine should be stored between 2°C and 8°C.

Immunizing Antigens, Adjuvants, Excipients, or Preservatives

Each of the desired capsular serotypes of *S. pneumoniae* is grown separately in soy peptone liquid culture medium. Capsular polysaccharides are collected and purified. For Pneumovax 23, the polysaccharides are combined in an isotonic saline solution, and phenol is added at 0.25% as a preservative. For Prevnar 13, individual saccharides are directly conjugated to CRM_{197} using reductive amination to form the 13 different glycoconjugates. The individual glycoconjugates are adsorbed to aluminum phosphate as the adjuvant and formulated in a stabilizing buffer containing 100 mcg polysorbate 80 and 295 mcg of succinate. Prevnar 13 is preservative-free. Neither vaccine contains natural rubber latex in the stoppers, syringe plungers, or tips.

Contraindications for Vaccine

PPSV-23 should not be administered to children less than 2 years of age. Pneumococcal vaccines are contraindicated for use in anyone with a previous life-threatening allergic reaction to a prior dose or to any vaccine components.

Warnings and Precautions

Syncope or near-syncopal episodes can occur due to vasovagal responses to needles or injections. Vaccine may be given during a mild illness such as a common cold but should be delayed for those with moderate to severe illness, with or

without fever, until after recovery. Immunologic responses may be diminished in immunocompromised individuals. Vaccines will not prevent disease caused by non-vaccine capsular types.

Safety during pregnancy has not been established. Reduced immune responses to Zostavax have been observed when administered concomitantly with PPSV23; therefore, the two vaccines should be administered at least 4 weeks apart when feasible.

Children who receive Prevnar 13 and inactivated influenza vaccine concomitantly have an increased risk of febrile seizures.

Common Side Effects

Common side effects in first time recipients of PPSV-23 include injection site discomfort (60%), injection site swelling (20%), headache (18%), injection site redness (16%), fatigue (13%), and myalgia (12%). Adverse events seen in infants and toddlers who receive PCV-13 include irritability (>70%), injection site tenderness (>50%), decreased appetite or changes in sleep patterns (>40%), fever (20%), and injection site redness or swelling (20%). Similar types and rates of reactions are seen in children aged 5–17 yrs.

Post-vaccination rates of fever decrease with age. Serious adverse events including bronchiolitis, gastroenteritis, and pneumonia (0.9% each) and sudden infant death (0.06%) are consistent with age-specific background rates.

Vaccine Efficacy and Immunogenicity

PPSV23 induces serotype-specific antibody responses in >80% of immunized healthy adults within 2–3 weeks. Post-licensure data indicate that the vaccine is 56–75% effective in preventing invasive disease caused by vaccine serotypes. Vaccine-induced antibody titers persist for up to 5 years. PPSV23 vaccination has no effect on nasopharyngeal colonization. Lower and less durable antibody responses are seen for serotypes 6B, 9V, 19F, and 23F.

PCV-13 has been shown to be 86–96% effective against invasive disease caused by vaccine serotypes among children less than 5 yrs of age who receive the recommended four-dose series. Among adults ≥65 yrs, PCV-13 has been shown to be between 47% and 59% effective against invasive disease caused by vaccine serotypes, 38–70% effective in preventing nonbacteremic pneumonia caused by vaccine serotypes, and between 6% and 11% effective in preventing all-cause pneumonia.

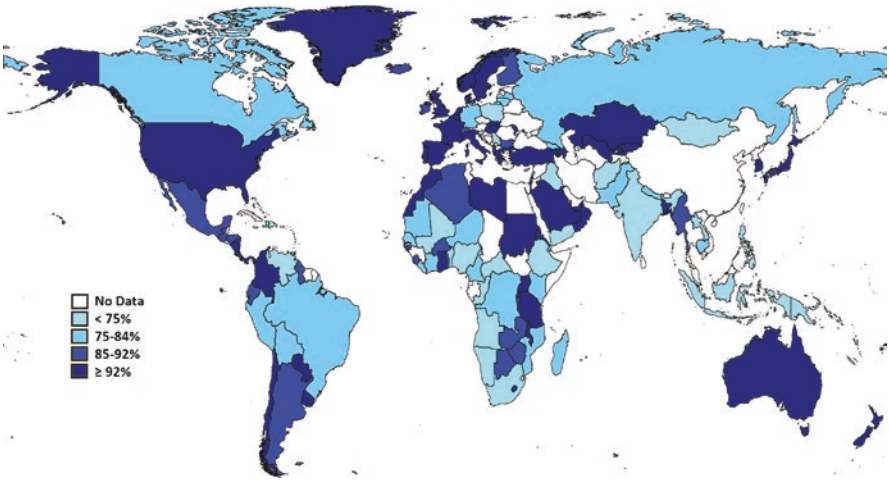

Fig. 23.4 The 2018 World Health Organization and UNICEF estimates of coverage rates for three doses of conjugate pneumococcal vaccine by country. (Source: World Health Organization. Data used to generate graph obtained from https://www.who.int/immunization/monitoring_surveillance/data/en)

Impact of Vaccine on Disease Burden

Between 2000 and 2018, 142 (72%) of the 194 World Health Organization member states introduced a pneumococcal conjugate vaccine into their National Immunization Program. Estimated completion rates for the three-dose primary series during infancy vary by country (Fig. 23.4). Overall, global child mortality from invasive pneumococcal disease has declined by more than 50% since 2000. Progress continues, as 17 additional countries have announced their commitment and plans to introduce PCV over the next 3 years.

In the United States, rates of invasive pneumococcal infection caused by serotypes included in the original 7-valent PCV vaccine serotypes of PCV7 have declined by 99% since Prevnar was introduced in 2000. The introduction of PCV13 in 2010 helped to prevent further problems with replacement serotypes that began to emerge in 2004 and 2005. It is estimated that widespread use of PCV13 prevented 30,000 cases of invasive pneumococcal infection and 3000 deaths during its first year of use in the United States.

Pneumococcal vaccines are safe and highly effective in reducing disease burden caused by this ubiquitous pathogen. The development and widespread use of conjugate vaccines for universal vaccination starting at 2 months of age has led to dramatic reductions in childhood morbidity and mortality from pneumonia, sepsis, and meningitis. Conjugate vaccine-associated reductions in pneumococcal

nasopharyngeal colonization rates in young children have the added benefit of reducing the reservoir of the pathogen, resulting in a herd immunity benefit for all age groups. While the steady progress with global vaccine uptake continues in many parts of the world, further efforts are still needed across several of the most populous, resource-poor, high-risk nations of Africa and Asia.

References and Suggested Reading

World Health Organization

https://www.who.int/immunization/diseases/pneumococcal/en/.

U.S. Centers for Disease Control and Prevention

https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html.

Vaccine Information Sheets

https://www.cdc.gov/vaccines/hcp/vis/vis-statements/pcv13.pdf.
https://www.cdc.gov/vaccines/hcp/vis/vis-statements/ppv.pdf.

Pneumovax23 Package Insert

https://www.fda.gov/media/80547/download.

Prevnar13 Package Insert

https://www.fda.gov/media/107657/download.

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Chapter 24
Polio

Cynthia Bonville and Manika Suryadevara

Polio Infection

Etiology

Poliovirus, a member of the *Enterovirus* genus and the Picornaviridae family, is a non-enveloped, single-stranded, positive RNA virus. There are three serotypes (1–3) of polioviruses. Immunity to one type does not confer immunity to the other types. This virus is stable at acidic pH, allowing for survival in the acidic environment of the stomach.

A stone image depicting the Egyptian priest, Ruma, with a shortened, withered leg, consistent with paralytic poliomyelitis, suggests that virus circulation could date back to as early as 1400 BCE. It took until 1789 for the first clinical description of poliomyelitis, "a debility of the lower extremities," to be reported. In 1908, a 9-year-old boy was hospitalized in Vienna, Austria, with a nonspecific flu-like illness. Over the next few days, he developed rapidly progressive paralysis, acute respiratory failure, and ultimately death. Austrian scientists, Karl Landsteiner and Erwin Popper, described his autopsy findings to be consistent with poliomyelitis, a condition long thought to be due to an infection. Unable to identify bacteria in this boy's central nervous system homogenates, Landsteiner and Popper hypothesized a virus etiology to poliomyelitis when they injected these homogenates into monkeys and they developed paralysis and died [4].

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Pre-vaccine Epidemiology

Prior to vaccine, poliovirus widely circulated in warm areas with poor hygiene and sanitation. In these regions, communities are continuously exposed to the virus starting as early as young infants, resulting in frequent boosts to immunity throughout one's lifetime. Improved hygiene and sanitation in temperate regions, especially European countries and the United States, led to a reduction in polio exposure and community immunity to infection and ultimately a rise in poliomyelitis cases. In 1916, a major outbreak of polio in Brooklyn, New York, resulted in over 2000 deaths in NYC alone and over 6000 deaths across the country. In 1938, 13 years after being paralyzed, himself, by poliovirus, President Franklin D. Roosevelt created the National Foundation for Infantile Paralysis (which ultimately became the March of Dimes) to fund polio research. Within 10 years, the campaign had raised almost $19 million for the cause. Dr. Jonas Salk was chosen to lead the polio vaccine development program.

Over the following decades, polio outbreaks in the United States would continue to increase in both frequency and size, with reports from the 1940s describing 13,000–20,000 paralytic cases occurring each year. With peak infection occurring during the summertime, children who finished the school year healthy and well would return to school in the fall crippled by the disease. Parents were afraid to let their children play outside. Travel restrictions were in place for locations affected by poliovirus, with quarantines imposed to isolate sick individuals. In 1952, alone, poliovirus infected 60,000 children, paralyzed over 21,000, and killed over 3000 across the country. By 1955, Dr. Salk's inactivated poliovirus vaccine (IPV) was approved, but then replaced 6 years later, by Dr. Albert Sabin's live attenuated oral poliovirus vaccine (OPV). Worldwide, poliovirus continued to paralyze more than 1000 children, each day. In 1988, the Global Polio Eradication Initiative (GPEI) was established to eliminate wild and vaccine-related polioviruses from all regions of the world.

Transmission

Poliovirus is most commonly transmitted via the fecal-oral route, through direct contact with contaminated feces. Transmission through direct contact with respiratory specimens and contaminated food, water, and fomites can also occur. A highly contagious virus, seroconversion occurs in almost all household contacts of infected individuals. Poliovirus is most contagious the week before and after symptom onset but may continue to be excreted in the stool for up to 6 weeks.

Upon acquisition, viral replication occurs in the pharynx and the gastrointestinal tract prior to invasion of bloodstream and hematogenous spread to distal sites, particularly the central nervous system. Viral replication in the motor neurons of the anterior horn and brainstem results in neuronal death and clinical manifestations of poliomyelitis [5].

Clinical Presentation

Up to 70% of infected children will be asymptomatic, yet can still shed virus and transmit infections to others. Table 24.1 describes the variety of clinical presentations that may occur as a result of poliovirus infection. The mortality rate of paralytic polio ranges from 2–5% for children, 15–30% for adults, and 25–75% for individuals with bulbar involvement. Post-polio syndrome (PPS) affects 25–40% of adults who survive polio infections as children, often 15–40 years prior. Manifestations include gradual, progressive weakness and atrophy of affected muscles, generalized fatigue, joint pain, and worsening skeletal deformities. While rarely life-threatening, PPS may interfere with one's ability to independently perform activities of daily living.

Management

There is no antiviral therapy available for the treatment of polio infection. Management of infection is supportive care.

Table 24.1 Clinical manifestations of poliomyelitis infection

Disease classification	Manifestations
Abortive poliomyelitis	25% of infections Nonspecific flu-like illness: fever, sore throat, lethargy, headache, abdominal pain, nausea No central nervous system involvement Symptoms last less than week, then complete recovery
Non-paralytic aseptic meningitis	1–5% of infections Prodrome with flu-like illness which resolves prior to neck stiffness, back and leg pain, +/− paresthesias Symptoms last up to 10 days, then complete recovery
Paralytic poliomyelitis	<1% of infections Prodrome with flu-like illness which resolves prior to development of acute flaccid paralysis[a] Most commonly affects proximal rather than distal muscles
Spinal polio	Most common Asymmetric paralysis most often affects legs
Bulbar polio	Least common Infection limited to cranial nerve involvement Paralysis of diaphragm and intercostal muscles can lead to acute respiratory failure
Bulbospinal polio	Combination of bulbar and spinal polio Paralysis of diaphragm and intercostal muscles can lead to acute respiratory failure

[a]Acute flaccid paralysis: acute onset of flaccid paralysis of at least one limb, decreased tendon reflex of affected limb, no loss of sensation or cognition

Prevention

The primary approach to community-wide prevention includes routine administration of the polio vaccine.

Polio Vaccine

Vaccine Characteristics

The inactivated poliovirus vaccine (IPV) is the only available vaccine available in the United States to prevent against polio infection. Polioviruses, types 1, 2, and 3, are individually grown in Vero cells (monkey kidney cells), concentrated by ultrafiltration, and purified by liquid chromatography. Each monovalent suspension is inactivated with formalin, quantitated, and pooled into a trivalent vaccine suspension. This vaccine is available alone or in combination with other pediatric vaccines [Table 24.2].

Vaccine Storage, Preparation, and Administration

All poliovirus vaccines available in the United States should be refrigerated (2 °C–8 °C), not frozen, and protected from light. The vaccine product should not be administered if discolored or contains particulate matter. A 0.5 mL dose of vaccine is administered intramuscularly.

IPOL is supplied as a multidose vial. The suspension should be clear and colorless.

Pediarix is supplied as single-dose, prefilled syringes. Shake syringe contents vigorously until it becomes a homogenous, turbid, white suspension.

Kinrix is supplied as single-dose vials and single-dose prefilled syringes. Shake contents vigorously until it becomes a homogenous, turbid, white suspension.

Pentacel is supplied in two components: (a) single-dose vials of liquid vaccine (DTaP-IPV) and (b) lyophilized HIB vaccine (ACTHIb). Reconstitute the lyophilized HIB vaccine component with the liquid DTaP-IPV component immediately before use. Resuspended product should be a cloudy, uniform, white to off-white suspension.

Quadracel is supplied as single-dose vials. Suspension should be uniform, white, and cloudy. Vaxelis is supplied in single-dose vials. Suspension should be uniform, white, and cloudy.

Table 24.2 Poliovirus vaccine products available in the United States

Vaccine product	Vaccine immunogen	Vaccine ingredients	Approval and indication
IPOL (IPV)[a] Sanofi Pasteur Approved 1990	Polioviruses 1, 2, 3	Neomycin, streptomycin, polymyxin B, residual calf bovine serum albumin, 2-phenoxyethanol, formaldehyde	6 weeks of age and older
Pediarix (DTaP-IPV-HBV)[a] GlaxoSmithKline Approved 2002	Diphtheria toxoid, tetanus toxoid, acellular pertussis antigens[b], hepatitis B surface antigen, polioviruses 1, 2, 3	Aluminum salts, sodium chloride, residual formaldehyde, polysorbate 80, neomycin sulfate, polymyxin B, yeast protein Caps of prefilled syringes made of natural rubber latex	Approved for use as a three-dose series between the ages 6 weeks to 6 years born to hepatitis B surface antigen negative mothers A different vaccine product must be used for the fourth dose IPV at 4–6 years of age
Kinrix (DTaP-IPV) GlaxoSmithKline Approved 2008	Diphtheria toxoid, tetanus toxoid, acellular pertussis antigens[b], polioviruses 1, 2, 3	Aluminum hydroxide, sodium chloride, residual formaldehyde, polysorbate 80, neomycin sulfate, polymyxin B Caps of prefilled syringes made of natural rubber latex	Approved for use as a booster dose (fifth dose DTaP, fourth dose IPV) at 4–6 years of age; particularly for those who received Infanrix[d] and/or Pediarix as infants
Pentacel (DTaP-IPV-HIB)[a] Sanofi Pasteur Approved 2008	Diphtheria toxoid, tetanus toxoid, acellular pertussis antigens[b], Hib covalently bound to tetanus toxoid, polioviruses 1, 2, 3	Aluminum phosphate, polysorbate 80, 2-phenoxyethanol, residual glutaraldehyde, residual bovine serum albumin, sucrose, residual formaldehyde, streptomycin, neomycin, polymyxin B	Approved for use as four-dose series in infants aged 6 weeks through 4 years. A different vaccine product must be used for the booster dose IPV at 4–6 years of age
Quadracel (DTaP-IPV) Sanofi Pasteur Approved 2015	Diphtheria toxoid, tetanus toxoid, acellular pertussis antigens[b], polioviruses 1, 2, 3	Aluminum phosphate, polysorbate 80, 2-phenoxyethanol, residual formaldehyde, residual glutaraldehyde, residual bovine serum albumin, sucrose, formaldehyde, streptomycin, neomycin, polymyxin B	Approved for use as a booster dose (fifth dose DTaP, fourth dose IPV) at 4–6 years of age; particularly for those who received Pentacel and/or Daptacel as infants

(continued)

Table 24.2 (continued)

Vaccine product	Vaccine immunogen	Vaccine ingredients	Approval and indication
Vaxelis (DTaP-IPV-HIB-HBV) MSP Vaccine Company Approved 2018	Diphtheria toxoid, tetanus toxoid, acellular pertussis antigens[b], Hib covalently bound to OMP[c] Hepatitis B surface antigen Polioviruses 1, 2, 3	Aluminum, polysorbate 80, residual amounts of formaldehyde, glutaraldehyde, bovine serum albumin, neomycin, streptomycin, polymyxin B, ammonium thiocyanate, yeast protein	Approved for use as a three-dose series between the ages 6 weeks to 4 years A different vaccine product must be used for the fourth dose IPV at 4–6 years of age

[a]IPV inactivated poliovirus vaccine, protecting against serotypes 1, 2, 3; DTaP diphtheria-tetanus-acellular pertussis vaccine; HBV hepatitis B vaccine; HIB *Haemophilus influenzae* type b vaccine
[b]Acellular pertussis antigens: inactivated pertussis toxin, filamentous hemagglutinin, pertactin, +/− fimbriae
[c]Outer membrane protein complex of *N. meningitidis* serogroup B
[d]Infanrix vaccine: DTaP alone

Vaccine Recommendations

The ACIP recommends that poliovirus vaccine be routinely administered as a four-dose series at ages 2 months, 4 months, 6–18 months, and 4–6 years. IPV vaccine can be administered as early as 6 weeks of age. A final dose of IPV vaccine should be administered after 4 years of age, regardless of the number of doses received previously. Under-immunized children should complete the vaccine series. An accelerated schedule (with a minimum interval of 4 weeks between the first three doses and a minimum interval of 6 months between doses 3 and 4) can be used for children who are traveling to polio-endemic regions and need protection sooner than the regular schedule would offer. These children should still receive a final dose of IPV vaccine after 4 years of age.

Children, specifically refugees and immigrants, do not need further poliovirus vaccines if there is written documentation of series completion of either IPV or trivalent oral poliovirus vaccine (tOPV). Of note, tOPV was the only oral poliovirus vaccine used around the world prior to April 1, 2016. Otherwise, the use of monovalent, bivalent, or unspecified oral poliovirus vaccines are not considered valid. Children who have not completed the vaccine series with either IPV or tOPV prior to entry in the United States should be fully immunized with IPV as per catch-up vaccine recommendations. Furthermore, all previously under- or unimmunized household contacts of children adopted from regions with circulating wild poliovirus or vaccine-derived poliovirus should be fully vaccinated with IPV.

Adults at higher risk for acquiring infection (travelers to areas of endemic infection, healthcare workers with close contact with polio-infected patients, laboratory workers handling poliovirus) should be immunized against poliovirus with the number of doses dependent on prior vaccination status. Unimmunized adults should

receive a three-dose series, with 4–8 weeks between doses 1 and 2 and 6–12 months between doses 2 and 3. If protection is required sooner than this timeline will allow, each of the three doses should be administered at a minimum of 4-week intervals. If protection is required even sooner, two doses of IPV can be administered at least 4 weeks apart. At the very least, a single dose of IPV vaccine should be administered. Partially immunized adults should complete the vaccine series regardless of the time interval since the last dose. Adults who have been fully immunized can receive a single lifetime booster dose of IPV vaccine if at persistently high risk of acquiring infection.

Contraindications and Precautions to Polio Vaccine

IPV vaccine is contraindicated in patients who have had an anaphylactic or severe allergic reaction to a prior dose of IPV vaccine or to a vaccine component (including 2-phenoxyethanol, formaldehyde, neomycin, streptomycin, or polymyxin B). The contraindications to the combination vaccines are similar to those of the vaccine components when separately administered. Vaccination of individuals with an acute febrile illness should be postponed until after recovery.

Adverse Events

Most common adverse reactions to IPV include redness, swelling, and pain at the site of injection, fevers, and irritability. The adverse reactions following combination reactions are similar to those of the vaccine components when separately administered.

Immunogenicity

Over 95% of IPV vaccine recipients produce protective antibodies to each of the three serotypes after two doses of vaccine. Almost all individuals develop long-term immunity after three doses of IPV vaccine.

Impact of Vaccine on Disease Burden

The inactivated poliovirus vaccine (IPV), developed by Salk to target all three serotypes, was first licensed and approved for use to protect against poliomyelitis in the United States in 1955. Less than 10 years later, American physician and

microbiologist, Albert Sabin's live attenuated trivalent oral polio vaccine (tOPV) was approved for use in the United States and essentially replaced Salk's IPV. Table 24.3 reviews the similarities and differences between the inactivated and the live attenuated oral poliovirus vaccines.

While IPV is highly immunogenic, it induces little intestinal immunity. When an individual who has been previously immunized with IPV is infected with poliovirus, the virus replicates in the gastrointestinal tract, resulting in fecal shedding and transmission of infection. Therefore, IPV is effective in individual disease prevention but does not stop community transmission. On the other hand, OPV administration induces mucosal immunity resulting in interruption of community transmission. Similar to IPV, seroconversion is near 100% after three doses of OPV. However, widespread use of oral poliovirus vaccine can rarely lead to vaccine-associated paralytic poliomyelitis (VAPP), reported in 1 case per 750,000 children receiving their first dose of vaccine. Even more rarely, in communities with suboptimal OPV vaccination rates, vaccine virus may circulate, mutate, and acquire neurovirulence, becoming vaccine-derived poliovirus. In countries where polio is endemic, OPV is the primary method of polio prevention with a goal of inducing individual immunity and stopping community transmission. When polio has been eliminated from a region, IPV is preferred to maintain immunity without the risk of VAPP and circulating vaccine-derived polioviruses.

In an effort to eliminate community-wide transmission of polio in the United States, the tOPV replaced IPV for routine and universal administration in the national immunization program in 1963. Subsequently, disease incidence in the United States dropped dramatically, and the last indigenously acquired case of poliomyelitis occurred in 1979 (Fig. 24.1). Between 1989 and the late 1990s, while there were no indigenous poliovirus infections, there were eight to nine cases of VAPP reported each year. Based on the lack of indigenous polio infections,

Table 24.3 Benefits and disadvantages of the two types of poliovirus vaccines

	Oral poliovirus vaccine	Inactivated poliovirus vaccine
Vaccine characteristics	Live attenuated Monovalent, bivalent, trivalent	Inactivated Trivalent
Immunogenicity	Highly immunogenic after three doses; lifelong immunity	Highly immunogenic after three doses; lifelong immunity
Notes	Should not be administered to immunocompromised individuals or their household contacts	Can be administered to immunocompromised individuals and their household contacts
Benefits	Effectively induces intestinal immunity Less expensive than IPV Does not require trained healthcare worker	Highly immunogenic No risk of VAPP[a]
Disadvantages	Can rarely result in VAPP or circulating, neurovirulent vaccine-derived poliovirus	Induces limited intestinal immunity Much more expensive than OPV Requires trained healthcare worker

[a]VAPP vaccine-associated paralytic poliomyelitis

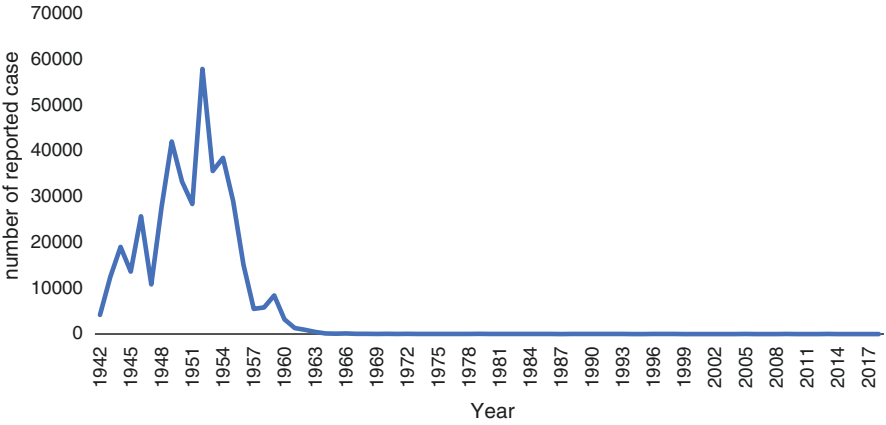

Fig. 24.1 Number of polio cases reported in the United States, 1942–2018

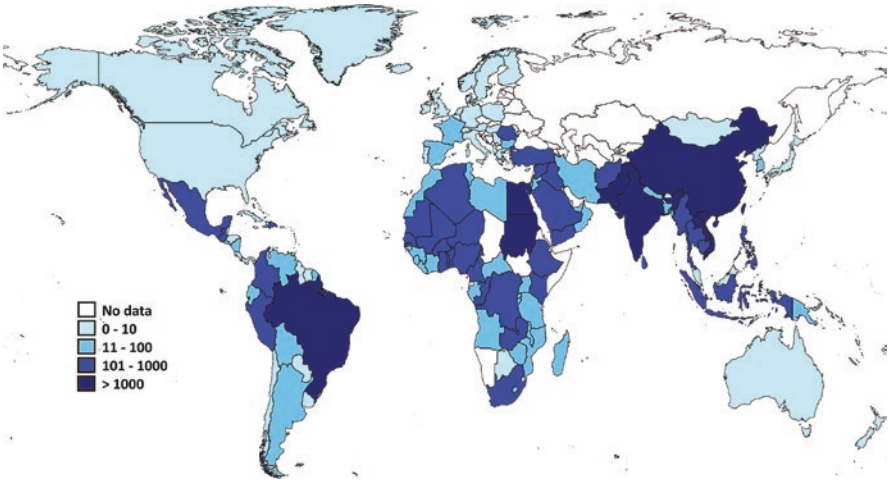

Fig. 24.2 Number of polio cases reported across the world, 1980

persistence of reported VAPP, and a lower risk of importing wild poliovirus into the United States, in 1997, the ACIP modified polio prevention recommendations to include sequential administration of two doses of IPV, followed by two doses of OPV. In 2000, the United States was able to move to an all IPV vaccine series to maintain immunity to polio while eliminating the risk of VAPP and vaccine-derived poliovirus in this country.

Established in 1988, the Global Polio Eradication Initiative (GPEI) is the largest public-private partnership for public health. Over the past 20 years, more than 20 million volunteers have immunized nearly 3 billion children in 200 countries. The GPEI Polio Endgame Strategy, 2019–2023, plans to eradicate polio through

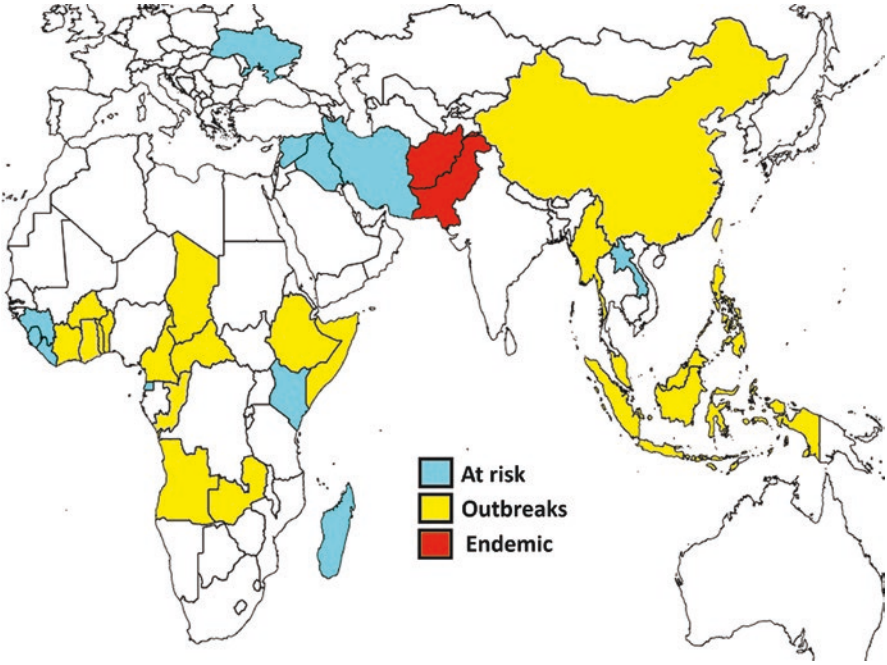

Fig. 24.3 Map depicting polio-endemic, outbreak, and at-risk countries as of 2018. The remaining counties have eliminated polio

programs which detect and interrupt transmission, strengthen immunization programs, implement mass immunization campaigns, transition from OPV to IPV where possible, and increase active surveillance of environmental sewage. Since the start of the program, the global incidence of disease has reduced by over 99%, preventing paralysis in 16 million people and preventing over 1.5 million deaths. The success of the polio eradication program can be seen in the differences between Fig. 24.2 (global disease burden in 1980) and Fig. 24.3 (countries where polio remains endemic). The Americas were declared polio-free in 1994, the Western Pacific Region in 2000, Europe in 2002, and Southeast Asia in 2014. Poliovirus serotypes 1 and 3 have already been eradicated. However, with poliovirus serotype 2 still endemic in two countries, Afghanistan and Pakistan, there is a risk for reestablishment of either wild poliovirus or circulating vaccine-derived virus from OPV in areas that have been declared polio-free, particularly in countries with low vaccine uptake (Fig. 24.3). It is crucial for all countries to maintain high vaccination rates to achieve global eradication of polio. Vaccination awareness campaigns persist across at-risk areas of the world. Evidence for the multiagency effort involving Rotary International, the Bill & Melinda Gates Foundation, GAVI, the World Health Organization, UNICEF, and other stakeholders can be seen in Fig. 24.4, a montage

Fig. 24.4 A montage of three photographs taken in November 2019 in the city of Accra, Ghana, located geographically in West Africa

of three photographs taken in November 2019 by one of the authors (JBD) during a visit to Accra, Ghana, West Africa. The last case of wild-type polio reported from Ghana was in 2000. If successful, polio will be the second human infection in history to be eradicated.

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Chapter 25
Rabies

Cynthia Bonville and Joseph Domachowske

Rabies Infection

Etiology

Rabies encephalitis is a central nervous system infection of humans and animals that is almost universally fatal once symptoms begin. It is caused by *Rabies lyssavirus*, the type species of the *Lyssavirus* genus of the family *Rhabdoviridae*. The pathogen is an enveloped, single-stranded, negative-sense RNA virus with a cylindrical morphology.

Epidemiology

Rabies causes an estimated 59,000 deaths in humans annually. A total of 95% of cases occur in Asia and Africa among poor populations in remote rural areas where awareness and access to appropriate PEP (post-exposure prophylaxis) is limited or nonexistent. Figure 25.1 shows the global distribution of cases reported to the WHO in 2017, but only a small fraction of cases are reported, with many of the highest-risk countries providing no data at all. For example, 60% of all human rabies cases in Asia occur in India where both dog and human rabies are endemic, yet available data are not reported to the WHO. Almost all of the world's cases of human rabies result from dog bites. Dog-mediated rabies has been eliminated in Western Europe, Canada, USA, Japan, and some Latin American countries due to mass dog

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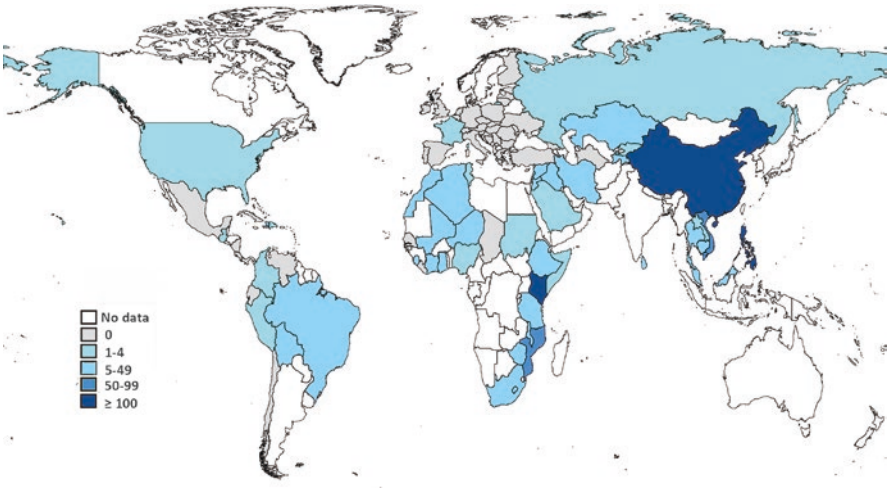

Fig. 25.1 2017 World Health Organization reported deaths from rabies by country

vaccination campaigns and has never been a problem in Australia or the majority of islands in the Western Pacific. The annual global economic burden of rabies infection is close to $9 million per year due to direct costs of PEP, lost income seeking PEP, premature death, livestock losses, dog vaccination, dog population management, and surveillance.

Prior to 1960, most human rabies in the USA followed exposures to rabid dogs. Collectively, vaccination campaigns for pets and state mandates related to responsible dog ownership led to control and then the near elimination of canine rabies throughout the country. Between 1960 and 2018, 125 cases of human rabies were reported in the USA: 36 (28.8%) were epidemiologically linked to dogs while visiting foreign countries, and 89 (71.2%) infections were acquired domestically, 62 (69.6%) of which were transmitted by bats. Despite an ongoing reservoir of rabies in wild animals including bats, raccoons, skunks, foxes, and coyotes, rabies has not been reintroduced into the dog population because of the efforts to maintain high vaccine coverage rates in pets. Rabies management programs that target raccoons, foxes, and coyotes are also available for deployment as needed.

Between 2017 and 2018, approximately 55,000 individuals sought PEP following a possible rabies exposure at an average cost of $3800, not including wound care or hospital charges yielding an estimated annual human PEP cost of $209 million. These costs are compounded by the additional public health resources needed for human and animal rabies diagnostics and pet vaccination together totaling more than $500 million annually.

Transmission

Rabies is spread to humans by bites or scratches from infected mammals such as domestic or feral dogs, cats, or ferrets and wild carnivores including bats, foxes, raccoons, skunks, jackals, mongooses, and coyotes. Rodents and lagomorphs (rabbits and hares) are not known to transmit the disease. The incubation period following the bite or scratch of an infected animal is usually between 1 and 3 months but can vary from 1 week to more than 1 year. The length of the incubation period depends on the animal species that transmitted the virus, the infecting inoculum, the anatomical site of entry and severity of the bite, the virulence of the infecting strain, and the immune status of the person who was bitten. Less commonly, rabies can be transmitted from infectious material such as the saliva or nervous system tissue that comes into direct contact with the mucous membranes of an individual's eyes, nose, or mouth. Transmission has also been reported via inhalation of virus-containing aerosols during cave exploration where virus can be present in bat guano at very high concentrations. Rare reports of rabies transmission have also been reported following inadvertent transplantation of infected corneas.

Rabies travels from the peripheral nerves at the inoculation site to the central nervous system via retrograde axonal transport. The time between exposure and the development of central nervous system symptoms is directly proportional to the distance between the inoculation site and the brain. When the virus reaches the brain, its replication becomes exponential.

Clinical Presentation

The initial symptoms of rabies infection include vague, general complaints of malaise, anorexia, fever, and/or headache. Pain, tingling, pricking, or a burning sensation may develop at the inoculation site. Patients characteristically become irritable and anxious, sometimes describing an intense feeling of doom and hopelessness even before they become aware of their diagnosis.

Most human rabies infections progress rapidly and dramatically in a clinical form referred to as furious rabies. Patients are unable to sleep and become agitated, aggressive, hyperactive, and disoriented. Symptoms of hydrophobia, aerophobia, hypersalivation, hallucinations, and seizures alternate with periods of lucidity, progress to coma, and then death from cardiorespiratory arrest over a period of 2–10 days.

The paralytic form of rabies is less common, accounting for approximately 20% of human cases. The course is more protracted and less dramatic. Muscle paralysis, starting at the site of the inoculation, becomes generalized ultimately leading to coma and then death.

Globally, 99% of human rabies cases are acquired from infected dogs. In areas of the world where dog rabies has been eliminated, most human infections are caused by strains that originate in bats.

Management

There is no effective treatment for rabies once symptoms develop. The infection is almost universally fatal. Post-exposure prophylaxis (PEP) after a bite prevents rabies. Immediate PEP includes cleansing of the wound with soap and water followed by the administration of rabies immune globulin and the first dose in a series of rabies vaccination. The vaccine series is completed by administering subsequent doses on days 3, 7, and 14. Individuals who are immunosuppressed should also receive a fifth dose of vaccine on day 28. Ideally, PEP is started within 24 hours of the exposure.

Prevention

The most cost-effective strategy for preventing rabies in humans is to vaccinate dogs and to prevent dog bites through education and promotion of responsible pet ownership. Bait containing oral vaccine has been used in attempts to control the spread of rabies in wild animals. Complex logistics and cost have limited the success of such programs. Humans who are bitten or scratched by an animal with known or suspected rabies should receive PEP as soon as possible. PEP starts with immediate and extensive washing and local treatment of the wound. After a minimum of 15 minutes is spent cleaning the area with soap and water, povidone-iodine or another topical agent with virucidal capacity should be applied. Tetanus vaccination status should be reviewed and updated when necessary. The wound should be left uncovered and not closed with sutures if feasible to allow bleeding and drainage. Large wounds requiring sutures should be injected with rabies immune globulin prior to closure. The first dose of the rabies vaccine series should be administered intramuscularly into the deltoid area and arrangements made to complete the series of doses as recommended.

Rabies Vaccine

Rabies vaccines for humans have been available for more than 100 years. French scientists, Pasteur and Roux, developed the first vaccine in 1885 using live virus harvested from the spinal cord of an inoculated rabbit that was attenuated by drying.

A 9-year-old boy, Joseph Meister, was the first human to receive the live attenuated vaccine derived from the rabbit's neural tissue after being mauled by a rabid

dog. For him, it was life-saving. The vaccine product was, however, highly reactogenic, prone to causing unusual neurologic side effects, and associated with a high risk that the rabies virus would revert to the virulent form.

In attempts to develop safer vaccines, inactivated formulations emerged next. Fermi, Semple, and others used phenol to inactivate the virus, thereby eliminating its potential to revert to virulence. Production was moved to larger animals, including sheep, to improve vaccine yield. Serious neurologic adverse events remained problematic with some people developing vaccine-associated paralysis or "allergic" encephalomyelitis. These late post-vaccination events were caused when immunized individuals mounted immune responses to epitopes of the animal myelin protein present in the vaccine that cross-reacted with their own human myelin. Sheep brain vaccines were still used in Ethiopia as recently as 2015.

Progress toward safer rabies vaccines came when technology became available to move production out of mammalian brain. The first product to do so successfully was an inactivated vaccine derived from virus grown in embryonated duck eggs. The vaccine is safe, relatively easy to produce, and inexpensive to manufacture, but large doses are needed to induce protective responses due to its low immunogenicity. The formulation is still used globally in select countries. The next step in advancing the progress of rabies vaccines was the move to generating inactivated vaccine from virus grown in cell culture. As a group, these vaccines have been the most widely used for the last three decades. They are more amenable to large-scale production, much safer, and highly immunogenic in small doses.

Rabies is nearly 100% preventable when vaccines are used as recommended. The logistics regarding their use depends on whether the goal is pre-exposure prophylaxis (PrEP) to individuals at risk or post-exposure prevention of clinical disease after a known exposure (PEP).

Two vaccine formulations are approved and available for use in the USA. Inactivated vaccine derived from virus grown in MRC-5 human diploid cell culture is marketed under the brand name Imovax by Sanofi Pasteur, and an inactivated chick embryo cell vaccine is sold as RabAvert, by GlaxoSmithKline. Both vaccines are indicated for the prevention of rabies in all age groups, can be administered as either PrEP or PEP, and are provided in single-dose vials of lyophilized vaccine product that requires reconstitution prior to use. Each dose of the vaccine is administered as a 1 mL intramuscular injection in the deltoid muscle. Dosing schedules differ based on host factors and whether the vaccine is being administered for use as PrEP or as PEP (Table 25.1).

Table 25.1 Rabies vaccine dosing schedules

	Primary vaccine dosing schedule	Given with RIG?	Vaccine re-dosing schedule following an exposure	Given with RIG?
PrEP	3 doses given on days 0, 7, and 21 or 28	No	2 doses given on days 0 and 3	No
PEP	4 doses given on days 0, 3, 7, and 14	Yes[a]	2 doses given on days 0 and 3	No

[a]When indicated, the dose for rabies immune globulin is 20 IU/kg

Immunizing Antigen

The inactivated virus included in Imovax is derived from rabies strain PM-1503 grown in and harvested from cultured MRC-5 cells. Virus is concentrated by ultrafiltration, inactivated by beta-propiolactone, then freeze-dried in unit dose vials. RabAvert is made using inactivated low-egg-passaged (LEP) Flury strain virus derived from infected primary cultures of chicken fibroblasts. The infected fibroblasts are grown in synthetic cell culture medium supplemented with human albumin, polygeline, and antibiotics.

Harvested virus is inactivated with beta-propiolactone and concentrated using zonal ultracentrifugation in a sucrose density gradient. The vaccine product is stabilized with buffered polygeline and potassium glutamate and then lyophilized as single-dose vials.

Adjuvants, Excipients, or Preservatives

Each dose of Imovax contains <100 mg human albumin, <150 mcg neomycin sulfate, <20 mcg phenol red, and <50 parts/million beta-propiolactone. It is preservative-free.

Each dose of RabAvert contains ≤12 mg polygeline, ≤0.3 mg human serum albumin, ≤3 ng ovalbumin, 1 mg potassium glutamate, 0.3 mg sodium Ethylenediaminetetraacetic acid (EDTA), ≤10 mcg neomycin, ≤200 ng chlortetracycline, ≤20 ng amphotericin B, and small quantities of bovine serum. It is preservative-free.

US Pediatric Immunization

The safety and efficacy of both US rabies vaccine formulations have been established in children using the same 1.0 mL dose recommended to be given to adults. PrEP should be considered for children living in or visiting remote, high-risk areas using a three-dose schedule. PEP should be administered to any child with a known or possible rabies exposure using a four- or five-dose schedule. A fifth dose is recommended when vaccinating individuals who are immunosuppressed.

US Adult Immunizations

PrEP using rabies vaccine is recommended using risk categories. Those at continuous risk of exposure that is unlikely to be recognized, such as laboratory personnel working with the virus, should be immunized with a three-dose series given on days 0, 7, and 21 or 28. Serologic testing should then be performed every 6 months with

booster doses of vaccine administered to maintain a neutralization serum titer of ≥1:5 via rapid fluorescent focus inhibition testing (RFFIT). Those at frequent risk, defined as episodic exposures to both known and unknown sources, including personnel in rabies diagnostic laboratories, veterinarians, veterinary staff, animal control staff, wildlife rangers and animal handlers working in enzootic regions, spelunkers, and all individuals who frequently handle bats regardless of the US geographical area, should be immunized with a three-dose series given on days 0, 7, and 21 or 28. Serologic testing should then be performed every 2 years with booster doses of vaccine administered to maintain a neutralization serum titer of ≥1:5. Individuals with an infrequent risk are those where the source of an episodic exposure is almost always identified, as might occur in travelers to endemic areas with limited access to appropriate medical care, especially to regions where modern, safe, and effective vaccines are in short supply or known to be unavailable. The vaccine series is administered as three doses on days 0, 7, and 21 or 28, but follow-up serologic testing is not necessary. Other than members of the groups listed above, the US population at large, including those living in areas with epizootic rabies, is considered to be at rare risk of exposure. PrEP or serologic testing is not recommended for those included in this group.

When an individual presents following a known or suspected exposure to rabies, PEP prophylaxis is *ALWAYS* indicated. Specific recommendations for how PEP is administered depends on the individual's prior vaccination status since recipients of PrEP may have residual partial immunity from prior doses. The primary objective of PEP is to provide protection against disease as soon as possible. Individuals who have not been immunized previously should receive a single dose of human rabies immune globulin, at a dose of 20 IU/kg. Preparations that are available in the USA are shown in Table 25.2. The entire dose should be used to infiltrate the wound if possible. When the size and/or anatomic location of the wound precludes the direct injection of the entire dose into the area, any remaining volume should be injected intramuscularly at a site distant to that used for the first dose of vaccine. Immediately following wound care, individuals should also receive their first dose of rabies vaccine. The first dose is followed by three more doses on days 3, 7, and 14 to complete PEP. A fifth dose of vaccine may be considered for immunocompromised individuals on day 28 to complete the series. PEP recommendations for individuals who were previously immunized are approached differently. Following the cleansing of the wound, rabies immune globulin is NOT administered because it may blunt the memory response to rabies antigen. Two doses of rabies vaccine are given to boost the responses to prior doses, one immediately and another 3 days later.

Table 25.2 Preparations of human rabies immune globulin available in the USA

Brand name	Manufacturer	Concentration[a]
HyperRab	Grifols	150 IU/mL
HyperRab S/D	Grifols	300 IU/mL
Imogam Rabies-HT	Sanofi Pasteur	150 IU/mL
KEDRAB	Kedrion Biopharma and Kamada Ltd.	150 IU/mL

[a]When indicated, the dose for rabies immune globulin is 20 IU/kg

Contraindications for Vaccine

Rabies vaccine is contraindicated for use as PrEP in those with a previous life-threatening allergic reaction after a prior dose and for those with known severe allergies to vaccine components. Since rabies infection is invariably fatal, there are no absolute contraindications for using rabies vaccine as PEP.

Warnings and Precautions

Rabies vaccine should not be injected into the gluteal area because suboptimal antibody responses may result. Serum sickness-type reactions have been reported in 7% of individuals receiving a booster dose for PrEP.

Rare cases of Guillain-Barre-like transient neuroparalytic illness that resolve without sequelae have been described in vaccine recipients. Other rare events that have been reported include anaphylaxis, meningitis, encephalitis, transient paralysis, Guillain-Barre syndrome, myelitis, retrobulbar neuritis, and multiple sclerosis.

When administering PEP to any person with a history of hypersensitivity, emergency equipment and medications should be available for immediate use including epinephrine (1:1000), corticosteroids, and oxygen. Once initiated, PEP should NOT be interrupted or discontinued because of local or mild systemic adverse reactions. Such reactions can be managed using anti-inflammatories, antihistamines, and/or antipyretics.

Common Side Effects

Local injection site reactions are common but mild and self-limiting. Most vaccinated individuals experience some pain, erythema, swelling, or itching at the injection site.

Common systemic reactions include mild to moderate headache (10–52%), myalgia (15–53%), malaise (20%), dizziness (15%), or lymphadenopathy (15%) that self-resolve in 2–3 days.

Immunogenicity and Estimated Vaccine Effectiveness

The post-vaccination antibody titer used as the surrogate for immune protection following vaccination varies by agency. The CDC specifies a 1:5 titer, indicative of complete inhibition, using RFFIT; the WHO specifies a concentration of 0.5 IU/mL using RFFIT. A study performed in Iran, involving 45 individuals bitten by rabid

dogs or wolves, showed that PEP using one dose rabies immune globulin and six doses of inactivated rabies vaccine given on days 0, 3, 7, 14, 30, and 90, with the first dose administered within 14 days of the exposure, was 100% effective at preventing rabies. Similarly, data from the US CDC involving 511 people bitten by rabid animals showed that PEP using one dose rabies immune globulin and five doses of inactivated rabies vaccine given on days 0, 3, 7, 14, and 28 was 100% effective at preventing rabies.

PrEP immunogenicity studies from the USA, UK, Croatia, and Thailand all indicated that the recommended PrEP vaccine regimen, with vaccine doses given on days 0, 7, and 21 or 28, yielded 100% seroprotection.

In the USA, no failures have been reported after using PEP as recommended.

Failures have been reported from abroad, with all but two clearly linked to deviations in the PEP protocol.

WHO Vaccine Recommendations

All WHO prequalified vaccines are now supplied as the lyophilized active component to be reconstituted with diluent prior to administration. Following reconstitution, the vaccine should be used immediately but may be stored for up to 6 hours at 2–8 ° C.

Impact of Vaccine Introduction

The USA and many European and Latin American countries have eliminated rabies as a public health problem through mandatory canine vaccination programs and reliable access to human PEP. In the USA, the number of human rabies deaths has declined from over 100 each year in the early 1900s to between 1 and 3 per year, despite major epizootics of animal rabies in specific geographic regions. Since 1983, human and dog rabies in the WHO Region of the Americas declined by 95% and 98%, respectively.

References and Suggested Reading

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https://www.who.int/health-topics/rabies#tab=tab_1.
http://apps.who.int/neglected_diseases/ntddata/rabies/rabies.html.

US Centers for Disease Control and Prevention

https://www.cdc.gov/rabies/index.html.

Vaccine Information Sheet

https://www.cdc.gov/vaccines/hcp/vis/vis-statements/rabies.html.

Global Alliance for Rabies Control

https://rabiesalliance.org/.

Imovax Package Insert

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Rabavert Package Insert

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Chapter 26
Rotavirus

Cynthia Bonville and Joseph Domachowske

Rotavirus Infection

Etiology

The genus *Rotavirus* includes ten species, A through J, of non-enveloped, double-stranded RNA viruses belonging to the family *Reoviridae*. The viral genome consists of 11 double helical RNA segments, each encoding 1 or 2 virus-specific genes. *Rotavirus A*, the most commonly identified species, accounts for more than 90% of human rotavirus infections. The virus targets the gastrointestinal tract causing acute gastroenteritis. Symptomatic illness is most common during infancy and young childhood, although individuals are repeatedly infected throughout their lifetime. Strains of *Rotavirus A* are categorized based on the characteristics of two surface capsid viral proteins. Glycoprotein VP7 defines the G serotype and capsid protein VP4 defines the P serotype. To date, at least 32 and 47 G and P types have been identified, respectively. The genes encoding each of the specific G and P types are passed on separately to progeny viruses, so a variety of different combinations are found on the surface of *Rotavirus A* isolates. The prevalence of the individual G types and P types infecting humans varies geographically and changes from season to season, but only a few combinations of G and P types predominate. The most common infecting serotypes of *Rotavirus A* are G1P8, G2P4, G3P8, G4P8, and G9P8. Neutralizing antibodies that are produced to either the G or P protein confer at least partial protective immunity to infection with serotypes that include either of the same G and P types on the surface.

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Epidemiology: Global

Serotypes of *Rotavirus A* are the most common cause of diarrheal disease among infants and young children throughout the world. Virtually all children are infected with rotavirus at least once by 5 years of age. Globally, the peak incidence of rotavirus gastroenteritis occurs between 6 and 24 months of age, with the most severe outcomes observed between 3 and 35 months of age. Rotavirus is endemic to all countries worldwide. The peak incidence of severe disease occurs at a younger age in high-mortality countries when compared to lower-mortality countries. Infants residing in low-income countries have more symptomatic episodes. There is a marked seasonality of outbreaks across temperate regions of the world with distinct peaks seen during the winter months. Infections occur year-round in most tropical countries, with illness in Africa being most prominent during the dry season. Infecting genotype diversity is highest in countries of Africa, Asia, and South America. Globally, the rapidly emerging genotypes G12P6 and G12P8 combined with ongoing activity of disease caused by genotypes G1P8, G2P4, G3P8, G4P8, and G9P8 together account for 90% of all human infections. In 2013, there were an estimated 215,000 rotavirus-associated deaths among children <5 years of age. More than 90% of these deaths occurred in low- and low-middle-income countries with the highest mortality rates seen in Africa (Fig. 26.1). Children from the five countries of India, Nigeria, Pakistan, Democratic Republic of the Congo, and Angola account for more than half (54%) of the world's rotavirus deaths. The highest impacted regions are those that have not yet or only very recently introduced rotavirus vaccine as part of their national immunization program (Fig. 26.2).

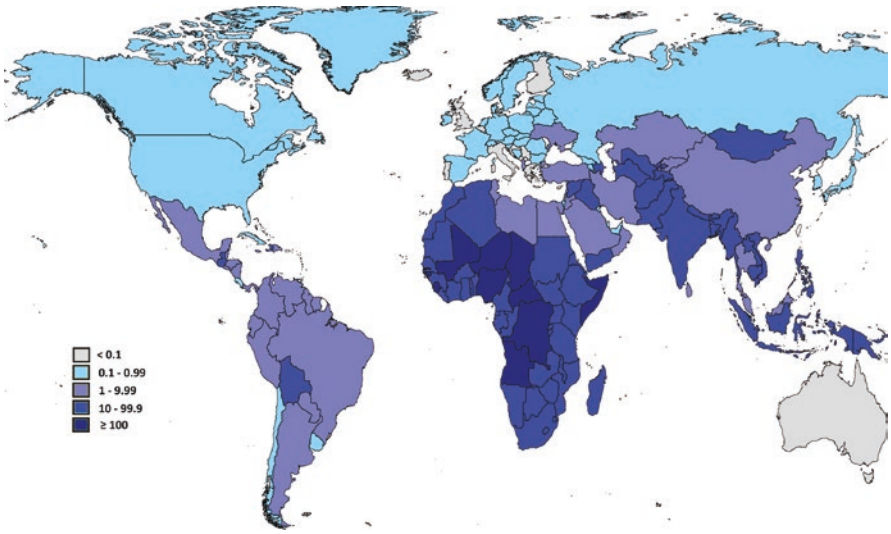

Fig. 26.1 Shown are 2013 rotavirus mortality rates per 100,000 children under 5 years of age by country. (Source of data to develop map: https://www.who.int/immunization/monitoring_surveillance/burden/estimates/rotavirus/en/)

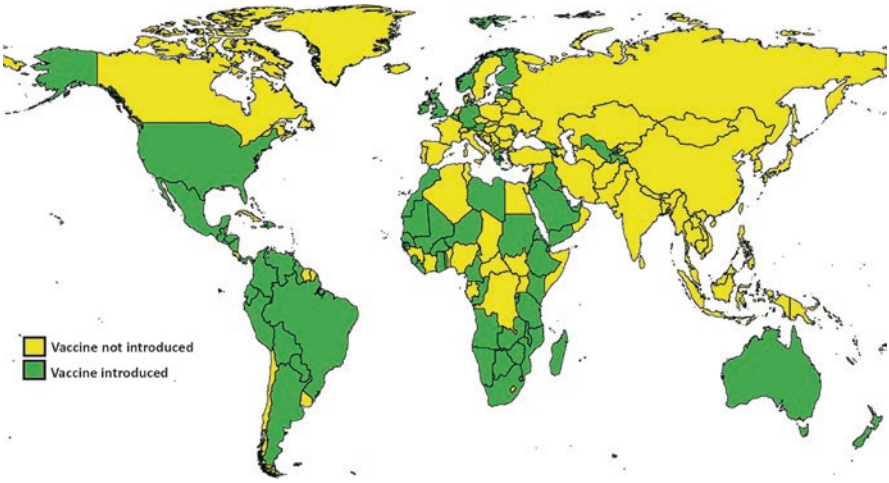

Fig. 26.2 Shown are countries that have introduced and not introduced rotavirus vaccine during infancy as of 2016. (Source of data to develop map: https://www.who.int/immunization/monitoring_surveillance/burden/estimates/rotavirus/en/)

Epidemiology: United States

The introduction of rotavirus vaccine to the universal infant immunization schedule in 2006 resulted in near elimination of disease during the 5 years that followed. Since then, cases still occur sporadically throughout the year with increases in disease activity noted during the winter and early spring. Infection with mild to moderate disease can occur in healthy vaccinated individuals, and disease outbreaks still occur where vaccination coverage is high due to the emergence of novel strains. G12P8 has become a fairly common replacement strain in some areas. In March 2017, it was responsible for a childcare center outbreak in Long Beach, California, where it affected 27 children and 4 staff members including an 86-year-old volunteer. The clinical triad of fever, vomiting, and diarrhea was incomplete in most, and the overall age distribution in the children was somewhat atypical, but the outbreak was otherwise quite classic for those seen during the pre-vaccine era. There were no associated hospitalizations or deaths.

Transmission

Rotavirus infection is highly contagious. Like other non-enveloped viruses, rotaviruses are quite resistant to inactivation under many environmental conditions. Infection is transmitted via the fecal-oral route and from contact with contaminated fomites. A dose inoculum of ten viral particles is sufficient to cause disease. The virus replicates in the small intestine epithelium, only very rarely causing viremia.

As many as 100 billion infectious viral particles are shed per gram of fecal material during the peak of virus replication. Children less than 5 years of age are at the highest risk regardless of hygiene practices or clean water access. Repeat infections during childhood induce sufficient partial heterotypic immunity that most infections later in life are minimally symptomatic, if at all.

Clinical Presentation

Following an incubation period of 1–3 days, the virus invades the mucosa of the small intestine causing malabsorption and gastrointestinal fluid losses. Illness is heralded by the abrupt onset of a clinical triad including fever, vomiting, and watery diarrhea typically lasting for 3–7 days. Prolonged diarrheal symptoms may persist due to disaccharidase deficiency that accompanies the destruction or atrophy of intestinal villi.

Complications may include severe dehydration, electrolyte imbalance, and metabolic acidosis secondary to gastrointestinal losses of bicarbonate. Without volume resuscitation, death ensues. Infection does not generate sterilizing immunity, but does reduce the severity of subsequent infections. Partial heterotypic immunity is seen with infecting strains that share the same G or P type with a previously infecting strain.

Management

No antiviral treatment is available. Rehydration therapy, with correction of electrolyte abnormalities and acid-base balance, is the standard of care. Spread of infection can be prevented with careful attention to hand hygiene and surface disinfection with appropriate products, especially during outbreaks. Cohorting and isolating those who are infected helps to prevent nosocomial transmission during hospitalization.

Rotavirus Vaccine

The first rotavirus vaccine to be approved for use in the United States was marketed by Wyeth-Lederle under the name RotaShield in 1998. The tetravalent rhesus monkey-human reassortant vaccine was withdrawn from the US market 1 year later in 1999 because post-licensure safety data indicated that first-time vaccine recipients had an increased risk of developing a form of intestinal blockage called intussusception. The risk was found to be caused by the vaccine at a rate of 1 excess case per 12,000 first-time vaccine recipients. Two safe and effective vaccines would emerge

more than 8 years later. Both remain currently available as two of the four WHO prequalified vaccines. RotaTeq is a pentavalent human-bovine reassortant virus vaccine marketed by Merck Sharp and Dohme since 2006, and Rotarix is a monovalent, live attenuated G1P8 vaccine marketed by GlaxoSmithKline since 2008. The vaccines provide some level of immunity to most circulating rotavirus strains.

Vaccines Available in the United States

RotaTeq (Merck) is provided as a ready-to-use liquid stored at 2 °C to 8 °C (never frozen). The dose should be administered as soon as possible once removed from refrigeration. It is approved for use in infants 6 weeks to 32 weeks of age and is recommended as a three-dose series at 2, 4, and 6 months of age. Available data support its use in pre-term infants according to chronological age.

Rotarix (GSK) is provided as a lyophilized powder for reconstitution. The lyophilized powder and diluent are stored at 2 °C to 8 °C (never frozen). After reconstitution, it should be administered within 24 hours. Rotarix is approved for use in infants 6 weeks to 24 weeks of age and is recommended as a two-dose series at 2 and 4 months of age.

Vaccine Characteristics

Immunizing Antigen

RotaTeq is a pentavalent reassortant vaccine. Four of the reassortant viruses included in the vaccine express one of the outer capsid proteins (G1, G2, G3, or G4) from a human rotavirus parent strain together with the P8 attachment protein derived from a bovine rotavirus parent strain. The fifth reassortant rotavirus expresses the P8 attachment protein from the human rotavirus parent strain together with the outer capsid protein G6 derived from a bovine rotavirus parent strain.

Each of the five reassortants are propagated individually in Vero cell cultures and then isolated, concentrated, and combined in a suspension of buffered stabilizer solution containing sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, and trace amounts of fetal bovine serum.

The plastic dosing tube and cap are latex-free.

Rotarix is a monovalent, live attenuated human rotavirus G1P8 strain propagated in Vero cells and then isolated, concentrated, and lyophilized. Vaccine diluent includes calcium carbonate as an antacid to protect vaccine virus during passage through the acidic stomach environment. The tips of the prefilled diluent applicators contain natural rubber latex.

Additives and Excipients

RotaTeq contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, and trace amounts of fetal bovine serum. It is preservative-free and latex-free. DNA fragments derived from porcine circovirus types 1 and 2 are detectable in the vaccine. Replication-competent porcine circovirus types 1 and 2 have not been recovered from the vaccine. Porcine circoviruses do not cause disease in humans.

Rotarix contains amino acids, dextran, sorbitol, sucrose, and Dulbecco's Modified Eagle Medium (DMEM). DMEM contains sodium chloride, potassium chloride, magnesium sulfate, ferric nitrate, sodium phosphate, sodium pyruvate, D-glucose, concentrated vitamin solution, L-cysteine, L-tyrosine, amino acid solution, L-glutamine, calcium chloride, and phenol red. The tip of the prefilled diluent applicators contains natural rubber latex. The vaccine is preservative-free. DNA fragments derived from porcine circovirus type 1 are detectable in the vaccine. Replication-competent porcine circovirus type 1 has not been recovered from vaccine. Porcine circovirus type 1 does not cause disease in humans. Liquid diluent contains calcium carbonate, sterile water, and xanthan.

Vaccine Recommendations

In the United States, the recommended rotavirus immunization schedule depends on the formulation being used. RotaTeq is a three-dose series recommended to be given at 2, 4, and 6 months of age. Rotarix is a two-dose series, recommended to be given at 2 and 4 months of age. For both vaccines, the minimum age for the first dose is 6 weeks. The maximum age for the first dose is 14 weeks and 6 days. The minimum interval between doses is 4 weeks. The maximum age for the final dose is 8 months and 0 days. If the brand is unknown for doses 1 and 2, the schedule should follow the three-dose regimen.

When using Rotarix, if the infant spits out or regurgitates "most of the dose," consider administering a replacement dose during the same visit. When using RotaTeq, a replacement dose is not recommended if the infant spits out or regurgitates any portion of the dose.

Contraindications to Vaccine

Contraindications to rotavirus vaccine include a previous life-threatening allergic reaction following a previous dose, a known severe allergy to any vaccine component, a medical history of an uncorrected congenital malformation of GI tract known to predispose the infant to developing intussusception, a history of intussusception, an existing diagnosis of severe combined immunodeficiency, babies who are

moderately or severely ill, and infants born to mothers who were treated with biologic response modifiers during pregnancy.

Warnings and Precautions for Vaccine Use

Careful consideration should be weighed prior to immunizing infants with a history of gastrointestinal disorders or weakened immune systems. Precaution should be used when vaccinating infants who have close contact with individuals diagnosed with immunodeficiency disorders as horizontal transmission of vaccine strain virus has been described.

Side Effects and Adverse Events

Both RotaTeq and Rotarix are very well tolerated.

Adverse events that occurred at a higher incidence within 42 days of any dose among RotaTeq vaccine recipients compared to controls included diarrhea (24% vs 21%), vomiting (15% vs 14%), otitis media (15% vs 13%), nasopharyngitis (7% vs 6%), and bronchospasm (1% vs 0.7%). During one of the largest placebo-controlled clinical vaccine trials ever completed involving approximately 70,000 infants, 6 cases of intussusception were reported among vaccine recipients and 5 among placebo recipients within 42 days of dosing. At follow-up, 365 days after receiving their first dose, a total of 13 and 15 cases of intussusception were reported among vaccine recipients and placebo recipients, respectively.

Rotarix was also tolerated very well. Adverse events that occurred with greater frequency in vaccine recipients compared to controls during the 31 days following dosing included irritability (11% vs 8.7%) and flatulence (2.2% vs 1.3%). During the large placebo-controlled clinical vaccine trials involving approximately 63,000 infants, 6 cases of intussusception were reported among vaccine recipients and 7 among placebo recipients within 31 days of dosing. At follow-up, 100 days after receiving their first dose, a total of 9 and 16 cases of intussusception were reported among vaccine recipients and placebo recipients, respectively.

Serious Adverse Events Caused by Rotavirus Vaccine

Post-marketing surveillance data indicate that there is a very low risk of developing post-vaccination intussusception that was not evident even from the exceptionally large phase 3 clinical trials of RotaTeq (n = 69,625) and Rotarix (n = 63,225). Worldwide, this serious side effect occurs in approximately 1 to 6 per 100,000 immunized. When it does occur as a vaccine-associated serious adverse reaction, it

typically follows the first dose by 7 to 10 days. The infant develops episodic bouts of abdominal pain that manifest as crying, often while pulling their legs up to their chest. Each episode may last only a few minutes but recurs several times each hour. A stool with the consistency of currant jelly is sometimes seen. Severe allergic reactions occur at rates less than one per million doses.

Estimated Effectiveness or Efficacy from Post-licensure Experience

Clinical trials of Rotarix vaccine indicate a 78.9% efficacy against gastroenteritis of any grade severity through two rotavirus seasons following vaccination and 83% to 96% reduction in hospitalizations due to severe disease through two rotavirus seasons, including 73–95% protection against non-G1 serotypes that expressed P8. Clinical trials showed that RotaTeq was 72% effective against gastroenteritis of any grade severity and 98% to 100% protective against severe gastroenteritis caused by any naturally occurring rotavirus regardless of type. Pooled efficacy against hospitalizations or ED (emergency department) visits following the full-series RotaTeq or Rotarix is 84% and 83%, respectively.

Impact of Vaccine Introduction

The gradual uptake of rotavirus vaccine throughout the world has already made a huge impact on disease-associated morbidity and mortality. Worldwide, all-cause diarrheal deaths among children <5 years old declined from 528,000 in 2000 to 146,480 in 2015.

Diarrheal illness has also decreased among unvaccinated older children and adults secondary to the herd immunity effect of vaccinating infants against rotavirus infection.

A 2017 analysis of 57 articles from 27 countries indicated that among children less than 1 year of age, all-cause hospitalizations and/or emergency department visits for acute gastroenteritis declined by an average of 32% following the introduction of vaccine.

By 2011, Mexico and Brazil had documented 22% and 41% declines in childhood deaths from diarrheal disease, and Mexico, Brazil, El Salvador, and Panama had documented a 17% to 51% decline in hospitalizations for acute gastroenteritis following vaccine introduction. In total, an estimated 122,000 rotavirus hospitalizations and 600 rotavirus deaths were averted across Latin America in 2015 alone.

Reports from Africa indicate that rotavirus vaccine prevented an estimated 21,000 deaths during 2016. Vaccine implementation in Tanzania reduced all-cause diarrhea admissions to Haydom Hospital by nearly 50%. In Ghana, projections

indicate that the vaccine will prevent 2.3 million cases and 11,000 deaths from rotavirus disease between 2012 and 2031 with an associated economic savings of between $7 and $11 million.

In the United States, during the pre-vaccine era, rotavirus infection was responsible for causing more than 400,000 acute care visits, more than 200,000 emergency department visits, between 55,000 and 70,000 hospitalizations, and between 20 and 60 deaths annually, with an estimated cost of $1 billion. Pre-vaccine annual mean rotavirus-associated hospitalization rates of 16 per 10,000 children less than 5 years of age had declined to just under 1 per 10,000 (94%) by 2012. A review of commercial insurance claims for children less than 5 years old between 2007 and 2011 showed that rotavirus vaccine had prevented 176,587 hospitalizations, 242,335 emergency department visits, and more than 1 million outpatient visits for diarrhea, with an associated cost savings of $924 million over 4 years.

Live attenuated rotavirus vaccines have proven safe and highly effective in preventing acute gastroenteritis caused by almost all of the major circulating serotypes worldwide. In resource-poor areas of the world, their impact is life-saving. The World Health Organization and Global Alliance continue working with national governments and nongovernment organizations, such as Rotary International, to expand vaccine use across the highly impacted regions of Africa and Asia.

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Vaccine Information Sheet

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PATH

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Rotateq Package Insert

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Chapter 27
Rubella

Manika Suryadevara

Rubella Infection

Etiology

Rubella virus, a single-stranded, positive-sense, enveloped RNA virus, is the only member of the *Rubivirus* genus, in the *Matonaviridae* family. This virus is readily inactivated by lipid solvents, formalin, ultraviolet light, low pH, and heat.

Pre-vaccine Epidemiology

Rubella, first identified in the early 1800s, was recognized as the cause of a benign febrile exanthematous illness of childhood. In the 1940s, however, an Australian ophthalmologist, Norman McAlister Gregg, noted a significant uptick in the number of infants with congenital cataracts seen in his practice. In addition to the abnormal eye findings, these babies also had evidence of cardiac defects. Gregg set out to determine whether a single teratogen could explain this unusual constellation of findings. Calculating back from date of birth, he determined that all of the infants' mothers were pregnant during the severe rubella outbreak of 1940. He then went back and questioned the mothers of the affected babies and learned that all but one developed rubella infection early during their pregnancy. The one mother who did not was so busy taking care of her other children that she could not remember whether or not she was ill at the start of pregnancy [1]. Although initially met with skepticism from the medical community, subsequent studies confirmed Gregg's

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hypothesis that rubella infection during pregnancy had devastating effects on fetal development. Currently, rubella is a leading cause of vaccine-preventable birth defects.

Studies of congenital rubella syndrome (CRS) during the European and US epidemics of the 1960s found that this disease process was not limited to the eyes and heart but also caused problems with brain development and cochlear atrophy. Up to 4 of every 1000 neonates were born with CRS [2]. In a large rubella epidemic that occurred in the United States during 1964 and 1965, there were 12.5 million rubella cases, > 11,250 fetal deaths, and > 20,000 cases of congenital rubella syndrome leading to >8000 deaf children and 3580 blind and deaf children [2]. Globally, where introduction of rubella-containing vaccines has been slow, congenital rubella syndrome continues to devastate babies. In 1996 alone, there were ~ 22,000 children born with CRS in Africa, ~46,000 in Southeast Asia, and 12,634 in the Western Pacific Regions.

Transmission

Rubella is transmitted through direct or droplet contact from nasopharyngeal secretions. Infected individuals are most contagious from a few days prior to through 7 days following onset of rash. Rubella virus replicates in the nasopharynx and regional lymph nodes. Within a week, viremia occurs with seeding of distal sites. Viremia in pregnant women leads to transplacental transmission of infection to the fetus.

Clinical Presentation

Rubella causes two distinct forms of infection: postnatal rubella infection and congenital rubella syndrome.

Postnatal Rubella Infection

Up to half of all postnatal rubella infections are asymptomatic. When clinical disease is present, it is typically mild starting with low-grade fevers and lymphadenopathy, most often affecting posterior auricular, posterior cervical, or suboccipital lymph nodes. Two to 3 days later, the patient develops a generalized, erythematous maculopapular rash. This exanthem starts on the face and spreads to the feet within 24 hours, lasting for about 3 days. Transient polyarthralgia or polyarthritis can be

seen and, while rare in children and adult men, can affect up to 70% of adult women. Joint symptoms most often involve the fingers, wrists, and knees and can be quite disabling, lasting for approximately 4 weeks. Complications from postnatal rubella infection are uncommon but can be severe, including encephalitis (1 per 6000 cases) and thrombocytopenia (1 per 3000 cases).

Congenital Rubella Syndrome

Rubella infection during pregnancy has the potential to result in congenital rubella syndrome (CRS). The highest risk occurs in infants born to mothers who were infected during the first 12 weeks of gestation, with risk of CRS decreasing with increasing gestation at the time of infection. The most common manifestation of CRS is sensorineural hearing loss. Other findings include ophthalmologic, cardiac, hematologic, and neurologic deficits (Table 27.1). CRS is associated with impaired hematopoiesis. In cases where the fetal bone marrow is sufficiently stressed, extramedullary hematopoiesis continues in the liver, spleen, and skin explaining why the cardinal manifestations of CRS include hepatosplenomegaly and a characteristic skin eruption referred to as a "blueberry muffin" rash. The raised violaceous skin lesions are islets of hematopoietic activity. Some of the CRS manifestations may not present until later in childhood, including diabetes mellitus and progressive encephalopathy, which can resemble subacute sclerosing panencephalitis. Children with CRS have a higher incidence of autism than the general population.

Table 27.1 Manifestations of congenital rubella syndrome

Ophthalmologic
Cataracts
Pigmentary retinopathy
Microphthalmos
Congenital glaucoma
Cardiac
Patent ductus arteriosus
Pulmonary artery stenosis
Other right ventricular outflow defects
Neurologic
Sensorineural hearing loss
Behavioral disorders
Microcephaly
Growth restriction
Interstitial pneumonitis
Radiolucent bone disease
Hepatosplenomegaly
Thrombocytopenia
Dermal hematopoiesis ("blueberry muffin" rash)

Management

There is no antiviral therapy available for the treatment of rubella infection. Management of infection is supportive care.

Prevention

The primary approach to community-wide rubella prevention includes the routine, universal use of a live attenuated rubella vaccine. In the United States, vaccination is administered in a two-dose series of the combined measles-mumps-rubella (MMR) vaccine, starting at age 1 year. Neither vaccination nor immune globulin is recommended for prevention of infection following exposure to rubella. However, it is recommended that eligible, susceptible individuals be vaccinated against rubella after an exposure to provide protection against any future exposures. Mothers who are found to be rubella seronegative during pregnancy should be immunized in the immediate postpartum period.

Live Attenuated Rubella Vaccine

Vaccine Characteristics

In the United States, live attenuated rubella-containing vaccine is derived from the RA 27/3 rubella virus strain grown in human diploid cell cultures. While rubella vaccine virus is manufactured separately from measles and mumps vaccine strains, only the combined MMR (measles mumps, and rubella) and MMRV (measles, mumps, rubella varicella) vaccines are sold in the United States (Table 27.2).

Vaccine Storage, Preparation, and Administration

MMR and MMRV are supplied as lyophilized virus to be stored between −50 °C and 8 °C and protected from light at all times. Improperly stored vaccine may lose potency. Sterile, preservative-free water is provided as the diluent and may be stored in the refrigerator (2–8 °C) or at room temperature. Prior to reconstitution, the vial containing the lyophilized vaccine should be stored at 2 °C to 8 °C. Once reconstituted, the vaccine should be administered immediately. After reconstitution, MMR vaccine can be refrigerated for up to 8 hours prior to use. MMRV must be administered within 30 minutes. Each 0.5 mL dose of vaccine is given by subcutaneous injection.

Table 27.2 Rubella-containing vaccine products available in the United States

	MMR[a] vaccine	MMRV[a] vaccine
Brand name (manufacturer)	MMR II (Merck)	ProQuad (Merck)
Age of administration	12 months of age and older[b]	12 months–12 years
Vaccine ingredients		
Active ingredients	Attenuated measles, mumps, rubella viruses	Attenuated measles, mumps, rubella, varicella viruses[c]
Stabilizer	Sorbitol, sucrose, gelatin, human albumin	Sorbitol, sucrose, gelatin, human albumin
Acidity regulators	Sodium phosphate, sodium chloride	Sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, sodium bicarbonate, potassium phosphate monobasic, potassium chloride, potassium dibasic, potassium phosphate monobasic
Cell culture growth	Fetal bovine serum	Bovine calf serum
Antibiotics	Neomycin	Neomycin
Preservative	None	None
Others		Residual MRC-5 cells

[a]MMR measles-mumps-rubella; MMRV measles-mumps-rubella-varicella
[b]MMR vaccine may be given to infants 6–11 months if living in an area of epidemic or traveling to endemic region
[c]Measles, mumps, and rubella components are similar between MMR and MMRV, but MMRV achieves higher measles geometric mean titers than MMR; varicella component in MMRV has higher potency than monovalent varicella vaccine, but varicella geometric mean titers are similar between the two vaccines

Vaccine Recommendations

In the United States, routine administration of rubella vaccine consists of a single dose of rubella-containing vaccine administered after 1 year of age. Since rubella-containing vaccine is only offered in combination with measles and mumps vaccines in the United States, recommendations include two doses of MMR vaccine (dose 1 at 12–15 months of age and dose 2 at 4–6 years of age). It is important to remember that any dose of MMR vaccine given before the first birthday is not valid because of the possibility that residual maternally derived (transplacental) antibodies will neutralize the vaccine strain viruses before they can induce an active immune response in the infant. A two-dose series should still be administered starting after 12 months of age. Refer to Chap. 18 “Measles” for information regarding the use of MMR and MMRV in children.

The main goal of rubella vaccination is the prevention of congenital rubella syndrome. To this end, special considerations for rubella vaccination include ensuring that adolescents and women of child-bearing age are immune to rubella infection.

Table 27.3 Evidence of immunity to rubella infection

Fulfilling any one of the following is evidence of immunity to rubella infection
Written, dated documentation of at least one rubella-containing vaccine at 12 months of age or older
Laboratory evidence of immunity
Laboratory confirmation of disease
Born before 1957

Table 27.3 lists the criteria used to establish immunity to rubella. Post-pubertal females without documentation of rubella immunity should be immunized if they are not pregnant. These individuals should be counseled to avoid pregnancy for at least 28 days following vaccination. Along these lines, all pregnant women should receive prenatal serologic screening for rubella immunity. Non-immune individuals should be vaccinated immediately postpartum. Seronegative individuals who have already received two doses of MMR vaccine in the past should receive a single dose of MMR vaccine postpartum, with no need for further serologic testing afterward. Furthermore, all susceptible healthcare personnel who may be exposed to rubella-infected patients or who may provide care to pregnant women should be rubella immune. Seronegative healthcare workers should be immunized.

Contraindications to Rubella Vaccine

Refer to Tables 4–6 in Chap. 18 "Measles" for contraindications, precautions, and considerations for MMR vaccine administration. As with other live attenuated vaccines, MMR vaccination is contraindicated during pregnancy. If a pregnant woman receives rubella vaccine or if she becomes pregnant within 4 weeks of receiving a vaccine, she should be counseled regarding the theoretical risk to the fetus; however, vaccine strain virus has never been shown to cause CRS in infants born to women who received vaccine during pregnancy.

Adverse Events

Other than injection site reactions, side effects to rubella vaccine typically occur 7–10 days following vaccination in non-immune individuals. Therefore, these effects are more likely to occur after the first rather than subsequent doses of rubella-containing vaccine. Refer to Table 7 in Chap. 18 "Measles" for adverse reactions following receipt of MMR vaccination. Adverse reactions that are specifically related to the rubella vaccine include fever, lymphadenopathy, arthralgias, and arthritis. The joint symptoms tend to be transient and are more common in adolescent and adult females than in males and young children.

Immunogenicity

Neutralizing serum antibodies are produced in 95% of individuals who receive a single rubella-containing vaccine at or after 12 months of age. Data show that a single dose of vaccine induces long-lasting immunity in over 90% of immunized individuals.

Impact of Vaccine on Disease Burden

In the early 1960s, there was a push for vaccine development to prevent the devastating effects of rubella infection during pregnancy. Using cell culture techniques, two US laboratories separately isolated the rubella virus and weakened the virus through cell culture passage to produce live attenuated rubella vaccines. In 1971, the RA 27/3 rubella vaccine was chosen by Maurice Hilleman to be incorporated into the newly combined measles-mumps-rubella (MMR) vaccine, which continues to be used today [3].

The optimal approach for vaccination was not initially clear. The United States introduced the rubella-containing vaccine in their infant immunization schedule, but CRS persisted (albeit at reduced rates) because pregnant women were still exposed to children and adults with rubella infection [3]. The United Kingdom, on the other hand, focused on immunizing adolescent girls; however, CRS persisted (also at reduced rates) because of vaccine refusals and exposures to males infected with rubella [3]. Ultimately, the United States combined strategies to include focus on both infant immunization and targeted vaccination of adolescent girls and women of child-bearing age, leading to the successful elimination of rubella from the country in 2004 [3].

In 2011, the World Health Organization (WHO) recommended that countries which have not yet introduced rubella-containing vaccines take advantage of their measles elimination program to also prevent CRS. By using measles-rubella (MR) or measles-mumps-rubella (MMR) vaccines, instead of monovalent measles vaccines, and maintaining vaccination rates above 80%, countries could eliminate endemic rubella infection. In 2009, the Americas were the first of the WHO regions to be declared free of endemic rubella.

Currently, 168 (87%) of the 194 WHO members, including all countries in the Americas, European, and Western Pacific Region, have introduced rubella-containing vaccines (Fig. 27.1). Estimated global vaccine coverage of 69% has resulted in a 97% decline in reported rubella cases, worldwide [4]. The regions of Africa and Southeast Asia have the lowest rubella vaccine coverage rates and continue to report the highest rates of CRS (Fig. 27.2). As of mid-2020, rubella has been eliminated in 81 (42%) of the world's nations (Fig. 27.3) [5].

Disease eradication is defined as the reduction of disease incidence to zero, with no further need to continue control measures. Rubella is a good candidate for

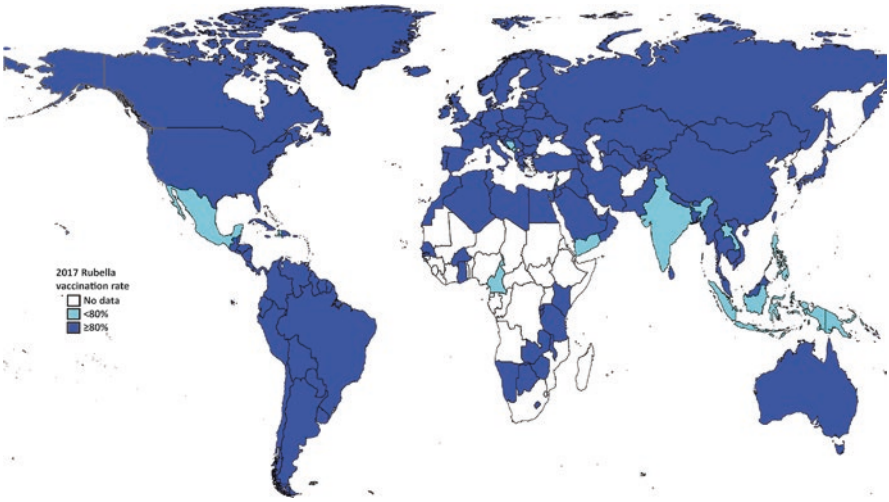

Fig. 27.1 Global rubella-containing vaccine coverage rates, 2017

Fig. 27.2 The number of reported congenital rubella syndrome cases by country, 2017

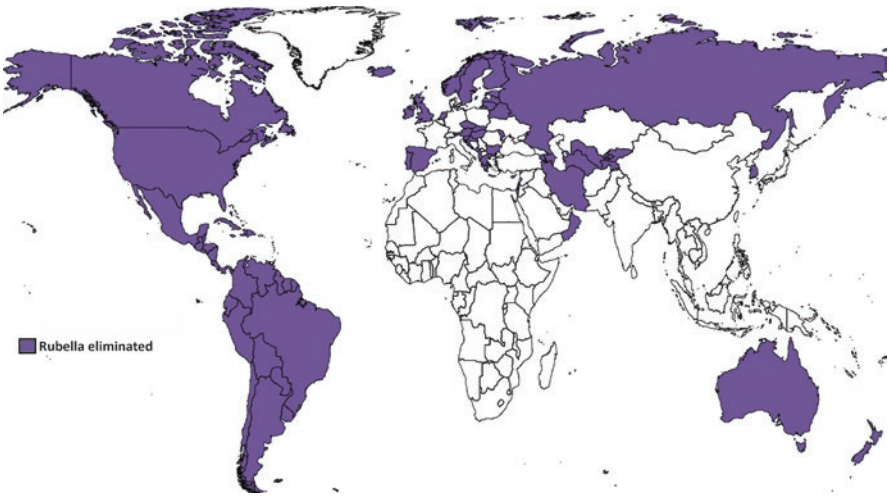

Fig. 27.3 Countries where rubella infection has been verified to be eliminated

eradication, given that humans are the only host, safe and effective vaccines are widely available, accurate diagnostic tools exist, and public health systems are already in place to implement immunization programs. The recent successful elimination of rubella infection from the WHO Americas Region is proof of the concept that rubella can, 1 day, be globally eradicated.

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Chapter 28
Smallpox

Cynthia Bonville and Manika Suryadevara

Smallpox Infection

Etiology

Variola virus, a double-stranded DNA virus, is a member of the *Orthopoxvirus* genus in the *Poxviridae* family. Other orthopoxviruses that infect humans include vaccinia, cowpox, and monkeypox viruses. Orthopoxviruses have highly conserved structural proteins, providing cross-protection following natural infection or vaccination.

Pre-vaccine Epidemiology

Smallpox is believed to date back to the third century BCE in the Egyptian empire. Written reports from the fourth century in China also describe a similar disease. Global spread of virus corresponds with spread of civilizations over time, from China to Korea and Japan and then to Africa and Western Europe. Colonization brought infection from Europe and Africa to the Americas and then lastly Australia. It is estimated that 400,000 people died from smallpox each year in Europe during the eighteenth century. Most of the survivors had some form of sequelae, whether it be significant scarring and deformities or blindness. With a mortality rate of 30%, smallpox has killed millions of people around the world.

It was well-known that infection with smallpox offered protection from future disease. Variolation (named after the variola virus), a deliberate inoculation of

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susceptible individuals with dried smallpox scabs, became the initial method of disease prevention. Variolation results in a mild form of disease followed by lifelong immunity. This disease-preventing procedure had been used for centuries in Asia and Africa prior to its introduction in Europe in the eighteenth century. Variolation was introduced to the US colonies in 1721 after Reverend Cotton Mather learned about this procedure from his slave, Onesimus, who had been previously inoculated. A smallpox outbreak in Boston that year had sickened half of the city's residents and claimed the lives of 15% of those infected. To prevent further devastation from the disease, Mather advocated for Boston physicians to adopt variolation. In response, there was wide opposition to variolation among both Boston residents and physicians for reasons including that variolation goes against God's will and that the procedure was untested and could worsen the spread of infection throughout the community. Despite the anti-inoculation movement, which went as far as throwing a hand grenade into Mather's house, Dr. Zabdiel Boylston started a variolation program to inoculate volunteers. Using a statistical approach comparing death after natural infection with death after variolation, he showed that variolation reduced mortality rates from 15% to 2%, likely the first time an analysis like this was used to evaluate a medical procedure [1].

Fifty years later, during the Revolutionary War, smallpox outbreaks killed many of George Washington's troops costing them battle wins, as the majority of the British army were nearly all immune. In the last 2 weeks of May 1776, 25% of American troops died of smallpox. The following year, Washington mandated variolation for his soldiers, following which time smallpox was no longer an obstacle to successful defeat of the British Army [2, 3].

It had long been understood that dairymaids infected with cowpox were later protected from smallpox infection. Edward Jenner hypothesized that cowpox could be used to inoculate susceptible individuals as a deliberate method of smallpox protection [1]. In 1796, Jenner used fresh cowpox lesions on the hands of a young dairymaid to inoculate an 8-year-old boy, James Phipps. Over the next 10 days, Phipps developed a febrile illness with axillary discomfort and reduced appetite but then clinically improved. A few months later, Jenner inoculated the boy with fresh smallpox lesion. He never displayed signs of infection, supporting Jenner's initial hypothesis [1]. At some point in the 1800s, the virus used in smallpox vaccine switched over from cowpox to vaccinia virus. Over time, vaccination began to replace variolation as a safer and more effective method to prevent smallpox.

In 1809, the first of the nation's immunization laws was passed in Massachusetts requiring their residents to be vaccinated against smallpox. Other states followed suit with compulsory vaccination laws. Opposition to mandated vaccinations grew nationwide, resulting in some states repealing their newly enacted laws. One hundred years later, when a smallpox outbreak spread through Cambridge in 1902, the city's board of health mandated that adult residents be vaccinated or pay a fine. Henning Jacobson refused both and appealed to the US Supreme Court. In 1905, the Supreme Court ruled that the states had the power to enact laws to protect public health and that "the liberty secured by the Constitution of the United States to every

person within its jurisdiction does not import an absolute right in each person, to be, at all times and in all circumstances wholly free from restraint" [4]. To further support for compulsory vaccinations, in the 1922 case of *Zucht v King*, the US Supreme Court upheld the city ordinance to require smallpox vaccination to attend public and private schools [5].

Transmission

Smallpox is transmitted through inhalation of airborne virus through droplets from oropharynx of infected people. Transmission via direct contact with skin lesions or contaminated fomites has also been reported. Individuals are contagious from the onset of oral lesions until the crusted skin lesions separate. As individuals with smallpox infection were often very ill and bedridden, secondary cases were typically limited to household contacts, with attack rates approaching 60% prior to vaccination.

Clinical Presentation

There are two clinical forms of smallpox infection, variola major and variola minor, with each form caused by a different strain of the virus.

Variola Major

This is the more severe form of smallpox infection. Illness begins with a prodrome phase with symptoms of high fevers, malaise, prostration, headaches, back pain, abdominal pain, and vomiting. Individuals are very ill and weak during this period. After 2–4 days, the infected person begins to feel better. Oropharyngeal lesions develop within a day, enlarging, ulcerating, and spreading. These lesions have a high virus titer, and as such, individuals in this stage of infection are highly infectious. Within the next 24 hours, a cutaneous rash develops. Within variola major disease, there are four clinical presentations of rash eruption.

Ordinary Smallpox

This type of smallpox infection is the most common, occurring in over 85% of unvaccinated individuals. Fevers tend to lessen as exanthematous rash starts. The rash begins as a few macules on the face ("herald spots"), spreading to the trunk and

distal extremities, including palms and soles, within 24 hours. Over the next 1–2 days, these macules develop into papules. After 1–2 days, they progress to clear fluid-filled vesicles, with an erythematous halo around the lesions, which may be umbilicated or become confluent. By the following day, the vesicles become hard pustules, filled with thick opaque fluid ("pearls of pus"), deep into the dermis. Crusting of the lesions begins to occur by day 10. Crusts separate in the third week of infection, leaving extensive scarring at the site of infection. Once the crusting separates, the individual is no longer infectious. Throughout the duration of infection, the lesions exhibit the same stage progression at any given time period.

Complications of smallpox include extensive scarring, bacterial superinfection of skin lesions, facial deformities, blindness from corneal scarring, encephalitis, osteomyelitis, spontaneous abortions or stillbirths, and male infertility. Mortality rate during epidemics were reported to be up to 30% in unimmunized population, with the highest risk of dying among pregnant women, children younger than 1 year, and adults older than 30 years. Survivors have lifelong immunity.

Modified Smallpox

This mild form of smallpox infection occurs in ~5–10% of cases, primarily in individuals with prior natural or vaccine-induced immunity. Skin lesions, in this form, are fewer in number, are more superficial, and evolve quickly, with crusting occurring within a few days. Fever is usually absent. Modified smallpox resembles varicella (chickenpox) infection and is rarely fatal.

Flat Smallpox

Also known as malignant smallpox, this form is very rare and thought to be associated with cellular immunodeficiency. Skin lesions in this form develop slowly; remain flat, soft, and velvet to the touch; and never progress to the pustular stage. Severe constitutional symptoms, including high fevers, persist even after rash onset. Most cases are fatal.

Hemorrhagic Smallpox

This is an uncommon form of smallpox, occurring in less than 1% of cases. Illness consists of a prolonged prodromal period, with no defervescence, followed by the development of rash with bleeding into the skin lesions and disseminated intravascular coagulopathy. Other hemorrhagic manifestations include subconjunctival bleeding, mucosal bleeding, and hematuria. Death due to toxemia and multi-organ failure occurs within a week.

Variola Minor

This mild form of smallpox is clinically indistinguishable from variola major. Yet, it causes less severe systemic illness and has rapid rash evolution, less scarring, and less fatalities.

Management

There is no proven treatment for smallpox infection. Management of infection is primarily supportive care. Three antiviral therapies, tecovirimat, cidofovir, and brincidofovir, have demonstrated effectiveness against poxviruses in vitro and in animal studies, although effectiveness in humans infected with smallpox is not known. Based on studies in prairie dogs challenged with monkeypox virus and safety studies in humans, in July 2018, the FDA approved tecovirimat to be the first drug available for treatment of smallpox infection. The Centers for Disease Control and Prevention's Strategic National Stockpile consists of tecovirimat and cidofovir in case of a public health emergency. Vaccinia immunoglobulin is indicated for management of immunization complications, including eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, vaccinia infections in individuals with skin conditions, and other vaccinia infections. Vaccinia immunoglobulin is not used to treat smallpox infection.

Smallpox Vaccine

Vaccine Characteristics

Smallpox vaccine has not been routinely administered in the United States since the 1970s. In fact, no government currently recommends routine smallpox vaccination. However, smallpox vaccine is available for potential exposure. Vaccination within 3–4 days after exposure can protect against fatal infection and should be administered as soon as possible in these cases. The Centers for Disease Control and Prevention have three vaccines in their Strategic National Stockpile to prevent smallpox among laboratory and healthcare workers at high risk of occupational exposure and for post-exposure prophylaxis in the case of an emergency event.

ACAM2000, manufactured by Emergent Product Development Gaithersburg, Inc., was approved by the FDA in 2007 for active immunization against smallpox infection. Over 95% of individuals develop protective neutralizing antibody levels in response to primary vaccination. This replication-competent vaccine consists of live vaccinia virus, not variola virus, so it will not cause smallpox infection. Other vaccine ingredients include HEPES buffer, human serum albumin, sodium chloride,

mannitol, glycerol, phenol, and trace amounts of neomycin and polymyxin B. Vaccination causes a local vaccinia virus infection at the epidermis and surrounding dermis of the injection site, as well as subcutaneous tissue and draining lymph nodes. Transient viremia occurs and may result in rash, fever, headaches, and body aches. Vaccinia virus can be transmitted from immunized individual to unvaccinated persons through close contact with the inoculation site. Special care of the inoculation site is required to prevent spread of virus to distal sites and to unvaccinated close contacts.

JYNNEOS, manufactured by Bavarian Nordic A/S, was approved by the FDA in 2019 for the prevention of smallpox and monkeypox in adults of ages 18 years and older determined to be at high risk for these infections. This replication-deficient smallpox vaccine uses the live attenuated Modified Vaccinia Ankara. Other vaccine ingredients include Tris buffer, sodium chloride, benzonase, and gentamicin.

Aventis Pasteur Smallpox Vaccine (APSV) uses a live, replication-competent vaccinia virus. Other vaccine ingredients include glycerol, phenol, and brilliant green. This investigational vaccine is not yet licensed or approved by the FDA. With a safety profile that is expected to be similar to that of ACAM2000, this vaccine can be supplied under an investigational new drug (IND) or emergency use authorization (EUA) in emergency situations where ACAM2000 is unavailable.

Vaccine Storage, Preparation, and Administration

ACAM2000 is supplied as a lyophilized powder and a packaged diluent. The lyophilized powder is stored frozen (−15 °C to −25 °C) but can be refrigerated (2 °C–8 °C) for up to 18 months. The provided diluent is stored at room temperature (15 °C–30 °C). The powder should be brought to room temperature prior to reconstitution with 0.3 mL of the diluent. Vaccine administration should only be performed by healthcare providers trained in the multiple puncture technique. A two-pronged (bifurcated) stainless steel needle is used to puncture the upper arm over the insertion of the deltoid muscle 15 times within a 5 mm diameter in a few seconds. The puncture should be superficial but vigorous enough to create blood drops. The area of inoculation should be covered with gauze and a semipermeable barrier. Discard all residual vaccine product and paraphernalia as a biohazard. Vaccine "take" is evaluated 6–8 days post-inoculation.

JYNNEOS is supplied as single-dose vials, which are stored frozen (−25 °C to −15 °C) and protected from light. These vials should be brought to room temperature before use. Thawed suspension should be milky, light yellow to pale white without particulate matter. Discard if discolored and particulate matter present. A 0.5 mL dose is administered subcutaneously.

APSV is supplied as 0.25 mL aliquots in a sterile 2 mL glass vial. 1 mL of provided diluent is added to the aliquot to yield 500 doses. Vaccine is administered as

a 2.5 μL dose by the same multiple puncture technique as ACAM2000. Biohazard disposal of all vaccine-contaminated materials is required.

Vaccine Recommendations

As of 2015, Advisory Committee on Immunization Practices (ACIP) recommendation for smallpox vaccine specifies the use of ACAM2000 vaccine for routine vaccination of laboratory personnel with direct contact with cultures of or animals infected with replication-competent vaccinia virus, recombinant vaccinia virus, or other human-infecting orthopoxviruses. Certain US military personnel are also eligible for vaccination in cases of potential bioterrorism threat. Healthcare personnel who treat patients with vaccinia virus infections and anyone administering ACAM2000 should be offered vaccine. Individuals at very high risk of acquiring infection should be vaccinated every 3 years [6]. In the event of an emergency outbreak, the CDC will work with federal, state, and local officials to determine vaccine need.

Individuals aged 18 years or older at high risk for occupational exposure to orthopoxviruses who are not eligible to receive ACAM2000 could receive JYNNEOS. This vaccine is administered as two doses separated by 4 weeks in unimmunized individuals. Previously vaccinated individuals only require a single dose. Specifically, JYNNEOS could be considered for laboratory workers directly handling cultures or animals infected with orthopoxviruses, who are immunosuppressed or have an allergy to ACAM2000.

Contraindications to Smallpox Vaccine

As per the package insert, ACAM2000 is contraindicated in people with severe immunodeficiency (such as bone marrow transplants, primary or acquired immunodeficiency) who are not expected to benefit from vaccine. As per ACIP vaccine recommendations, contraindications for nonemergency use of ACAM2000 include a vaccinee or vaccinee's household contacts with a history of atopic dermatitis or other exfoliative skin conditions, age less than 1 year, pregnancy, breastfeeding, primary or acquired immunodeficiency, and underlying heart disease (including those with three or more known cardiac risk factors). Active eye disease treated with topical steroids, moderate to severe illness on the day of vaccination, and an allergy to any vaccine component are other contraindications to ACAM2000. In addition, contraindications to JYNNEOS include previous severe allergic reaction to vaccine or any vaccine component. Of note, there are no absolute contraindications for emergency use, and anyone directly exposed may be offered vaccine if the benefits outweigh the risks.

Adverse Events

Common adverse reactions to smallpox vaccines include fever, fatigue, myalgia, folliculitis, urticaria, and headaches, with events more likely to occur after primary vaccination than re-vaccination. Inadvertent inoculation of other sites is the most common complication of vaccination. Across all ACAM2000 studies, 97% and 92% of vaccinia-naïve and previously immunized recipients, respectively, experienced at least one adverse event.

Severe adverse reactions occur more commonly in children younger than 5 years of age and people receiving primary vaccination. These complications, including myocarditis, pericarditis, encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme, eczema vaccinatum, blindness, and fetal death in pregnant women, may rarely lead to severe disability and permanent neurologic sequelae. Death, most often a result of sudden cardiac death, encephalitis, progressive vaccinia, or eczema vaccinatum, following vaccination is a rare event, occurring in approximately one case per million primary vaccinations and one case per four million re-vaccinations. Deaths have also been reported among unvaccinated contacts of immunized individuals. CDC provides a consultation service to help clinicians diagnose and manage patients with suspected vaccinia virus vaccine adverse reactions. Information about how to access this service is on the CDC smallpox vaccine adverse event website (https://www.cdc.gov/smallpox/clinicians/vaccine-adverse-events5.html).

Impact of Vaccine on Disease Burden

Throughout the nineteenth century, smallpox was widespread in the United States. National vaccination programs led to significant reduction in disease burden and elimination of smallpox from the country by 1949. Ten years later, the World Health Organization announced its plan for global eradication of smallpox, although a lack of coordinated infrastructure, funds, personnel, and vaccine prevented achievement of its mission. With smallpox still endemic in Asia and Africa, in 1967, the WHO Strategic Action Plan for Intensified Eradication Program was launched, with improved freeze-dried vaccine stock, the development of the bifurcated needle to simplify vaccine administration, enhanced surveillance systems, and mass immunization campaigns. In developed countries, mass vaccination was successful in inducing population-wide immunity. However, this strategy was more difficult to implement in developing countries with limited resources required for vaccination. In eastern Nigeria, for example, the strategy of case finding and isolation led to the disappearance of smallpox from the region even with less than half of the population vaccinated [7].

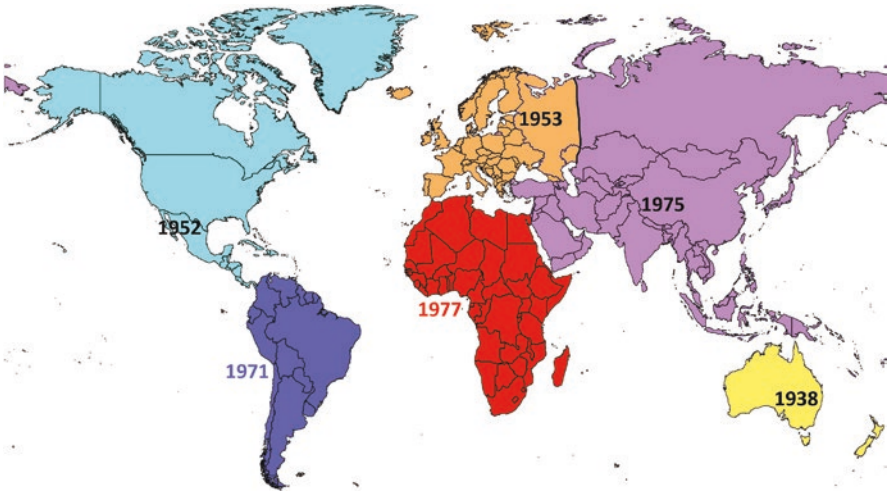

Fig. 28.1 Map depicting the year that smallpox was eliminated from the continent

In 1971, with smallpox disease still endemic in Asia and Africa, Bangladesh declared independence from Pakistan. Over the course of prior 4 years, this country devastated by war and famine suffered from an estimated 225,000 smallpox cases and 40,000 smallpox deaths. Following independence, national leadership implemented measures including enhanced surveillance, rewards for reporting infection, and disease containment through isolation and vaccination [8]. As smallpox was effectively contained and eliminated, in 1975, 3-year-old Rahima Banu, living in Kuralia, Bangladesh, was the last person to be infected with endemic variola major. Two years later, the last case of naturally acquired smallpox (variola minor form) occurred in the Merca District of Somalia. In 1980, the World Health Assembly declared the world free of naturally occurring smallpox, marking the first, and so far only, time that global eradication of an infectious disease was achieved (Fig. 28.1).

In the 1970s, routine smallpox vaccination in the United States was discontinued for infants (1971), healthcare workers (1976), and international travelers (1982) as risks of vaccination outweighed its benefits. After declaration of smallpox eradication, all virus stocks were either destroyed or given to four labs in the United States, Russia, England, and South Africa. In 1984, England and South Africa destroyed or transferred their stocks, leaving the CDC in Atlanta, Georgia, and the State Research Center for Virology and Biotechnology in Russia as the only two labs with virus stocks. The CDC Strategic National Stockpile still contains vaccines and therapeutics, however, to protect its citizens in the case of bioterrorism or smallpox emergencies.

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WHO https://www.who.int/csr/disease/smallpox/en/

Chapter 29
Tetanus

Joseph Domachowske

Tetanus Infection

Etiology

Tetanus is caused by a toxin produced by *Clostridium tetani*, a spore-forming anaerobic, gram-positive bacillus. Tetanus infections result when *C. tetani* spores are introduced into wounds or injuries that have created an anaerobic environment. Circumstances that produce tetanus-prone wounds and injuries are listed in Table 29.1. Fecal contamination of the umbilicus has been the source of infection in some cases of neonatal tetanus where cultural practices include placing mud packs on the umbilical stump.

Epidemiology

Tetanus spores are ubiquitous in the soil all over the world, so the incidence of tetanus in a population primarily reflects the level of success a nation is able to achieve from their immunization program. Tetanus remains common in countries with suboptimal immunization coverage rates, inadequate or low-quality prenatal care, and/or unsafe traditional or cultural umbilical cord care practices and where newborn deliveries without the assistance of trained health professionals are a routine. In 1990, 356,000 deaths from tetanus were reported worldwide. Vaccination campaigns, with special attention directed to preventing neonatal tetanus, were highly successful, and by 2013, 59,000 deaths from tetanus were reported, a decline of

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Table 29.1 Tetanus-prone wounds and injuries

Any wound that is contaminated with:
Dirt or soil
Feces
Saliva, from animal bites
All puncture wounds
All wounds that result in an avulsion injury
Gunshot wounds
Any wound created by a penetrating projectile
Crush injuries
Burns
Frostbite

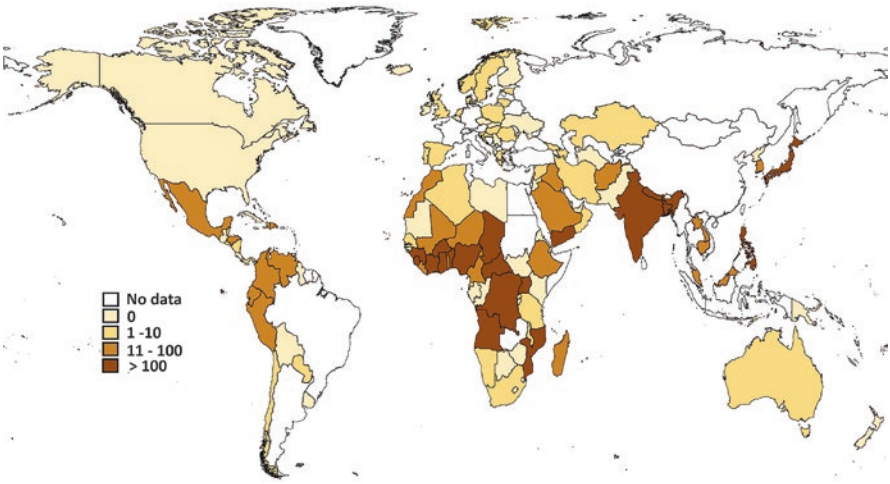

Fig. 29.1 World map showing the total number of tetanus cases reported to the World Health Organization in 2018

more than 80%. Countries reporting cases of tetanus to the World Health Organization in 2018 are shown in Fig. 29.1.

Transmission

The pathogen can be found as normal large intestinal flora in a large number of animal species and is ubiquitous in the environment. Transmission occurs when environmental spores contaminate a wound. A classic example of a tetanus-prone injury is a dirty puncture wound to the foot, such as stepping on a rusty nail while walking barefoot on the garden. Following contamination of a wound, the incubation period for tetanus ranges from 3 days to 3 weeks with most cases presenting within a week.

Spores are stable in the environment indefinitely and withstand prolonged exposures to phenol, ethanol, and formaldehyde. Inactivation is only achieved chemically using iodine, glutaraldehyde, or hydrogen peroxide. Heat is also effective, but autoclaving must reach 121 °C for at least 15 minutes.

Clinical Presentation

The onset of tetanus is gradual, presenting over 1 day to 1 week and then progressing to extremely painful generalized muscle spasms. These and other typical symptoms of tetanus are summarized in Table 29.2. Clinically, four types of tetanus are recognized based on the most prominent signs and symptoms (Table 29.3). Generalized tetanus is the most common form. Localized tetanus isolated to muscle groups immediately surrounding the contaminated would is less common and may

Table 29.2 Symptoms associated with tetanus

Painful jaw clenching, tightness, or cramping
Sudden involuntary muscle spasms
Generalized muscle stiffness, typically painful
Trouble swallowing
Low-grade fevers
Excessive sweating
Tachycardia
Headache

Table 29.3 Identifying characteristics of the four recognized clinical forms of tetanus

Generalized tetanus
Most common clinical form
"Lockjaw" progressing to involve other skeletal muscle groups
Muscle spasms
Opisthotonus from tetanic contractions of the paraspinal muscles
Risus sardonicus or "sardonic smile" from facial muscle tetany
Localized tetanus
Pain and weakness at the wound site
Progression to localized muscle spasms or rigidity
Cephalic tetanus
A form of localized tetanus involving cranial nerve dysfunction
Associated with infected wounds of the neck and head
Neonatal tetanus
Generalized tetanus in a newborn
Absence of protective maternal immunity
Contamination of the umbilical stump during or after a home delivery
High risk among cultures where mud or cow dung is applied to the umbilical stump to control bleeding

be overlooked unless or until a more generalized form manifests. Cephalic tetanus is essentially a localized form of tetanus that involves dysfunction of one or more of the cranial nerves following the contamination of a neck or head wound. Neonatal tetanus is generalized tetanus in a susceptible newborn following exposure to spores present in dirt, mud, or feces. Infants born at or near term to mothers who are tetanus immune are also immune to tetanus by virtue of transplacental anti-tetanus neutralizing antibody. This passive immunity wanes over time but allows protection against tetanus while the infant completes their three-dose primary series of tetanus toxoid vaccine at 2, 4, and 6 months of age.

Management

The medical management of tetanus requires hospitalization and care by a multidisciplinary team including intensivists; hospitalists; specialists in neurology, infectious disease, and rehabilitation; clinical pharmacists; and specialized nursing. Immediate goals are to stabilize the patient's airway and circulation, eradicate the pathogen, and neutralize the tetanus toxin. The antibiotic of choice to treat tetanus is metronidazole. Penicillin G may be used as an alternative. Unbound toxin can be neutralized quite efficiently by administering human tetanus immune globulin (TIG). If TIG is not available, pooled human immune globulin may be given intravenously, although it contains a lower concentration of neutralizing antibody. Tetanus toxin binds to its target on the presynaptic membrane irreversibly, so while TIG can prevent worsening of symptoms by neutralizing unbound toxin, it offers no relief from existing symptom. Recovery is slow and gradual over several months because the process requires the growth of new presynaptic connections. Supportive care with meticulous attention to pain control is needed well into the convalescent phase of the illness.

Tetanus Vaccine

Tetanus vaccine is among the most simple and elegant immunizations available. The vaccine immunogen, tetanus toxoid, is a derivative of tetanus toxin that has been rendered nontoxic. Monovalent vaccine formulations of tetanus toxoid are not currently available anywhere in the world. Instead, tetanus toxoid is one of two or more components included in a growing variety of combination vaccine formulations. All formulations of tetanus vaccine presently in use also include diphtheria toxoid (abbreviated DT and Td), and all those that contain immunogens beyond tetanus and diphtheria toxoids all include pertussis antigens (DTaP and Tdap) (see Table 29.4). Lower case "d" is used to indicate the lesser amount of total diphtheria toxoid included in vaccines used in formulations given as booster doses to individuals older than 7 years (Td and Tdap). The DT vaccine formulation is not commonly

Table 29.4 Available combination vaccines that include tetanus toxoid

Combination vaccine	Brand name	Manufacturer	Diseases targeted for prevention
DT	None	Sanofi Pasteur	Diphtheria, tetanus
Td	Tenivac	Sanofi Pasteur	Tetanus, diphtheria
DTaP	Daptacel Infanrix	Sanofi Pasteur GlaxoSmithKline	Diphtheria Tetanus Pertussis
Tdap	Adacel Boostrix	Sanofi Pasteur GlaxoSmithKline	Tetanus Diphtheria Pertussis
DTaP, HepB, IPV	Pediarix	GlaxoSmithKline	Diphtheria Tetanus Pertussis Hepatitis B Polio
DTaP, IPV	Kinrix Quadracel	GlaxoSmithKline Sanofi Pasteur	Diphtheria Tetanus Pertussis Polio
DTaP, IPV, Hib	Pentacel	Sanofi Pasteur	Diphtheria Tetanus Pertussis Polio *Haemophilus influenzae* type B
DTaP, IPV, HepB, Hib	Vaxelis	MSP Vaccine Company	Diphtheria Tetanus Pertussis Polio Hepatitis B *Haemophilus influenzae* type B

used but is available to provide protection against diphtheria and tetanus in infants and young children for whom pertussis vaccination is contraindicated. For younger children, quadrivalent (adding in polio immunogens, abbreviated DTaP-IPV), pentavalent (adding either hepatitis B or *Haemophilus influenzae* type B, DTaP-IPV-HepB and DTaP-IPV-HIB), and hexavalent (adding both hepatitis B or *Haemophilus influenzae* type B immunogens, DTaP-IPV-HepB-HIB) combination vaccines are also widely used throughout the world. During young childhood, five doses of tetanus and diphtheria (capital "D") toxoid-containing vaccines are recommended to be administered at ages 2, 4, 6, and 15–18 months and at 4–6 years. The first dose may be administered as early as 6 weeks of age. The use of pentavalent or hexavalent vaccines at 2, 4, and 6 months has the benefit of reducing the number of injections needed at each immunization visit (Fig. 29.2). Other benefits of combination vaccines are discussed in Chap. 35.

Starting at age 7 years, and throughout adulthood, vaccine formulations that contain the lesser amount of diphtheria toxoid, as indicated in the vaccine abbreviation with a lower case "d," as in Td and Tdap, are used (see also Chap. 10).

a

Age ▶ / Vaccine ▼	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months
Rotavirus			Rota	Rota	[Rota]			
Diphtheria, Tetanus, Pertussis			DTaP	DTaP	DTaP		DTaP	
Hepatitis B	HepB	HepB				HepB		
Haemophilus influenzae type b			Hib	Hib	[Hib]	Hib		
Inactivated Poliovirus			IPV	IPV		IPV		
Pneumococcal			PCV	PCV	PCV	PCV		
Influenza						Influenza (2 doses)		
Measles, Mumps, Rubella						MMR		
Varicella						Varicella		
Hepatitis A						HepA (2 doses)		
Total Injections	1	0-1	4-5	4	4-6	7-11		

b

Age ▶ / Vaccine ▼	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months
Rotavirus			Rota	Rota	[Rota]			
Diphtheria, Tetanus, Pertussis			DTaP-IPV-Hep-B at 2, 4, and 6 mos				DTaP	
Inactivated Poliovirus								
Hepatitis B	HepB							
Haemophilus influenzae type b			Hib	Hib	Hib	Hib		
Pneumococcal			PCV	PCV	PCV	PCV		
Influenza						Influenza (2 doses)		
Measles, Mumps, Rubella						MMR		
Varicella						Varicella		
Hepatitis A						HepA (2 doses)		
Total Injections	1		3	3	4	9		

c

Age ▶ / Vaccine ▼	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months
Hepatitis B	HepB	HepB				HepB		
Rotavirus			Rota	Rota	[Rota]			
Diphtheria, Tetanus, Pertussis			DTaP-IPV-HIB at 2, 4, and 6 mos				DTaP-IPV-HIB	
Haemophilus influenzae type b								
Inactivated Poliovirus								
Pneumococcal			PCV	PCV	PCV	PCV		
Influenza						Influenza (2 doses)		
Measles, Mumps, Rubella						MMR		
Varicella						Varicella		
Hepatitis A						HepA (2 doses)		
Total Injections	1	0-1	2-3	2	3-4	7-9		

d

Age ▶ / Vaccine ▼	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months
Hepatitis B	HepB							
Rotavirus			Rota	Rota	[Rota]			
Diphtheria, Tetanus, Pertussis			DTaP-IPV-HIB-HepB at 2, 4, and 6 mos				DTaP-IPV-HIB	
Haemophilus influenzae type b								
Inactivated Poliovirus								
Pneumococcal			PCV	PCV	PCV	PCV		
Influenza						Influenza (2 doses)		
Measles, Mumps, Rubella						MMR		
Varicella						Varicella		
Hepatitis A						HepA (2 doses)		
Total Injections	1	0	2	2	2-3	7-8		

Fig. 29.2 Pediatric immunization schedule from birth to 18 months of age when using (**a**) DTaP with individual component vaccines, (**b**) DTaP-IPV-HepB combination vaccine, (**c**) DTaP-IPV-HIB combination vaccine, and (**d**) DTaP-IPV-HIB-HepB combination vaccine

The Advisory Committee on Immunization Practices (ACIP) recommends that booster injections of tetanus toxoid be given every 10 years for life and when a tetanus-prone injury occurs more than 5 years since the last dose. Tdap vaccine is recommended for all 11- or 12-year-old children, primarily to boost their pre-existing immunity to pertussis. Td or Tdap vaccine is recommended for subsequent, every 10-year boosters. Td vaccine is also used for tetanus wound prophylaxis since monovalent tetanus toxoid vaccine is no longer available, and booster doses of Tdap vaccine are recommended during each pregnancy. Anytime a tetanus toxoid-containing combination vaccine is used in such contexts to boost immunity to tetanus or pertussis, the dose is valid to reset the 10-year clock for the next recommended dose.

Immunizing Antigen

The production of tetanus vaccine requires growing *Clostridium tetani* in liquid culture medium under conditions that encourage optimal toxin production. When ready to be harvested, the culture medium containing the toxin is separated from the bacteria by filtration and then purified by fractionation with ammonium sulfate, dialysis, gel filtration, ion-exchange chromatography, or a combination of these biochemical techniques. Next, the concentrated, now purified tetanus toxin is inactivated. Exposure to the proper concentration of formaldehyde for the proper period of time partially denatures the toxin. These changes in the tertiary structure of the toxin convert the toxigenic protein to a toxoid protein. The tetanus toxoid retains immunogenicity but is rendered nontoxic. Amino acids, such as lysine or glycine, may be added to facilitate cross-linking and prevent reversion. After purification and sterilization, the product is tested for sterility, purity, toxicity, and reversion to toxicity. During the final step, tetanus toxoid is adsorbed onto an aluminum salt adjuvant. The final product can be used, as is, to fill unit dose syringes for administration as monovalent tetanus vaccine or combined with other immunogens. Final preparation of all tetanus toxoid-containing combination vaccines, including Td, Tdap, DT, DTaP, DTaP-IPV, DTaP-HepB-IPV, DTaP-HIB-IPV, and DTaP-HepB-HIB-IPV, requires that each of the necessary immunogens be prepared and quality tested separately.

Additives and Excipients All tetanus toxoid-containing vaccines include an aluminum salt adjuvant that is added during the final manufacturing steps. Monovalent tetanus toxoid vaccines are not available for use. For a list of additives and excipients in diphtheria toxoid-containing vaccines, see details provided in Chaps. 3 and 4.

Contraindications to Vaccine

Tetanus toxoid-containing vaccines are contraindicated for use in individuals who developed a severe allergic reaction to a prior dose and for those with a known severe allergy to any vaccine component.

Side Effects and Adverse Events

Mild to moderate, self-limiting local injection site reactions are common with all tetanus toxoid-containing vaccines. Since infants who receive diphtheria toxoid-containing vaccines also typically receive other vaccines during the same visit, vaccine-specific and antigen-specific side effects are usually difficult to identify with any certainty. Fortunately, all of the tetanus toxoid-containing vaccines are very well tolerated. For example, in one study involving more than 27,000 infants who received DTaP at 2, 4, and 6 months of age, crying for 3 hours or longer was reported at a rate of 0.44 per 1000 doses, fever ≥40 °C at a rate of 0.35 per 1000 doses, and seizures at 0.07 per 1000 doses, and there were no reported hypotonic-hyporesponsive episodes (an uncommon reaction known to occur following the administration of whole cell DTP vaccine at rates of 0.67 per 1000 doses). Adolescents and adults who receive Td vaccine experience injection site pain (75–80%), redness (16–26%), or swelling (15–17%), which are rarely severe in nature. Fever between 38 °C and 39 °C occurs uncommonly (0.8–1.6%). Headache (23–25%), weakness (17–32%), malaise (15–17%), and joint pains (11–16%) are self-limiting and only rarely severe in quality.

Vaccine Immunogenicity

A serum tetanus antibody level of at least 0.01 IU/mL is considered the minimum protective level, while an antibody level of ≥0.10 IU/mL was used as the surrogate of protective immunity in most clinical vaccine trials. Tetanus toxoid-containing vaccines are highly immunogenic, inducing protective immune responses in all or nearly all of recipients after a three-dose primary series. The reliability of tetanus toxoid vaccines explains why immunized individuals almost never develop tetanus, even when a tetanus-prone injury occurs more than 5 years after the recipients' last booster. For example, clinical trial results from a study in US children who received four doses of DTaP at 2, 4, 6, and 15–17 months of age showed that after the third dose, 100% ($n = 1037$) achieved tetanus antibody serum concentrations of ≥0.10 IU/mL and, after four doses, 98.8% ($n = 681$) achieved antibody levels of ≥1.0 IU/mL, a full $\log_{10}$ higher than the recognized surrogate of immunity.

Tetanus is entirely vaccine preventable. Tetanus toxoid-containing vaccines are safe and highly effective at inducing protective immune responses starting in the newborn period. Infants born to unvaccinated mothers and individuals who are unvaccinated for any reason can be exposed to and develop tetanus at any time as the pathogen is ubiquitous in the environment. Adults should receive boosters of tetanus toxoid vaccine every 10 years to maintain protective immunity. Those who experience a tetanus-prone injury more than 5 years after their last dose of tetanus vaccine should be boosted at the time of the injury out of an abundance of caution.

References and Suggested Reading

World Health Organization

https://www.who.int/health-topics/tetanus/#tab=tab_1.

US Centers for Disease Control and Prevention

https://www.cdc.gov/tetanus/index.htm.

Vaccine Information Sheets

https://www.cdc.gov/vaccines/hcp/vis/visstatements/dtap.html.
https://www.cdc.gov/vaccines/hcp/vis/vis-statements/tdap.html.
https://www.cdc.gov/vaccines/hcp/vis/vis-statements/td.html.

FDA-Approved Package Inserts

Daptacel

https://www.fda.gov/vaccines-blood-biologics/vaccines/daptacel.

DT Vaccine

https://www.fda.gov/media/119411/download.

Infanrix

https://www.fda.gov/vaccines-blood-biologics/vaccines/infanrix.

Kinrix

https://www.fda.gov/vaccines-blood-biologics/vaccines/kinrix.

Pediarix

https://www.fda.gov/media/79830/download.

Pentacel

https://www.fda.gov/media/74385/download.

Quadracel

https://www.fda.gov/vaccines-blood-biologics/vaccines/quadracel.

Tenivac

https://www.fda.gov/media/76610/download.

Vaxelis

https://www.fda.gov/vaccines-blood-biologics/vaxelis.

Adacel

https://www.fda.gov/media/119862/download.

Boostrix

https://www.fda.gov/media/124002/download.

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Chapter 30
Tick-Borne Encephalitis

Cynthia Bonville and Joseph Domachowske

Tick-Borne Encephalitis

Tick-borne encephalitis is an acute viral infection of the brain caused by tick-borne encephalitis virus (TBEV), a member of the genus *Flavivirus* in the family *Flaviviridae*. Like other flaviviruses, TBEV is an enveloped positive-sense single-stranded RNA virus.

Three subtypes of the virus are recognized, European TBEV, Siberian TBEV, and Far Eastern TBEV virus, and two others have been proposed, Baikalian TBEV and Himalayan TBEV. TBEVs are neurotropic, causing a spectrum of disease from mild short-lived illness to severe life-threatening illness that results in severe neurologic sequelae or death.

Epidemiology

The epidemiology of TBEV infection varies by geography and by infecting virus subtype. Infections caused by the European subtype of TBEV are most prevalent across Western and Central Europe, Scandinavia, and Western Russia, while those caused by the Siberian subtype of TBEV are most prevalent in Eastern Europe, Russia, and Northern Asia. Illness caused by the Far Eastern TBEV subtype is generally restricted to China, Japan, and Eastern Russia (Fig. 30.1 and Table 30.1).

Disease prevalence varies from year to year, with large fluctuations in reported cases due to changes in climate, tick habitation, ecosystem shifts, deforestation, changes in land use, and human recreational activities.

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Fig. 30.1 Geographic distribution of infections caused by *tick-borne encephalitis virus* (Sources of data to develop the figure: https://www.ecdc.europa.eu/en/tick-borne-encephalitis and https://www.who.int/immunization/diseases/tick_encephalitis/en/)

Table 30.1 Defining characteristics for the three recognized subtypes of tick-borne encephalitis virus

	Tick-borne encephalitis virus subtype		
	European	*Siberian*	*Far Eastern*
Geographic distribution	Western and Central Europe	Eastern Europe, Russia, Northern Asia	China, Japan, Eastern Russia
Primary vector	*Ixodes ricinus*	*Ixodes persulcatus*	*Ixodes persulcatus*
Frequency of neuroinvasion	72–87%	21%	3–8%
Case fatality rate	1–2%	6–8%	20–40%

Between 1990 and 2009, nearly 170,000 confirmed cases were reported in Europe and Russia. Geographically, the highest global incidence is seen in Western Siberia explaining why Russia accounts for the majority of reported cases every year. Outside of Russia, total reported annual European cases fluctuate between 2000 and 4000. Tick-borne encephalitis is the most important tick-borne viral infection throughout Europe. It became a notifiable disease in 2012 with compulsory reporting required in 18 countries.

The 2018 European Centers for Disease Control surveillance data report included 3212 cases and 16 deaths. Rates of disease per 100,000 population were highest in Lithuania (13), Slovenia (7.4), and the Czech Republic (6.7) with the largest numbers of cases confirmed from the Czech Republic ($n = 712$), Germany ($n = 583$), and Lithuania ($n = 384$). Ninety-five percent of all cases occurred between May and November. Infections were more commonly reported in males (60.6%) and in adults between the ages of 45 and 64 years. The lowest reported rates were among children less than 4 years of age.

Transmission

TBEV infection is transmitted to humans via the bites of infected hard ticks.

The primary vector for the European subtype of TBEV is the common castor bean tick, *Ixodes ricinus*, although *I. nipponensis* fulfils the main role in Korea. The larger *Haemaphysalis* and *Dermacentor* tick species have also been shown capable of transmitting the infection. The taiga tick *I. persulcatus* serves as the primary vector for both the Siberian and Far Eastern subtypes of TBEV. Other ticks, including *Haemaphysalis* and *Dermacentor* species, play a secondary role in transmission in China. *I. ovatus* has been shown to transmit disease in Japan.

TBEV is maintained in nature via interactions between its tick vectors and a wide variety of animal hosts that include small (mice, moles, voles, hedgehogs, rabbits) and large (deer, elk, sheep, goats, cattle, horses, foxes, swine, canines) mammals and several migrating bird species. The ticks act as vectors and reservoirs, while the small mammalian hosts serve as primary amplifying hosts. Rodents and other small mammals remain completely asymptomatic despite high and persistent levels of viremia that render them infectious to ticks for up to several weeks. Ticks can become infected with virus transovarially or by feeding on infected small mammals. Once infected, ticks remain infected and can transmit the virus for their entire lifespan. Larger mammals serve as hosts to feed the tick vectors but rarely reach sufficient levels of viremia to infect them. When an infected tick feeds on a human, TBEV is transferred via the tick's saliva. Initial virus replication is local before spreading via the lymphatics and the bloodstream to invade susceptible tissues. TBEV is neurotropic targeting the medulla oblongata, pons, dentate nucleus, Purkinje cells, striatum, and the large motor neurons of the spinal cord anterior horns.

Clinical Presentation

Between 60% and 75% of TBEV infections are clinically very mild or asymptomatic. Following an incubation period of 7–14 days (range 2–28 days), those who develop symptoms can have a clinical course that is either monophasic or biphasic. The first phase of illness corresponds to the period of viremia and lasts for up to 8 days. Patients describe nonspecific symptoms that usually include fever, malaise, anorexia, muscle aches, headache, nausea, and vomiting. About 65% of patients recover completely. The remainder experience a period of wellness lasting for 1–8 days before beginning to experience signs and symptoms of the second phase of illness which are indicative of neurologic involvement. Neuroinvasion is most common among those infected with either the European (72–87%) or Siberian (21%) subtype of TBEV, while only 3–8% of infections caused by the Far Eastern subtype of TBEV involve the central nervous system. Clinically, the spectrum of neurologic manifestations of the infection includes meningitis (50%), meningoencephalitis (40%), meningoencephalomyelitis (10%), and encephalomyeloradiculitis/polyradiculoneuritis (3%). Associated symptoms may include high fever, headache, neck pain or stiffness, drowsiness,

altered mental status, cognitive dysfunction, pyramidal tract dysfunction, ataxia, focal or generalized seizures, and acute flaccid paralysis (especially around the shoulder girdle). The incidence, severity, and rate of neurologic sequelae increase with age. Long-term or permanent neurologic sequelae are common, occurring in approximately half of those infected. Case fatality rates are influenced by age and by the infecting virus subtype. The most lethal form of infection is caused by the Far Eastern TBEV subtype where up to 40% of infected individuals die. Central nervous system infection with the Siberian subtype of TBEV has a mortality rate of less than 10%, while only 1–2% of those infected with the European subtype will succumb to the infection. The neuroinvasive second phase occurs in 5–30% of children with symptomatic disease, but their clinical course is typically less severe than in adults, manifesting most commonly as aseptic meningitis without encephalitis.

Management

Specific antiviral treatment is not available. Mild to moderate symptoms are treated with symptomatic care. Central nervous system infections require hospitalization and careful attention to maintenance of fluid and electrolyte balance and nutrition. Analgesics, antipyretics, and anticonvulsants are used as necessary. Severe illness requires treatment under intensive care with careful attention to the maintenance of adequate cerebral perfusion pressure. Endotracheal intubation, mechanical ventilation, and inotropic cardiovascular support may be necessary.

A specific anti-TBEV immunoglobulin [Encegam, FSME-Bulin] has been used therapeutically in Russia and Kazakhstan with reports of 79% efficacy, but data from controlled clinical trials are not available. The once promising therapeutic was discontinued in Europe due to concerns raised regarding the possibility of antibody-enhanced disease.

Prevention

Disease prevention starts with careful attention to avoiding tick bites. Consumption of unpasteurized dairy products is also discouraged since transmission of TBEV from contaminated raw milk has been demonstrated. Prevention of tick bites includes avoiding wooded and brushy areas, avoiding tall grass and shrubs, and walking in the center of established trails when out hiking. A tarp should be used when sitting on the ground. Insect repellents should contain >20% DEET and be reapplied as necessary.

Permethrin-treated clothing and gear should be used for outdoor recreational and occupational activities that risk exposure to ticks.

Tick-Borne Encephalitis Vaccines

Type of Vaccines Available Globally

TicoVac/FSME-IMMUN and TicoVac Junior/FSME-IMMUN Junior are inactivated whole virus vaccines first licensed in 1976 in Austria and then subsequently approved for use in several other European countries. The vaccine is derived from the European subtype Neudörfl strain of TBEV. Unit doses are available in two formulations, both supplied in prefilled syringes. TicoVac is a 0.5 mL dose for IM injection for individuals of ages ≥16 years and TicoVac Junior is a 0.25 mL dose for IM injection for individuals 1–15 years of age. The vaccine is delivered as a three-dose primary series at 0, 1 to 3 months, and 5–12 months. While a three-dose complete immunization series is not practical for most travelers, an accelerated schedule can be started with doses administered on days 0 and 14, with the third dose scheduled 5–12 months after the first dose. Booster doses are generally recommended every 5 years but vary from country to country.

Encepur and Encepur Kinder/Encepur Children are inactivated whole virus vaccines derived from the European subtype, Karlsruhe (K23) strain of TBEV. The formulation was first licensed in 1991 in Germany for both adults and children.

Unit doses are available in two formulations, both supplied in prefilled syringes. Encepur is a 0.5 mL dose for IM injection for individuals of age ≥13 years, and Encepur Children is a 0.25 mL dose for IM injection for individuals 1–12 years of age. The vaccine is delivered as a three-dose primary series at days 0, 1 to 3 months, and 9–12 months. A booster dose is recommended 3 years after primary series completion, with subsequent boosters given every 5 years in most countries.

Other inactivated, whole virus formulations of TBEV vaccine currently on the market include TBE Moscow (Far Eastern subtype, Sofjin strain), Tick-E-Vac/Klesch-E-Vac (Far Eastern subtype, Sofjin strain), EnceVir/EnceVir Neo (Far Eastern subtype, 205 strain), and TBE-PHK (Far Eastern subtype, Sen-Zhang strain). Formulations, age indications, and vaccine schedule are brand-specific but similar to one another.

Immunizing Antigens

All available TBEV vaccines are inactivated whole virus formulations. Immunization with vaccines derived from different TBEV subtypes is thought to provide cross-protective immunity to all subtypes. The details regarding the growth, purification, and inactivation of vaccine strain viruses are unique to each product. While manufactured by different companies, the Neudörfl and K3 strains of the European subtype and the Sofjin and 205 strain of Far East subtype are all grown in cultures of chicken embryonic fibroblasts, harvested, inactivated by formaldehyde, and adsorbed to aluminum hydroxide as adjuvant. The Sen-Zhang strain of Far Eastern

subtype is grown in primary hamster kidney cells, harvested, inactivated with formalin, and adsorbed onto aluminum hydroxide as adjuvant.

Additives and Excipients

The details of the manufacturing process dictate the excipient residuals present in the final vaccine formulations. TicoVac contains traces of formaldehyde, gentamicin, neomycin, human serum albumin, sodium chloride, disodium phosphate dihydrate, and potassium dihydrogen phosphate. Aluminum hydroxide is added as the adjuvant.

Encepur contains traces of formaldehyde, gentamicin, neomycin, chlortetracycline, and sucrose. Aluminum hydroxide is added as the adjuvant. TBE-Moscow contains traces of formalin, <5 mcg protamine sulfate, <0.3 mg human albumin, <0.5 mcg bovine serum albumin, <5.5 mcg gelatin, <38 mg sucrose, and <0.5 μg chicken albumin. Aluminum hydroxide is added as the adjuvant. Tick-E-Vac/Klesch-E-Vac is antibiotic and preservative-free. Aluminum hydroxide is added as the adjuvant. EnceVir contains traces of formalin, <10 μg protamine sulfate, <0.25 mg human albumin, <30 mg sucrose, and kanamycin. Aluminum hydroxide is added as the adjuvant. TBE-PHK contains traces of formalin and human serum albumin. Aluminum hydroxide is added as the adjuvant. Thimerosal is added as a preservative.

Immunization Recommendations for Travelers

Only individuals at risk of significant tick exposure should be vaccinated before traveling. TBEV vaccines are not universally recommended for travel to any country. TBEV vaccines are not available in the United States. Individuals ≥1 year old who are traveling from the United States to TBEV-endemic regions and are planning to engage in outdoor activities involving a risk of tick exposure may consider being vaccinated in Canada or Europe; otherwise, prevention should be focused on preventing exposure to ticks. Resources for travelers, including interactive destination information, can be found at the following links: https://travel-vaccination.co.uk/region/europe/ and https://travelhealthpro.org.uk/factsheet/22/tick-borne-encephalitis.

Contraindications to Vaccine

TBEV vaccines are contraindicated for use in individuals with a history of a severe allergic reaction to a previous vaccine dose or to any vaccine component.

Warnings and Precautions for Vaccine Use

During pregnancy and while breastfeeding, vaccination is recommended in regions with a high incidence (>5 cases/100,000) of TBEV infection. The overall risks and potential benefits should be weighted for those residing in regions with only a moderate or low disease incidence (<5 cases/100,000). Vaccine does not offer complete protection to all recipients and may not offer complete protection in physiologically or medically induced immunocompromised individuals. Vaccine-induced protection is *not* lifelong. If exposure risk remains elevated, regular booster doses of the vaccine are needed.

Side Effects and Adverse Events

Inactivated whole virus TBEV vaccines have excellent safety profiles, free from serious adverse reactions. Mild to moderate self-limiting local injection site reactions are similar to those seen with most vaccine products and include injection site redness, swelling, and/or pain. Similarly, systemic reactions such as headache, fatigue, malaise, muscle pain, joint pain, and fever, when they do occur, are typically mild and self-limiting over a 1- to 2-day period. Symptom-directed relief using over-the-counter pain- and/or fever-reducing agents can be used as necessary. In general, systemic reactions tend to be more prominent after the first injection.

Vaccine Immunogenicity

Blinded, controlled clinical trials of EnceVir and TBE-Moscow showed 100% and >96% seroconversion rates in vaccinated adults and children, respectively. TBE-PHK seroconversion rates were 86% 6 months after completing the primary series and 77% 1 year later. Single booster doses were associated with 96% seroconversion.

Impact of Vaccine on Disease Burden

A Cochrane review that summarized 11 clinical trials involving 5063 total participants showed overall seroconversion rates of 92–100%. Austrian field studies performed between 1994 and 2001 showed that a three-dose whole virus inactivated TBEV vaccine series was 96.0–98.7% effective at preventing infection. Subsequent field studies performed between 2000 and 2011 confirmed an excellent overall field effectiveness of 96–99% following standard dosing recommendations and 91–92%

effectiveness following an irregular (nonstandard) vaccination schedule. Accelerated schedules, such as those recommended for high-risk travelers, showed rates of seroconversion in excess of 90% in recipients younger than 50 years of age and 80% seroconversion among those older than 50 years. Longitudinal studies show slower decline of neutralizing antibody following a single booster when compared to declines following the primary vaccine series. The durability of a single booster was shown to exceed 5 years in vaccinated individuals under 60 years of age, estimating ~80% protective efficacy at 10 years.

The public health benefit of implementing a targeted vaccine program in an area of high disease prevalence offers the most convincing evidence that the immunogenicity of TBEV vaccine translates into vaccine effectiveness. An excellent example was demonstrated between 1999 and 2003 in the Krasnoyarsk region of Russia where TBEV infection rates had reached nearly 50 cases per 100,000 population. A mass immunization program was introduced, reaching between 70,000 and 105,000 individuals each year. By 2003, TBEV infection rates had declined from 49 to 6 per 100,000 population. Immunized individuals were 20 times less likely to develop infection compared with those who were not vaccinated. The impact of the regional vaccine campaign during the 4-year effort estimated that at least 6000 infections had been prevented.

Central nervous system infections caused by TBEV are often life-threatening, particularly in older adults. Human infections are confined geographically to areas across most of Europe and Asia. The three virus subtypes currently recognized each have well-defined, overlapping geographic distribution. Children account for approximately 20% of cases and typically have much milder illness than do adults. Clinical illness severity is also highly dependent on the infecting subtype of the virus. The infection is transmitted to humans through the bite of an infected tick. Safe and effective inactivated whole virus vaccines are available for those residing in or traveling to endemic regions.

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Chapter 31
Tuberculosis

Cynthia Bonville and Joseph Domachowske

Tuberculosis

Etiology

Tuberculosis is a bacterial infection caused by *Mycobacterium tuberculosis*, a member of the *Mycobacteriaceae* family. The pathogen is an acid-fast aerobe that grows slowly in culture. The organism's doubling time is approximately 24 hours, so it usually takes several weeks before visible colonies appear on solid culture media.

Epidemiology

Globally, TB ranks among the top 10 causes of death and remains the leading cause of death from any single infectious agent. On average, one in every four persons on earth has latent TB infection, many of whom have a lifelong risk of developing and succumbing to active TB infection. The findings summarized in the 2018 Global TB Report are stunning. The estimated total disease burden of ten million new cases included more than one million children less than 14 years of age. The overall global mean incidence of new cases per year was 130 per 100,000 population, with the expected wide variation between countries, ranging from a low of fewer than 5 to a high of 500 per 100,000 population. Almost 90% of all new cases were reported from 30 countries already identified as high-burden nations, and 15–20% of new

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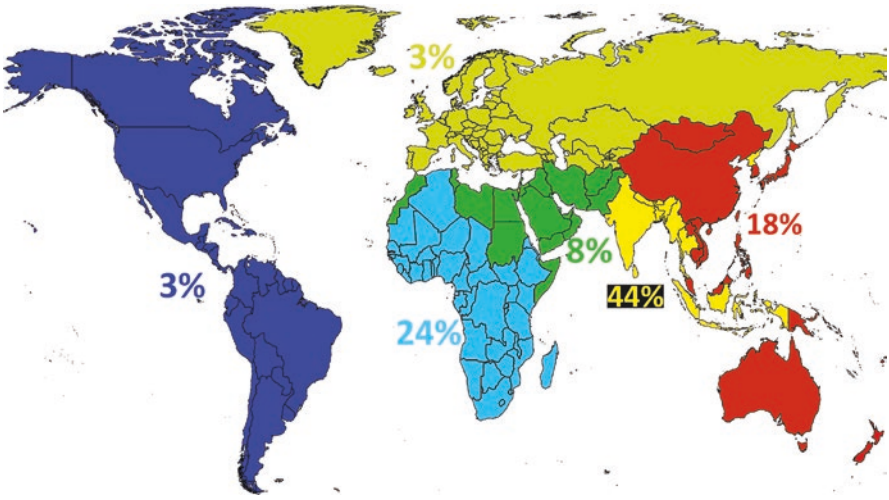

Fig. 31.1 Global distribution of new TB cases by World Health Organization region, 2018

cases were reported in children. The 2018 new TB case distribution, according to the World Health Organization regions, is shown in Fig. 31.1.

Worldwide, in 1 year, 1.5 million people died from TB. Of these, approximately 250,000 were HIV coinfected, and 205,000 were children. The vast majority of deaths occur in resource-poor nations. *TB is a disease that is inextricably linked to poverty*.

The epidemiology of TB infection in the United States was most recently summarized in the 2019 US Centers for Disease Control and Prevention Report. Approximately 13 million individuals have latent infection. 8920 new cases of active TB disease were reported, a 1.1% decrease from 2018. The US incidence rate of 2.7 cases/100,000 persons represented a 1.6% decrease from 2018. About 80% of all new infections were due to reactivation of latent infection acquired years earlier, mainly outside the United States. State-specific incidence rates per 100,000 population ranged from a low of 0.2 in Wyoming to a high of 8.1 in Alaska. Nearly half of all new cases were reported from the four states of California, Texas, New York, and Florida.

Transmission

TB is highly contagious and spreads from person to person via the airborne routine through the inhalation of 1- to 5-micron-diameter droplets aerosolized when an infected individual coughs, sneezes, or speaks. Inhalation of only a few bacilli is sufficient to establish infection. Individuals who develop cavitary pulmonary disease are especially contagious.

Clinical Presentation

Most individuals who become infected with *M. tuberculosis* remain asymptomatic for years. Clinically, this condition is referred to as latent tuberculosis (TB). Individuals with latent TB infection are not contagious to others. Most, but not all, will test positive for TB infection using the currently available diagnostic tools. Chest radiographs are normal. All individuals with latent TB infection carry a lifelong risk of developing active TB disease, but antibiotic treatment of the latent infection reduces the risk substantially.

Individuals who are the highest risk of developing active TB disease include those who are immunocompromised for any reason and those with underlying chronic medical conditions including diabetes mellitus, renal insufficiency, silicosis, alcoholism, and malnutrition. Other risk factors include the extremes of age, prior inappropriate/inadequate treatment for latent disease, and the use of illicit drugs. When compared with the general population, individuals living with human immunodeficiency virus (HIV) infection are almost 20 times more likely to develop active TB. Healthy, immunocompetent individuals with latent TB who are not treated with antibiotics have the greatest risk of developing active TB disease during their first 2 years of latent infection.

Active TB disease can develop within a few weeks following exposure or manifest years or even decades later. Individuals with latent TB infection who later develop any condition that compromises their immune function are at high risk for developing active disease.

Individuals with active TB infection become symptomatic based on the anatomic location of the disease. Signs and symptoms of pulmonary TB include cough, shortness of breath, and/or pleuritic chest pain. Hemoptysis is common as the infection advances. Associated systemic symptoms, such as persistent fevers, night sweats, weight loss (consumption), and severe fatigue, may become so impressive that they overshadow the respiratory symptoms. The disease onset is often insidious, so symptoms have often been present for weeks or months before the patient seeks medical attention. During this period, disease can be easily spread, especially to household and other close contacts. Extrapulmonary disease is most common among immunocompromised individuals and those at the extremes of age. Children are prone to developing tuberculous lymphadenitis, a condition also known as scrofula. Hematogenous spread of the pulmonary infection can lead to metastatic spread of infection to the meninges, the brain, the genitourinary tract, the joint spaces, and/or the bones, especially the vertebrae. TB meningitis is the most serious form of the infection. Symptoms include a low-grade fever, a constant severe headache, nausea, and drowsiness. Nearly all of those who survive the infection are left with moderate to severe neurologic sequelae.

Osteoarticular tuberculosis can affect any anatomic location, but the pathogen has a unique proclivity to seed the vertebral bodies. Vertebral osteomyelitis, often spreading to adjacent vertebrae, results in the narrowing of the involved disk spaces. The condition is also referred to as Pott's disease. Vertebral collapse with spinal cord impingement can lead to neurologic deficits, including permanent paraplegia.

Management

The treatment of active TB disease is a highly complex and ever-evolving topic that goes well beyond the scope of this chapter. Guidance from the US Centers for Disease Control and Prevention can be found at https://www.cdc.gov/tb/topic/treatment/default.htm.

Combination antibiotic treatment regimens are highly effective in curing active TB disease when given for a suitable length of time based on the isolate's susceptibility profile, the anatomic site and severity of the infection, and certain underlying host factors. Combination drug therapy is necessary for two main reasons. First, empiric therapy is almost always started before an isolate is available for susceptibility testing, and it's important that at least some of the medications included in the regimen are active against the isolate. And second, *M. tuberculosis* replicates so slowly that the selective pressure of a single agent can render the pathogen resistant during therapy. Special considerations must be weighed when treating multidrug-resistant isolates and when treating individuals who are pregnant, have central nervous system disease, or are HIV infected. Drug-to-drug interactions between the antibiotics used for the TB infection and medications used for pre-existing underlying illness must be reviewed carefully. Since antibiotics used to treat TB can cause a long list of side effects, and treatment regimens continue for several months, regular screening for drug toxicities is essential. Many public health programs require that all individuals who require treatment for active TB disease receive every dose of their medications while being directly observed by a healthcare professional, a strategy known as *directly observed therapy*. While substantial resources are required to do so, the risks of non-adherence can be disastrous. Therapeutic regimens for active TB disease require that patients take medications for between 4 and 12 months (sometimes longer). Breaks in the treatment course invite the emergence of drug resistance leading to poor outcomes for the patients. The relapse of disease can render the patient contagious again, potentially with a multidrug-resistant strain of the pathogen, posing a significant public health risk. Alternate treatment regimens that are available are usually less efficacious, are associated with higher rates of serious side effects, and are more costly.

Vaccine

The only TB vaccine available worldwide is a live bacterial formulation derived from *M. bovis* referred to simply as "BCG," an abbreviation for its formal but seldom used name bacille Calmette-Guérin. French scientists, Albert Calmette and Camille Guérin, developed the vaccine in the 1920s while working at the Pasteur Institute. After a tumultuous start, uptake of BCG began to improve during the 1940s. In response to growing public health concerns related to TB in the aftermath of World War II, the United Nations International Children's Emergency Fund

(UNICEF) and the Scandinavian Red Cross began to promote and coordinate aggressive vaccination campaigns. During the 1950s, clinical trials performed in the United Kingdom and the United States revealed major differences in BCG vaccine preparations that had such profound effects on vaccine efficacy that the findings drove the development of very discordant national vaccine policies. In the United Kingdom, the BCG Copenhagen strain showed 80% efficacy and was therefore recommended for routine adolescent vaccination. Worldwide many countries adopted some form of routine vaccination. In contrast, a similar study in the United States, using the BCG Tice strain, reported vaccine efficacy of less than 5%. The United States did not and has not adopted the use of BCG vaccine.

Multiple formulations of BCG are available globally, six of which are listed by the WHO as prequalified vaccines. All are derived from the same original BCG strain, but variations exist in growth characteristics, genetic composition, immune responses, efficacy, and national policies for their use. BCG vaccines have been widely adopted in TB-endemic countries as part of routine childhood immunization. A single dose is administered, commonly at birth.

Clinical experience has shown that the BCG vaccine, when given to young infants, offers about 90% protection against disseminated TB disease, including meningitis, and approximately 60% efficacy against pulmonary disease during childhood. Efficacy wanes during adolescence. The administration of BCG vaccine during childhood offers little to no protection against pulmonary tuberculosis during adulthood.

In the United States, BCG vaccine is only very rarely used. It is, however, made available by Organon Teknika Corporation, a subsidiary of Merck & Co., Inc. The vaccine is derived from live, attenuated, TICE strain BCG and received initial US FDA approval in 1989 for the prevention of TB in uninfected individuals who are at high risk for exposure and who have had a recent negative TB skin test result. The vaccine is supplied as a pair of unit dose vials; one vial contains $1–8 \times 10^8$ colony-forming units of lyophilized bacteria, and the other contains sterile water for injection to be used to reconstitute the active vaccine component. Adult doses are prepared by transferring 1 mL of the sterile water to one vial of lyophilized vaccine. Vaccine doses for infants are prepared by transferring 2 mL of the sterile water to one vial of lyophilized vaccine.

The vial containing the reconstituted vaccine is swirled gently until achieving a homogeneous suspension by visual inspection. Over-agitation should be avoided as it can result in clumping. Reconstituted vaccine that contains clumps should be discarded.

Administering BCG Vaccine

Unlike other vaccines that are given by subcutaneous or intramuscular injection using a needle and syringe, BCG vaccine is administered percutaneously using the sterile, wafer-like stainless steel multiple puncture device with 36 protruding points

that is provided with the vaccine purchase. After cleaning the deltoid region with alcohol or acetone and allowing the inoculation site to dry thoroughly, the patient's arm is positioned horizontally. Using a syringe, 0.2–0.3 mL of the reconstituted vaccine is dropped onto site and spread over a 1–2 inch area using the flat edge of multiple puncture device.

The puncture side of the device is then centered over the prepared skin, and while holding the arm firmly to keep the skin taut, the device is pressed downward with sufficient pressure to bury the points into the skin. Still pressure (no rocking motion) is maintained for 5 seconds, and then the device is removed and used to spread the vaccine contents evenly over the successful puncture sites. The inoculation site should be covered loosely and kept dry for 24 hours. The expected post-vaccination reaction includes the formation of a bluish-red pustule at the inoculation site in 2–3 weeks. The pustule ulcerates after week 6, forming a scab that heals within 3 months. Nearly all vaccinated individuals develop a permanent scar at the inoculation site. Individuals immunized with BCG are expected to develop tuberculin reactivity from skin testing 2–3 months following BCG vaccination. Revaccination of infants with negative skin tests who received BCG vaccine during the first month of life should be postponed until 1 year of age.

Additives and Excipients

During manufacturing, BCG bacteria are grown in medium containing glycerin, asparagine, citric acid, potassium phosphate, magnesium sulfate, and iron ammonium citrate. The final preparation is preservative-free.

Vaccine Storage and Handling

BCG vaccine vials should be stored under refrigeration (2–8 °C) and protected from direct sunlight. The vials of sterile water for injection should be stored between 4 °C and 25 °C. If not used immediately, reconstituted vaccine can be stored refrigerated (2–8 °C) for up to 2 hours.

Vaccine Recommendations

In the United States, guidance from the Advisory Committee on Immunization Practices (ACIP) states that the use of BCG vaccine is not generally recommended due to low risk of infection, variable effectiveness in preventing active TB disease, and potential interference with TB skin testing for those who may require TB screening later in life.

In the United States, BCG vaccine is very rarely indicated and almost never given. BCG should, however, be considered for infants and children known to be TB negative under the following conditions:

1. They have continuous and unavoidable exposure to an adult with untreated or ineffectively treated TB disease *and* they are unable to separate from that TB-infected adult *or* they cannot receive long-term preventive treatment themselves.
2. They have continuous and unavoidable exposure to an adult who is infected with *M. tuberculosis* that is resistant to *both* isoniazid *and* rifampin and they are unable to separate from that TB-infected adult.

Contraindications to Vaccine

BCG vaccine is contraindicated for use in those who developed a serious allergic reaction to a previous dose or any vaccine component. Infants, children, or adults with physiological or medically induced immunosuppression such as HIV infection, congenital immunodeficiency, cancer, organ transplantation, or treatment with steroids, alkylating agents, antimetabolites, or radiation should not receive BCG vaccine. The vaccine should not be administered to individuals previously infected with *M. tuberculosis*. Harmful effects have not been observed following the inadvertent administration to pregnant women, but safety in this population has not been proven.

Warnings and Precautions for Vaccine Use

BCG vaccine contains live bacteria and requires handling with careful attention to aseptic technique. Vaccine product and anything that comes in contact with the vaccine must be handled and discarded as a biohazard. BCG may cause a false-positive TB skin test, which can complicate TB management decisions; however, the vaccine is unlikely to result in a false-positive interferon gamma release assay blood test for TB.

Side Effects and Adverse Events

A local injection site reaction is expected and, when present, indicates a highly likelihood of an adequate response. The pustule formation can be associated with moderate axillary or cervical lymphadenopathy. Fever lasting more than 3 days following vaccination suggests the development of an active infection. Regional lymph nodes should be examined carefully as vaccine-associated regional

suppurative lymphadenitis with draining sinuses is an uncommon but well-described side effect of BCG. Acute febrile illnesses that could be consistent with an active BCG infection should be managed with the advice of an infectious disease expert. Antibiotic treatment directed against BCG should be started without delay being mindful that the BCG vaccine strain is intrinsically resistant to pyrazinamide.

Disseminated BCG infection is a very rare but potentially life-threatening complication that has been described 4 months to 2 years post-vaccination. Patients may develop conditions that appear clinically identical to pulmonary TB, TB meningitis, or TB osteitis of the long bones with or without associated erythema multiforme. Death from this complication occurs at a rate of 0.06–1.56 cases per million vaccine doses and is seen almost exclusively in patients who have developed an immunosuppressive condition.

Global Efforts to Reduce TB Morbidity and Mortality

In 2018, 153 countries worldwide included BCG vaccination as part of their routine childhood vaccination program, with 113 nations reporting immunization coverage rates exceeding 90%. The World Health Organization's End TB Strategy and the United Nation's Sustainable Development Goals for 2020 were to achieve a 20% reduction in TB incidence and 35% reduction in deaths per 100,000 population compared to 2015 rates.

Cumulative country data for 2015–2018 indicate some interval progress, but the overall reported 6.3% decline in TB incidence and 11% decline in deaths appear too distant from the 2020 goals to reasonably expect they can be achieved. Country-specific data, however, show some promising patterns suggesting that progress is on track for the nations of Kenya, Lesotho, Myanmar, Russian Federation, South Africa, Tanzania, and Zimbabwe, lending optimism that similar impact can be realized more broadly. Such optimism is reflected in the newly established 2030 goals to reduce global TB incidence by 80% and deaths by 90% reduction compared to 2015 rates. In addition to maintaining established infant BCG vaccination programs, efforts toward achieving the highly ambitious 2030 goals target treatment of 40 million active TB infections and 30 million latent infections between 2018 and 2022. Such large-scale efforts require large-scale resources. The World Health Organization, United Nations, and other international partners look to secure $13 billion per year to support diagnosis and treatment and an additional $2 billion to support research. Top research priorities include addressing the growing problem of multidrug-resistant infections and development of novel, more highly effective TB vaccines.

Reduce TB Morbidity and Mortality

Universal BCG vaccination was never implemented in the United States, yet rates of TB disease are now among the lowest in the world indicating the key importance of other TB prevention strategies. In the United States, the observed decline in TB rates over the last several decades can be attributed to an aggressive, coordinated, sustained, multicomponent approach that does not (yet) incorporate active vaccination. Each of the existing public health components is essential to maintain the current level of TB control. The logistics of maintaining programs for the early detection and treatment of active disease, careful and complete contact investigation, identification and preventive therapy for latent infection, and prevention of institutional transmission across healthcare settings, homeless shelters, and correctional facilities are complex and expensive. The discovery and implementation of safe and effective vaccines that prevent all forms of TB infection and disease in all age groups may, someday, simplify and reduce the costs associated with controlling TB.

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Vaccine Information Sheet

https://www.cdc.gov/tb/publications/factsheets/prevention/BCG.pdf.

Interactive BCG World Atlas, 2nd edition 2017 (either 2011 or 2017 data on vaccine use per country)

http://www.bcgatlas.org/index.php.

Kaiser Family Foundation

https://www.kff.org/global-health-policy/fact-sheet/the-u-s-government-and-global-tuberculosis-efforts/.

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Chapter 32
Typhoid Fever

Cynthia Bonville and Joseph Domachowske

Typhoid Fever

Etiology

Typhoid fever or simply "typhoid" is a serious systemic infection caused by *Salmonella enterica* subspecies enterica serovar Typhi, a Gram-negative bacillus belonging to the family *Enterobacteriaceae.* The use of official nomenclature to identify or describe the 6 subspecies and more than 2600 serotypes of the genus *Salmonella* offers an important level of precision for microbiologists, but most clinicians use *S. typhi* rather than "*Salmonella enterica* subspecies enterica serovar Typhi" to refer to the agent that causes typhoid fever. While taxonomically incorrect, this informal simplification of the name will be used in this chapter. The bacterium produces a polysaccharide capsule that serves as an important virulence factor by impairing opsonization, phagocytosis, and killing via the innate and adaptive host immune response. Outbreaks of disease remain common worldwide, especially in areas of poor sanitation and hygiene. The infection is spread from person to person via the fecal-oral route. Asymptomatic individuals who harbor the pathogen in the gastrointestinal tract serve as a reservoir for disease transmission. Typhoid fever, caused by *S. typhi*, should not be confused with typhus fever, a group of related infections caused by different species of *Rickettsiae*.

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Epidemiology: Global

Worldwide, between 11 and 20 million cases and more than 125,000 deaths from typhoid fever are reported annually. The geographical distribution of the infection varies widely with the highest rates of disease reported from regions of Africa, Southeast Asia, Latin America, and the Western Pacific, particularly among populations that lack access to clean water and adequate sanitation (Fig. 32.1). Across endemic areas, the incidence of disease is highest among school-age children followed by a steady decline through late adolescence and adulthood. In non-endemic areas, the sporadic cases that are reported tend to be distributed fairly evenly across age groups. Typhoid-associated deaths also differ from region to region where mortality rates range from a high of 7.2 per 100,000 population across sub-Saharan Africa to a low of <0.1 per 100,000 throughout North America, Europe, and Australia.

Epidemiology: United States

Typhoid fever was endemic in the United States during the late nineteenth and early twentieth centuries.

During the early 1900s, large multi-state outbreaks traced to untreated drinking water and the consumption of oysters harvested from areas heavily contaminated with human sewage helped to drive and expand ongoing public health efforts to

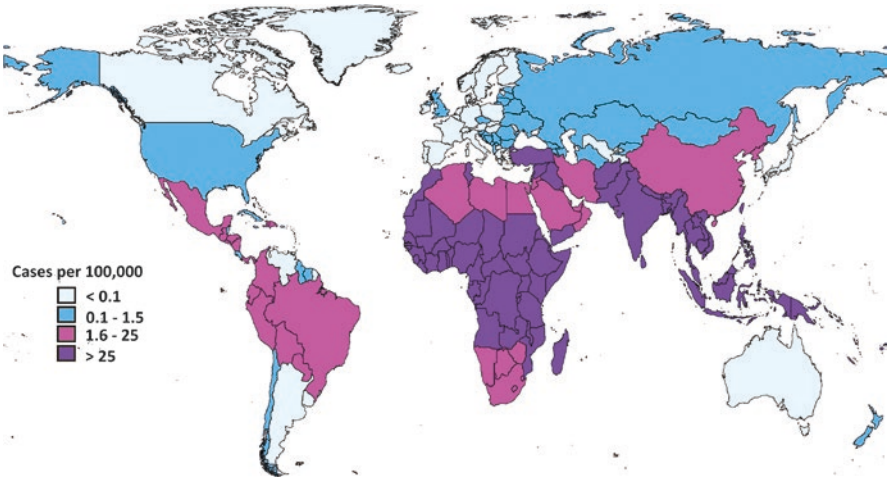

Fig. 32.1 This world map illustrates the reported incidence of typhoid fever per 100,000 population in 2017, colored according to each country's quartile ranking. (Source of data used to develop the original figure: https://www.contagionlive.com/outbreak-monitor?z=no&type=sub&category=salmonella)

chlorinate the water supply, improve sewage disposal, and improve food handling. These actions, together with the widespread use of typhoid vaccine among international travelers, led to a dramatic decline in reported cases despite the continued prevalence of chronic *S. typhi* carriers. Between the years 1960 and 1999, 60 outbreaks of typhoid fever, representing a total of 957 cases, were reported in the United States. Of these, 54 outbreaks were caused by domestic exposures to the pathogen. In contrast, most of the 350 cases reported between 2008 and 2015 were sporadic, with 85% reported among international travelers upon return to the United States.

Transmission

S. typhi, unlike many other members of the genus *Salmonella*, has no known animal or environmental reservoir. Humans harboring the pathogen are the only source for transmission to others. Disease is easily spread via the fecal-oral route from asymptomatic individuals who are colonized and from those who are acutely ill or convalescing. Failure of these individuals to practice good personal hygiene can result in fecal contamination of fomites, food, milk, and public water sources with subsidiary spread to others. Prior to complete understanding of the transmission cycle and the asymptomatic carrier state, food handlers excreting the bacteria in their feces were often the focal point of many epidemics across all global regions, including the infamous Mary Mallon, aka Typhoid Mary, of New York during the early 1900s. Today, typhoid fever is prevalent primarily in countries where handwashing is infrequent and sewage contamination of water is prevalent.

This transmission scenario underscores the importance of high standards in personal hygiene, water safety, sanitation, food hygiene, and pasteurization and explains why countries with inferior infrastructure due to struggling economies, disruptions due to warfare and civil unrest, or massive displacement of people are so problematic. It also highlights why US travelers to endemic regions outside of tourist and business centers should adhere to safe eating and drinking habits, adopting the "boil it, cook it, peel it, or forget it" motto as an additional safety precaution on top of vaccination. The US trend of increasing importation of fresh fruits and vegetables and processed foods from low-income, typhoid-endemic countries, which have been responsible for typhoid outbreaks in the past, such as a 2010 multistate outbreak due to frozen mamey pulp from a single manufacturer in Guatemala, also stresses the importance of maintaining domestic and international public health vigilance. When a virulent strain of the pathogen is inadvertently ingested, it passes through the stomach into the small bowel where it infects and colonizes macrophages and dendritic cells within the lamina propria. In a subset of infected individuals, the chronic intestinal infection leads to an asymptomatic carrier state. In others, systemic illness manifests after an incubation period ranging from 6 to 30 days. Multifocal, multisystem involvement results from lymphatic and/or hematogenous seeding of distant sites.

Clinical Presentation

The onset of typhoid fever is insidious with symptoms of fatigue and low-grade fevers becoming increasingly persistent over 3–4 days. Signs and symptoms of gastroenteritis, including nausea, vomiting, diarrhea, and abdominal pain, are common, but some older children and adults may also present with constipation. Headache, malaise, and anorexia are nearly universal. Complaints of persistent fevers as high as 40 °C are common and can be prolonged, lasting several weeks. Physical examination may reveal hepatosplenomegaly and/or "rose spots," a transient, pink to red maculopapular rash most prominent on the trunk. Untreated, typhoid fever can last 1 month or longer with 10–30% of cases ending in death. Antibiotic treatment reduces the case fatality rate to less than 1%. Serious complications from the infection are common and usually occur after 2–3 weeks of untreated illness. Between 10% and 15% of hospitalized patients develop life-threatening gastrointestinal hemorrhage, intestinal perforation, encephalopathy, or septic shock. Infection of the gallbladder is quite common and can lead to a chronic carrier state even following treatment with antibiotics. Overall, chronic carriage of *S. typhi* develops in 2–4% of individuals who recover from the acute illness.

Management

A diagnosis of typhoid fever requires treatment with antibiotics. Treatment shortens the length of the illness and reduces the frequency of complications, including death. The growing threat of antimicrobial resistance underscores the importance of securing a microbiologic isolate for susceptibility testing. Not unexpectedly, infections caused by multidrug-resistant (MDR) strains of the pathogen are associated with more severe illness, higher rates of complications, and increased mortality rates. Individuals infected with MDR strains of *S. typhi* also have higher rates of developing a prolonged asymptomatic carrier state. The preferred empiric therapy in adults is a fluoroquinolone-class antibiotic such as ciprofloxacin being mindful that fluoroquinolone resistance is now common in many endemic regions.

Azithromycin or ceftriaxone has been used successfully to treat typhoid fever caused by fluoroquinolone resistance strains; however, resistance to these agents has also emerged. During treatment with effective therapy, fever may persist for 3–5 days. Those with fevers persisting longer than 5 days on treatment should be evaluated for an extraintestinal source of infection such as an abscess or seeding of a bone or joint while reviewing and confirming appropriate antibiotic selection based on susceptibility data. Up to 10% of treated cases undergo relapse between 1 and 3 weeks after initial recovery. Additional antibiotic treatment is usually necessary. A small percentage of patients (1–4%) who recover from typhoid fever become asymptomatic chronic carriers, shedding the pathogen in their stool for 12 months or longer. Careful infection control procedures, including an evaluation of possible public health risks related to the patient's occupation, are essential to prevent outbreaks.

Typhoid Vaccines

Two formulations of typhoid vaccine are currently available in the United States. One is a live attenuated vaccine given by mouth, and the other is a capsular polysaccharide vaccine given by injection. Typhoid vaccines are not routinely recommended for children or adults living in the United States. The Advisory Committee on Immunization Practices currently recommends that typhoid vaccine be considered for travelers to endemic areas of the world, individuals who have close contact with carriers of *S. typhi*, and laboratory workers who are or who may be exposed to biologic samples or cultures that contain *S. typhi.*

The live attenuated typhoid vaccine, approved by the FDA in 1989 for use in individuals 6 years of age and older, is marketed by PaxVax under the brand name Vivotif. The Ty21a strain of *S. typhi* used to manufacture the vaccine lacks enzymes necessary to produce a complete polysaccharide capsule, but the bacteria synthesize sufficient polysaccharide during replication to elicit an immune response. The four-dose primary vaccine series consists of orally administered capsules to be taken at 48-hour dosing intervals. Each capsule should be swallowed with cool water (or other liquid), no warmer than 37 °C, 1 hour before or ≥2 hours after eating. Capsules should not be chewed. The four-dose primary series should be completed at least 1 week prior to travel. For those with ongoing risks for exposure, the vaccine series should be repeated every 5 years. The vaccine is provided as salmon to off-white colored capsules packaged in four-capsule blister packs. It should be stored between 2 °C and 8 °C.

The capsular polysaccharide typhoid vaccine, first approved by the FDA in 1994 for use in individuals 2 years of age and older, is currently marketed by Sanofi Pasteur under the brand name Typhim Vi. A single dose is administered as a 0.5 mL intramuscular injection containing 25 mg of vaccine antigen at least 2 weeks prior to travel. Booster doses are recommended every 2 years for those with ongoing risks of exposure. The vaccine is provided as a vial containing a clear, colorless solution that should be stored between 2 °C and 8 °C, never frozen.

Immunizing Antigen

The live attenuated *S. typhi* Ty21a strain is grown in fermenters in culture medium containing yeast extract, casein, dextrose, and galactose. When ready for harvest, bacteria are collected by centrifugation; mixed with a stabilizer containing sucrose, ascorbic acid, and amino acids; and then lyophilized. The lyophilized product is then mixed with lactose and magnesium stearate and used to fill gelatin capsules coated with an organic solution rendering them resistant to dissolution in stomach acid.

Polysaccharide vaccine is also derived from the Ty2 strain of *S. typhi*. Bacteria are grown in semisynthetic culture medium containing casein-derived raw materials. Concentrated bacterial cultures are inactivated with formaldehyde, and then the capsular polysaccharide is precipitated from the culture supernatant using

hexadecyltrimethylammonium bromide. The crude precipitate is purified using differential centrifugation and precipitation, and then the purified final product is suspended in an isotonic solution of phosphate-buffered saline. Phenol is added as a preservative at a final concentration of 0.25%.

Additives and Excipients

The live attenuated typhoid vaccine contains residual yeast extract, between 5 and 50×10^9 nonviable bacterial cells, 3.3–34.2 mg sucrose, 0.2–2.4 mg ascorbic acid, 0.3–3.0 mg amino acid mixture, up to 200 mg lactose, and 3.6–4.0 mg magnesium stearate. The capsules are made of gelatin.

The polysaccharide typhoid vaccine contains less than 100 mcg formaldehyde, residual polydimethylsiloxane or fatty acid ester-based antifoam, 4.150 mg sodium chloride, 0.065 mg disodium phosphate, 0.023 mg monosodium phosphate, residual casein-derived raw materials, residual hexadecyltrimethylammonium bromide, and 0.25% phenol.

Contraindications to Vaccine

Typhoid vaccines are contraindicated for use in individuals who have experienced a life-threatening allergic reaction after receiving a previous dose or who are known to have a severe allergy to any vaccine component. Moderately or severely ill individuals should postpone immunization until recovered.

Live attenuated typhoid vaccine is specifically not recommended for children <6 years old, pregnant women, immunocompromised individuals, or close (household) contacts of immunocompromised individuals.

Polysaccharide typhoid vaccine is specifically not recommended for children <2 years and should only be considered for pregnant women if clearly needed, being mindful to delay vaccination until the second or third trimester.

Warnings and Precautions for Vaccine Use

Live attenuated typhoid vaccine is not recommended for use in individuals with acute gastroenteritis. Vaccination should be delayed for >72 hours following the administration of any antibacterial agent, and antibiotics should be avoided until 72 hours after receipt of the final vaccine dose of the series. Vaccination should also be delayed for ≥10 days after taking the anti-malaria drug proguanil. The live attenuated typhoid vaccine can be administered to HIV-positive individuals who have a recent CD4 T-cell count above 200 cells per microliter.

Side Effects and Adverse Events

Typhoid vaccines are very well tolerated. When side effects are seen, they are generally mild and transient, resolving within 48 hours. The most common side effects seen following receipt of live attenuated typhoid vaccine are abdominal discomfort (6.4%), nausea (5.8%), headache (4.8%), fever (3.3%), diarrhea (2.9%), vomiting (1.5%), and rash (1.0%). As a group, the most common side effects seen from polysaccharide typhoid vaccine are those related to the injection site, including tenderness (97–98%), pain (27–41%), induration (5.1–14.8%), and erythema (3.7–5.1%). The most commonly reported systemic side effects include malaise (4–24%), headache (16.3–20.4%), nausea (1.9–8.2%), and myalgia (3.1–7.4%).

Impact of Vaccine on Disease Burden

A large, randomized, double-blind controlled live attenuated clinical vaccine trial involving 32,388 Egyptian children aged 6–7 years showed a 95% decrease in typhoid incidence over a 3-year period. A field trial of live attenuated vaccine in 82,543 Chilean children showed a modest 29% efficacy after 1 dose and 59% efficacy after two doses. Subsequent trials designed using three or four dose regimens showed that vaccine efficacy was highest (95.8%) using a four-dose regimen.

A randomized, double-blind, active vaccine-controlled trial of polysaccharide typhoid vaccine involving 3454 subjects who received Typhim Vi and 3454 controls who received 23-valent pneumococcal vaccine showed an overall protective efficacy of 74% during 20 months of follow-up. A vaccine immunogenicity trial that included 175 Indonesian children between 2 and 5 years of age showed that 96% of enrolled subjects developed a fourfold or greater increase in serum anti-capsular antibody concentrations.

Two immunogenicity trials performed in healthy US adults 18–40 years of age showed that 96% and 88% of subjects achieved a fourfold or greater rise in serum anti-capsular antibody concentrations when measured 4 weeks after receipt of a single intramuscular dose. Similar antibody levels were attained following primary and 27- or 34-month booster doses in US adults, responses that are typical for vaccines comprised of polysaccharide antigen. As with other pure polysaccharide vaccines, re-immunization does not elicit higher (boosted) antibody responses because polysaccharide antigens are processed by the immune system using a T-cell-independent pathway.

Typhoid fever is associated with substantial morbidity and mortality. Disease outbreaks can be largely prevented by providing access to clean water and sanitary conditions with focused attention on the management of human waste. Two formulations of typhoid vaccine are currently available, one derived from live attenuated *S. typhi* and the other comprised of capsular polysaccharide. The safety profiles for both formulations are excellent. Effectiveness data support their use in individuals

at high risk for exposure, but the protection provided from both vaccine types is incomplete and of relative short duration. Individuals with ongoing risks for exposure require booster doses of vaccine at regular intervals.

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Chapter 33
Varicella and Shingles

Cynthia Bonville and Manika Suryadevara

Varicella Zoster Infection

Etiology Varicella zoster virus (VZV), human herpesvirus 3, is a large enveloped double-stranded DNA virus with only one known serotype. This neurotropic virus is a member of the *Varicellovirus* genus belonging to the *Herpesviridae* family. VZV causes two clinical distinct disease forms. Primary infection with VZV causes varicella (chickenpox). Following recovery from chickenpox, the virus remains latent in the body until reactivation years later. Reactivation of dormant virus causes herpes zoster (shingles).

Evidence of chickenpox through descriptive reports dates back as early as the year 865 CE. Over time, varicella and zoster appear to have been studied as two separate and unrelated entities. In 1875, scientist Rudolf Steiner was the first to identify this process to be infectious, when he rubbed fluid of chickenpox lesions onto the skin of healthy volunteers and saw that they too developed a similar rash. Shortly after, in 1888, von Bokay reported the association between varicella and zoster after noticing that varicella-naïve children exposed to household contacts with zoster would then go on to develop chickenpox. Further supporting this idea was the identical appearance of the virions from both entities by electron microscopy. It wasn't until 1954 that scientist Thomas Weller isolated VZV from both chickenpox vesicular fluid and zoster lesions, confirming the theory that both entities were caused by the same pathogen.

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Pre-vaccine Epidemiology

VZV, endemic to all countries of the globe, is not a universally notifiable disease. Therefore, global estimates of disease burden are difficult to establish. Most pre-vaccine population-based varicella surveillance data are from high-income countries and suggest that almost all primary varicella infections occur before adolescence in temperate countries and in older age cohorts in the tropical regions. Before 1995, in the United States, specifically, the majority of individuals acquired varicella infection before adulthood. It is estimated that four million cases occurred annually (the size of the country's birth cohort), with the highest incidence of disease in children aged 1–4 years. Each year, there were ~11,000 varicella hospitalizations and 100–150 varicella-related deaths. While case fatality rates were not as high as some of the other vaccine-preventable diseases, varicella disease burden was associated with high societal and economic costs.

Herpes zoster incidence increases with increasing age, correlating with declining cell-mediated immunity. It is estimated that about half of adults will have had at least one episode of zoster by the age of 85 years.

In 1971, Dr. Michiaki Takahashi, of Japan, was the first person to isolate and attenuate a strain of the varicella virus. After obtaining a sample of vesicle fluid from an infected 3-year-old boy, Takahashi isolated varicella virus, now named the Oka strain (using the surname of the boy), and then weakened the virus via passage through serial cell culture to allow for vaccine production. In 1974, the live Oka strain varicella vaccine was first used in a Japanese hospital and successfully protected 23 varicella-naïve high-risk children from acquiring infection from another child admitted to the same pediatric ward with typical chickenpox infection. The live Oka strain vaccine is contained by the immune system but, like wild-type VZV, persists in a latent state in ganglia. In 1995, the FDA approved the first varicella-containing vaccine to be administered as a single dose for use in the United States, the first country to implement a routine childhood varicella vaccination program. The Oka strain continues to be used in the varicella and herpes zoster vaccines available around the world.

Transmission

Humans are the only reservoir for VZV. This virus is transmitted from infected person to susceptible person through airborne spread of infected respiratory secretions or inhalation of aerosols from or direct contact with vesicular fluid of both varicella and herpes zoster skin lesions. Varicella is approximately fivefold more contagious than herpes zoster. A highly contagious virus, nearly all susceptible household contacts of a varicella index case will be infected. Individuals with varicella infection are contagious from 1 to 2 days prior to rash onset until all lesions are crusted over, while those with zoster are contagious after rash eruption until lesions crust over.

Transmission of VZV during zoster manifestations can be reduced by covering localized lesions until resolution.

It is important to note that a varicella-immune individual will not develop shingles after exposure to chickenpox or shingles. On the other hand, varicella-susceptible individuals exposed to chickenpox or shingles are at risk for developing primary varicella (chickenpox) infection. Shingles occurs, as a reactivation of the virus, years to decades following the initial infection.

While varicella is associated with a strong seasonality in temperate regions, peaking in winter and early spring, herpes zoster occurs throughout the year with no seasonal pattern. VZV is heat-labile, surviving in the environment for only a few hours. It is readily inactivated by lipid solvents, detergents, and proteases.

Clinical Presentation

Primary varicella infection (chickenpox) is a classic disease of childhood. While a benign, self-limited disease in immunocompetent children, more severe infections with complications occur in adults and immunocompromised individuals. The incubation period is usually 10–14 days but can range from 10 to 21 days. In unimmunized children, the rash tends to be the first sign of disease. The macular rash becomes papular within 24 hours, before developing into clear fluid-filled vesicles on an erythematous base. These pruritic lesions are superficially located in the dermis layer. An influx of leukocytes results in pustular formation, which ultimately dries, crusts, scabs, and desquamates within a week. Lesions start on the head before spreading to the chest and back and then extremities, with the highest concentration of lesions usually on the trunk. Lesion numbers can range from 200 to 500. Mucosal involvement can occur. At any given time, successive crops at different stages of progression (asynchronous rash) may be seen all over the body, distinguishing varicella infection from other exanthematous infections. Fevers and myalgia often accompany rash onset but only persist for a few days. Recovery from infection usually provides lifelong immunity to chickenpox.

Primary varicella infection in unimmunized adults differs from that in children in that adults may present with a prodromal phase (fever, malaise, headache, abdominal pain) prior to rash onset. Compared to children aged 5–14 years, adults 45 years of age and older have a 4–50 times greater risk of hospitalization and 174-fold higher risk of death.

Breakthrough varicella occurs when wild-type VZV infection occurs more than 6 weeks following varicella vaccination. These infections tend to be milder with fewer lesions (less than 50), most lacking progression past the papule stage. Fever is low grade or absent.

Table 33.1 lists the general complications of primary varicella infection. Populations at increased risk for severe disease and complications to varicella infection include immunocompromised persons with no evidence of varicella immunity (including those with cellular immunodeficiencies, lymphoma, and leukemia and

Table 33.1 Complications of primary varicella infection

Localized bacterial superinfections of the skin	*Staphylococcus aureus* *Streptococcus pyogenes* Most common complication in children Most common cause of varicella-related visits or hospitalizations
Systemic bacterial infections	*Streptococcus pyogenes* Toxic shock syndrome, sepsis, necrotizing fasciitis, osteomyelitis, septic arthritis
Pneumonia	Primary varicella pneumonia or bacterial superinfection Most common complication in adults (usually caused by VZV) Bacterial pneumonia most commonly seen in infants
Central nervous system involvement	Cerebellar ataxia occurs 1 in 4000 cases, good prognosis Encephalitis can lead to seizures and coma Reye syndrome among children who take aspirin Vasculitis
Uncommon complications	Aseptic meningitis, transverse myelitis, Guillain-Barre syndrome, thrombocytopenia, hemorrhagic varicella, purpura fulminans, glomerulonephritis, myocarditis, arthritis, orchitis, uveitis, hepatitis, death

those receiving immunosuppressive treatments), pregnant women with no evidence of immunity, newborns of mothers who had varicella between 5 days before and 2 days after delivery, and premature infants exposed to varicella or zoster. Complications commonly seen in immunocompromised individuals infected with varicella include prolonged symptom duration, potential for hemorrhagic lesions, and visceral dissemination of infection to cause pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulation. Manifestations of primary varicella infection in symptomatic HIV-infected children may include ongoing development of lesions for months that may progress to non-healing ulcers that become necrotic and crusted. Retinitis can also be seen in this population. Primary varicella infection during pregnancy may result in fatal pneumonia. Infection in the first 20 weeks of gestation may rarely lead to congenital varicella syndrome, with intrauterine growth restriction, low birth weight, skin scarring, limb hypoplasia, and defects affecting the eyes and central nervous system. Newborns with primary varicella infection can have disseminated infection with a mortality rate of up to 30% if not appropriately treated. Infants who acquire primary varicella infection have a much higher risk of developing herpes zoster in the first few years of life.

Latency is an asymptomatic period that follows recovery from primary varicella infection. Virus enters nerve endings and is transported to the neurons in the dorsal sensory root ganglia, either through retrograde axonal transport from cutaneous lesions or through hematogenous transfer during viremia. Here, the virus remains dormant throughout one's lifetime, kept in check by the host's varicella-specific cell-mediated immunity.

Herpes zoster (shingles) is a clinically evident reactivation of latent varicella zoster virus that can occur decades after primary infection, with an estimated 32% lifetime risk of developing disease. Virus replication resumes in ganglion and spreads via the sensory nerve root and then peripheral nerves to the innervated target tissue. Clinical manifestations include a prodrome phase of headache,

Table 33.2 Complications of zoster infection

Postherpetic neuralgia	Persistent pain (ranges from mild to severe) persisting for months after resolution of rash Can be debilitating pain leading to loss of independence, social withdrawal, and depression Risk factors include age 50 years and older, extensive rash, trigeminal or ophthalmic rash distribution, severe pain before rash
Herpes zoster ophthalmicus	Involves ophthalmic division of trigeminal nerve If untreated can lead to stromal keratitis and acute retinal necrosis and can lead to reduced vision and ultimately blindness
Herpes zoster oticus (Ramsay Hunt syndrome)	Involves mandibular division of trigeminal nerve Causes facial paralysis and hearing loss in affected ear
Bacterial superinfection of lesions	Most often due to *S. aureus*
Neurologic complications	Cranial and peripheral nerve palsies Meningitis, meningoencephalitis, radiculitis, cerebellitis, myelopathy, vasculopathy
Viremia	Leading to pneumonia, hepatitis, disseminated intravascular coagulation, acute retinal necrosis, death
Disseminated shingles	Widespread distribution affecting at least 3 dermatomes Most often seen in immunocompromised individuals Can be difficult to distinguish from chickenpox

photophobia, malaise, fever, abnormal skin sensation, and pain that occur days to weeks prior to rash onset. The classic zoster rash is unilateral, occurring across one or two dermatomes (most commonly thoracic, cervical, or ophthalmic) without crossing the body's midline. Initially an erythematous maculopapular rash, clusters of vesicles subsequently develop into an itchy, tingling, painful rash. After 2–4 weeks, lesions dry, crust, and desquamate with full resolution. In some cases, the rash never develops (zoster sine herpete) despite symptoms of chronic radicular pain. Up to 4% of individuals with zoster are hospitalized due to complications of infections. Herpes zoster can occur in anyone who was previously infected with varicella or received a varicella vaccination, although the risk following vaccination is much lower than that following natural infection. Risk factors for herpes zoster include advancing age (due to declining cell-mediated immunity), immunosuppression (mainly cell-mediated), trauma or surgery in affected dermatome, and primary infection in early childhood. Table 33.2 lists the complications of zoster infection.

Management

Antiviral therapy is not recommended for the treatment of uncomplicated varicella infection in otherwise healthy children. Oral acyclovir (or valacyclovir) is recommended for the treatment of varicella infection in persons at increased risk for moderate or severe disease, including healthy people older than 12 years of age, those

Table 33.3 Evidence of immunity to varicella infection

Fulfilling any one of the following is evidence of immunity to varicella infection
Written, dated documentation of age-appropriate immunization
Laboratory evidence of immunity
Laboratory confirmation of disease
Varicella or herpes zoster diagnosed by a physician

with chronic cutaneous or pulmonary disorders, and those receiving long-term salicylate or corticosteroid therapy. Household contacts experiencing disease more severe than the index case and pregnant women with primary varicella infection should also be considered to receive antiviral therapy. Intravenous acyclovir is recommended for severe disease with multi-organ involvement, infection in immunocompromised patients (including those receiving high-dose corticosteroids for more than 14 days), and pregnant women with severe disease. Famciclovir is also available for the treatment of VZV infections in adults. Foscarnet can be used to treat infections with acyclovir-resistant VZV strains. Neither the primary varicella vaccine nor the herpes zoster vaccine can be used to treat infection.

Children with varicella should not receive salicylate-containing medications due to the increased risk of Reye syndrome. Treatment with ibuprofen may be associated with life-threatening streptococcal skin infections and should be avoided.

Prevention

The primary approach to community-wide varicella prevention includes the routine, universal use of live attenuated varicella vaccine as a two-dose series starting at age 1 year. If an individual without evidence of immunity to varicella (Table 33.3) is exposed to VZV, there are three available prophylactic strategies: vaccination, varicella zoster immunoglobulin (VariZIG) or intravenous immunoglobulin (IGIV) administration, and antiviral therapy with acyclovir or valacyclovir (Table 33.4). VariZIG, licensed in the United States in March 2013, can be obtained from FFF Enterprises (www.fffenterprises.com) and ASD Healthcare (www.asdhealthcare.com). IGIV can be used if VariZIG is unavailable.

Varicella Zoster Vaccine

Vaccine Characteristics

In the United States, live attenuated varicella-containing vaccine is derived from the Oka strain attenuated through serial passages in cell culture. The inactivated VZV vaccine to prevent herpes zoster consists of recombinant virus surface glycoprotein

Table 33.4 Prophylaxis recommendations for individuals with no evidence of immunity who are exposed to varicella infection

Susceptible individual	Prophylaxis recommendation[a]
Healthy individuals	
Younger than 1 year of age	No prophylaxis
1 year of age and older	
Exposure within 5 days	Varicella vaccine if not contraindicated
Exposure more than 5 days prior	No prophylaxis
Underlying high-risk conditions	
Immunocompromised children (cell-mediated immune defects) Pregnant women Newborn infants whose mother had chickenpox with 5 days before or 2 days after delivery Hospitalized preterm infant 28-week or more gestation whose mother had no evidence of immunity against varicella Hospitalized preterm infant less than 28-week gestation (or weight less than 1000 g) regardless of maternal immunity	VariZIG[b] IM <= 2 kg: 62.5 units 2.1–10 kg: 125 units 10.1–20 kg: 250 units 20.1–30 kg: 375 units 30.1–40 kg: 500 units >40 kg: 625 units Or IGIV[b] 400 mg/kg

[a]If vaccine is contraindicated and VariZIG or IGIV is not indicated or unavailable, oral acyclovir or valacyclovir can be initiated 7 days after exposure
[b]*VariZIG* varicella zoster immunoglobulin, *IGIV* intravenous immunoglobulin

E antigen. Three separate varicella-containing vaccines are licensed and available in this country. Primary varicella prevention occurs through the use of Varivax or ProQuad. Herpes zoster prevention occurs through Shingrix.

Primary Varicella Prevention

Varivax (Merck), licensed in the United States in March 1995, is a monovalent, live attenuated varicella vaccine administered to individuals of age 12 months and older. Other vaccine ingredients include sucrose, hydrolyzed gelatin, urea, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, and trace quantities of neomycin and bovine calf serum. This vaccine contains no preservatives.

ProQuad (Merck), licensed in the United States in September 2005, is a combination live attenuated measles, mumps, rubella, and varicella vaccine administered to children of ages 12 months through 12 years. This vaccine contains the same Oka strain of varicella virus as Varivax but at a three times higher concentration. Other vaccine ingredients include sorbitol, sucrose, gelatin, human albumin, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, sodium bicarbonate, potassium phosphate monobasic, potassium chloride, potassium dibasic, potassium phosphate monobasic, bovine calf serum, and neomycin. This vaccine contains no preservatives.

Herpes Zoster Prevention

Shingrix (GlaxoSmithKline), licensed in the United States in October 2017, is an inactivated, adjuvanted recombinant VZV surface glycoprotein E antigen vaccine administered to adults 50 years of age and older. Other vaccine ingredients include sucrose, sodium chloride, potassium dihydrogen phosphate, cholesterol, sodium dihydrogen phosphate dihydrate, disodium phosphate anhydrous, dipotassium phosphate, and polysorbate 80. This vaccine contains no preservatives.

Vaccine Storage, Preparation, and Administration

Varivax is supplied as a lyophilized vaccine and a sterile diluent. Vaccine is stored frozen between −50 °C and −15 °C. Vaccine may be stored refrigerated (2–8 °C) for up to 72 hours prior to reconstitution. Diluent is stored at room temperature (20–25 °C) or refrigerated (2–8 °C). Reconstitute the lyophilized vaccine with the provided sterile diluent. Reconstituted product is clear and colorless to pale yellow and should be used immediately. Discard if particulate matter is observed, discolored, or not utilized within 30 minutes. Administer immediately as 0.5 mL dose subcutaneously. All leftover vaccine and contaminated materials should be disposed of as a biohazard.

ProQuad is supplied as a lyophilized virus to be stored between −50 °C and 8 °C and protected from light at all times. Lyophilized vaccine vials may be stored refrigerated (2–8 °C) for up to 72 hours. Improperly stored vaccines may lose potency. Sterile, preservative-free water is provided as the diluent and may be stored in the refrigerator (2–8 °C) or at room temperature. Once reconstituted, the clear pale yellow to light pink vaccine should be administered immediately but can be refrigerated for up to 30 minutes if necessary. Each 0.5 mL dose of vaccine is given by subcutaneous injection. Biohazard disposal is required for all residual vaccine and contaminated materials.

Shingrix is supplied as a lyophilized varicella virus glycoprotein E antigen powder component and an $AS01_B$ adjuvant suspension component. Store both components refrigerated (2–8 °C). Reconstitute vaccine by withdrawing the entire content of supplied adjuvant suspension and transferring to vaccine vial. Gently shake until powder is completely dissolved. After reconstitution, vaccine may be stored refrigerated for up to 6 hours. 0.5 mL dose is administered intramuscularly.

Vaccine Recommendations

Primary Varicella Prevention

Varicella-containing vaccines are routinely recommended for all individuals 12 months of age and older, unless contraindicated. In the United States, the two-dose vaccine series is routinely administered at 12–15 months of age and 4–6 years of age. As with other live viral vaccines, varicella vaccine is not administered earlier than 1 year of age because residual circulating maternal antibody will neutralize the vaccine and impair the developing antibody response. Varicella vaccine doses administered 5 or more days prior to the first birthday are not considered valid for completion of the two-dose recommendation. Under such circumstances, the two-dose series should be initiated as early as 12 months of age, with the first dose of the repeat vaccination administered at least 28 days from the invalid dose.

Either the monovalent or combination vaccine may be used to prevent varicella infection. However, the CDC recommends using separate MMR and varicella vaccines for the first dose at age 1 year (unless the parents state a specific preference for MMRV) and using MMRV for the second dose. The first dose of MMRV vaccination is associated with higher risks of fever and febrile seizures for children 12–23 months of age than the first dose of MMR vaccination. However, since this difference is not seen with subsequent doses and in older age groups, the use of MMRV vaccine is recommended for the second dose to reduce the number of injections at that visit.

All previously unimmunized children, adolescents, and adults should receive two doses of varicella-containing vaccine. The recommended minimal interval between doses for children aged 12 months–12 years is 3 months, although a 28-day interval is considered valid. For individuals aged 13 years and older, the recommended minimum interval is 4 weeks. Combination varicella vaccine is not approved for use in this age group. To reduce VZV transmission in schools, all children should have received two doses of varicella vaccination or have evidence of varicella immunity prior to school entry (Table 33.3). Table 33.5 lists the vaccine recommendations for populations with altered immunity. Only monovalent varicella vaccines should be used for immunization in these cases. If Shingrix is inadvertently used instead of varicella vaccine, this dose is not valid. Two doses of varicella vaccine must be given.

Pregnant women susceptible to varicella infection should receive two doses of varicella vaccine following pregnancy. There is no need to delay postpartum vaccination because of breastfeeding. Healthcare personnel and other individuals at risk of VZV exposure (teachers, day care employees, residents, and employees of institutional settings) without evidence of varicella immunity (Table 33.3) should also receive two doses of varicella vaccine, 4–8 weeks apart.

Table 33.5 Recommendations for primary varicella vaccination among populations with potential altered immunity. Information from this table are from ACIP recommendations and Red Book Online

Special populations	Varicella vaccination recommendation
Immunocompetent persons who need immunosuppressive therapy	Two doses of varicella vaccine, at least 28 days apart, administered more than 4 weeks before treatment initiation if there is time
Severe immunosuppression, cell-mediated immunodeficiency	Varicella vaccination is contraindicated
Primary immunodeficiencies (without cell-mediated defects), chronic granulomatous disease	Two doses of varicella vaccine, at least 28 days apart
Completed immunosuppressive therapy for malignancy	Administer 2 doses of varicella vaccine when in remission, at least 3 months after therapy completed, evidence of restored immune status If cancer treatment regimen included anti-B cell antibodies, vaccination should be delayed at least 6 months
Hematopoietic stem cell transplant recipients	Administer 2 doses of varicella vaccine, beginning at least 24 months after transplantation, to varicella-seronegative patients if they do not have graft-versus-host disease and are immunocompetent and whose last dose of intravenous immunoglobulin was 8–11 months prior
HIV-infected individuals	Administer 2 doses of vaccine 3 months apart if children aged 1–13 years have a CD4+ (%) >= 15%; adolescents 14 years and older have a CD4+ absolute count >= 200 lymphocytes/mm^3 Oral acyclovir may be used if vaccination results in clinical disease
Long-term corticosteroid use	Varicella vaccination is contraindicated in individuals receiving systemic corticosteroids (at least 2 mg/kg/day or at least 20 mg of prednisone or its equivalent) for at least 14 days Vaccine can be administered later than 1 month after steroid discontinuation Inhaled, nasal, or topical steroid use is not a contraindication to vaccination
Household contacts of immunocompromised individuals	2 doses of varicella vaccine, at least 28 days apart, to reduce the likelihood of transmission of infection to the immunocompromised individual
Pregnancy	Pregnancy is a contraindication to varicella vaccination Pregnancy should be avoided for at least 1 month after immunization

Herpes Zoster Prevention

As of July 1, 2020, zoster vaccine live (Zostavax, Merck) will no longer be sold in the United States, leaving recombinant zoster vaccine (Shingrix) as the only vaccine available for zoster prevention in the country. Recombinant zoster vaccine may be used in adults aged 50 years and older, regardless of prior varicella or zoster

vaccination or disease history. No varicella (chickenpox) history screening is needed. Recombinant zoster vaccine is administered as a two-dose series, given 2–6 months apart. If the series is interrupted, there is no need to restart. Experts suggest that recombinant zoster vaccine may be given to individuals who have previously received zoster vaccine live (Zostavax), if more than 2 months has passed since immunization. Recombinant vaccines can be administered at the same time as other adult vaccines.

While persons with a history of herpes zoster should receive recombinant zoster vaccine, this immunization should be delayed if the individual is currently experiencing an episode of zoster. Vaccine can be administered after resolution of acute illness. Individuals with a history of chronic illness, including chronic renal failure, diabetes mellitus, rheumatoid arthritis, and chronic pulmonary disease, are eligible for vaccine receipt. ACIP recommends the use of recombinant zoster vaccine in individuals receiving low-dose immunosuppressive therapy (<20 mg/day of prednisone or equivalent) and those who are anticipating immunosuppression or who have recovered from an immunocompromising illness. The ACIP has not yet made recommendations for the use of recombinant zoster vaccine in immunocompromised patients or those receiving moderate to high doses of immunosuppressive therapy.

Contraindications to Varicella Vaccine

Contraindications to primary varicella vaccines (Varivax and ProQuad) include a history of severe allergic reaction to a prior varicella vaccine or any vaccine component (neomycin, gelatin), primary or acquired immunodeficiency states (see Table 33.5 for details), pregnancy, and any acute febrile illness or active infection, including untreated tuberculosis. Vaccines should be deferred in individuals who have a family history of immunodeficiency until the individual's immune status is fully evaluated. Receipt of antibody-containing blood products may require postponement of vaccination for a duration based on blood product type and dosage (see Table 18.6 of Chap. 18 for details). While no cases of Reye syndrome have been reported following varicella vaccination, it is still recommended that salicylates be avoided for 6 weeks after varicella vaccination. Vaccination should be postponed also if acyclovir, valacyclovir, or famciclovir has been received within 24 hours. Contraindications to the herpes zoster vaccine (Shingrix) include a history of severe hypersensitivity to recombinant zoster vaccine or any vaccine component.

Adverse Events

The most commonly reported adverse reactions to monovalent varicella vaccination (Varivax) include fevers and redness, swelling, and pain at the injection site. Varicella like rash, either localized to the site of injection or generalized, has also been reported among some vaccinees, more likely to occur with the first dose

compared to second. Refer to Table 18.7 in Chap. 18 for adverse reactions following receipt of MMRV (ProQuad) vaccination.

The most commonly reported adverse reaction to Shingrix include pain, redness, and swelling at the injection site. Systemic effects including myalgia, fatigue, headache, and fevers have been reported in almost half of vaccine recipients, some of which are severe enough to prevent daily activities.

Immunogenicity and Efficacy

Ninety-seven percent of children aged 12 months through 12 years have detectable antibodies after a single dose of varicella vaccination. This proportion increases to 99% of individuals 13 years and older after two doses. One dose of varicella vaccine is 81% (95% CI, 78%, 84%) effective at preventing all varicella disease and 98% (95% CI, 97%, 99%) effective at preventing moderate to severe disease. Two doses of varicella vaccine are 92% (95% CI, 88%, 98%) effective at preventing all varicella disease.

A phase 3 randomized placebo-controlled multicenter trial of Shingrix demonstrated a 97.2% (95% CI, 93.7%, 99%) reduction in herpes zoster and 100% reduction in postherpetic neuralgia in volunteers 50 years of age and older. A second study in volunteers 70 years of age and older demonstrated an 89.8% (95% CI, 84.3%, 93.7%) efficacy against herpes zoster and an 85.5% (95% CI, 58.5%, 96.3%) efficacy against postherpetic neuralgia in this age cohort.

Impact of Vaccine on Disease Burden

In the United States, by the year 2000, 5 years after implementation of a single dose of varicella vaccine in the national children's immunization program, there was a >70% decline in overall disease incidence in communities with vaccine uptake over 80% among children aged 19–35 months (Fig. 33.1). While the disease reduction was highest in the vaccinated children, these effects were seen in all age groups. In addition, between 1994 and 2002, there was a 74% reduction in varicella-related healthcare costs (a decline from $85 million to $22 million). Despite a decline in cases and adequate vaccination rates, some regions continued to have outbreaks, particularly among young students and in elementary schools, suggesting that a single dose of varicella vaccine was insufficient to fully prevent varicella outbreaks. In 2006, the addition of a second vaccine dose dropped the disease incidence even further to 2 cases per 1000 patient-years. Between 1995 and 2016, there has been an estimated 90% reduction in varicella morbidity and mortality. Further, vaccinating 1 million age-appropriate adults against zoster is estimated to prevent 70,000 cases of zoster, 20,000 cases of postherpetic neuralgia, 250,000 medical visits, and 8000 hospitalizations.

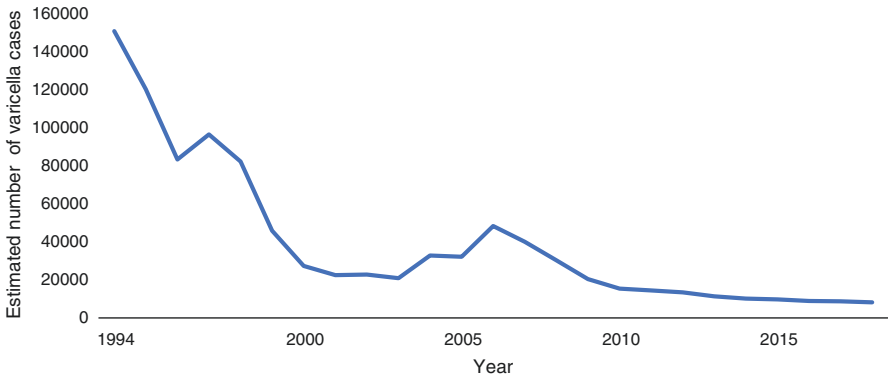

Fig. 33.1 Estimated number of varicella cases in the United States, 1994–2018

The World Health Organization estimates that the annual incidence of varicella disease is still 26–61 cases per 1000 unvaccinated individuals with 4.2 million severe cases per year leading to hospitalization and 4200 deaths per year. The WHO recommends that countries assess disease burden due to varicella before deciding whether to introduce the varicella vaccine into their national immunization program. Countries with a high disease burden of varicella and sufficient resources to reach and sustain vaccination rates of at least 80% should consider routine use of varicella vaccine. Vaccination rates below 80% may shift disease to the older age groups at higher risk for severe disease and complications. Overall, vaccine mortality in high-income countries dropped from 3 in 100,000 cases to 0.1 per 100,000 cases after widespread use of varicella vaccines in their regions.

Suggested Readings

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WHO

https://www.who.int/immunization/diseases/varicella/en/.

CDC

https://www.cdc.gov/chickenpox/index.html.
https://www.cdc.gov/shingles/index.html.

CDC VIS

https://www.cdc.gov/vaccines/hcp/vis/vis-statements/varicella.pdf.
https://www.cdc.gov/vaccines/hcp/vis/vis-statements/shingles-recombinant.pdf.

Varivax Package Inserts

https://www.fda.gov/media/119865/download (Frozen).

ProQuad Package Inserts

https://www.fda.gov/media/119880/download (Frozen, Recombinant Human Albumin).

Shingrix Package Insert

https://www.fda.gov/media/108597/download.

Chapter 34
Yellow Fever

Cynthia Bonville and Manika Suryadevara

Yellow Fever Infection

Etiology

Yellow fever virus, a positive, single-stranded enveloped RNA arbovirus, is a member of the *Flavivirus* genus, in the *Flaviviridae* family. Flaviviruses can be mosquito-borne, such as yellow fever, dengue, Japanese encephalitis, West Nile, and Zika viruses, or tick-borne, such as tick-borne encephalitis, Kyasanur forest disease, and Alkhurma hemorrhagic fever viruses.

Pre-vaccine Epidemiology

Originating in Africa, yellow fever was introduced into the Americas by Dutch slave traders in the 1640s. By the end of the decade, this disease, known as "black vomit" for the associated gastrointestinal bleeding, spread through the Caribbean with epidemics described in Yucatan, St. Kitts, Guadeloupe, and Cuba. In 1693, Sir Francis Wheeler arrived in Boston with his troops, after a military engagement in the Caribbean, unknowingly introducing the virus into New England. As a result, the early eighteenth century saw multiple yellow fever outbreaks in the tropical regions of the Americas and along eastern US seaports, most notably Charleston, Philadelphia, and New York [1].

In 1793, colonists of Saint Domingue, present-day Haiti, fled the region, suffering from both a yellow fever outbreak and a revolutionary war, and arrived at the

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Philadelphia seaport during a hot, mosquito-infested summer. Within weeks, Philadelphia residents began exhibiting symptoms of this hemorrhagic disease. It is estimated that 20,000 residents (many of whom were local and federal government officials) left the city to escape infection, while the death toll of those who stayed reached 100 per day until a cold front finally came through and eliminated the mosquito population. Ultimately, there were an estimated 11,000 cases of yellow fever, with a citywide mortality rate of 10%.

During the Philadelphia epidemic, Dr. Benjamin Rush, after careful review of the patients and city conditions, supported the theory that miasma or "bad air" was the cause of infection. Over the next century, there was an increase in the frequency and severity of yellow fever epidemics in US port cities [1]. During the spring and summer of 1878, infected passengers on steamships from Cuba brought yellow fever to New Orleans, where they were allowed to disembark without quarantine. Subsequently, yellow fever infection spread along shipping routes in the Mississippi River Valley, resulting in both mass exodus from these major cities and significant disease burden among residents who stayed. There were an estimated 120,000 cases of yellow fever and over 13,000 deaths in the Mississippi River Valley just in these few months. In response, public health departments were established in southern America and improved sanitation measures implemented, but the true vector of infection transmission still remained unclear.

In the late 1890s, a rebellion among Cuban nationalists led Spain to send 200,000 troops to the yellow fever-endemic Spanish colony. Cuban epidemiologist, Carlos Finlay, noted that while yellow fever claimed the lives of 1600 Spanish troops, only 65 Cubans were killed by infection, suggesting that unlike the Europeans, the Cubans were relatively immune to disease likely due to frequent exposure and resulting immunity. Similarly, when the United States joined the war (in what would be known as the Spanish-American war) at the end of the century, 1 US soldier died in battle for every 13 that succumbed to yellow fever infection.

Finlay suspected that mosquitoes, particularly the *Culex* mosquitoes known today as *Aedes aegypti*, were the cause of disease spread. Walter Reed, head of the US Army Yellow Fever Commission, and Commission member Jesse Lazear went to Cuba to pursue this theory. Lazear hatched mosquito eggs and allowed them to feed on yellow fever-infected patients. These infected mosquitoes were then allowed to feed on study volunteers, who then developed signs and symptoms of yellow fever. Even Lazear himself contracted yellow fever during these experiments and died in 1900. Reed's further studies confirmed that the *Aedes aegypti* mosquitoes were the predominant vector that transmitted yellow fever virus leading to large campaigns to control the mosquito vector [2]. In fact, following multiple failed attempts to build the Panama Canal due to loss of workers to yellow fever, successful completion of the canal occurred only after anti-mosquito measures were implemented. Further expansion of mosquito control effectively led to the control of yellow fever in the United States, with the last outbreak being in New Orleans in 1905.

While initial international efforts to prevent yellow fever focused on vector control (destroying mosquito breeding grounds), efforts moved toward vaccine

development in the 1920s. Later in the decade, yellow fever virus was isolated from both an infected 28-year-old man, Asibi, from Ghana (known as the "Asibi" strain) and from an infected man in Senegal (known as the "French" strain). The Asibi strain was passed through mouse embryo tissue culture and then chicken embryo tissue culture, leading to the production of the live attenuated 17D yellow fever vaccine by the Rockefeller Foundation. This vaccine was primarily used in the Western Hemisphere and England. A separate live, attenuated vaccine using the French strain was developed at the Pasteur Institute and was used in France and Africa. There were initial concerns regarding systemic and neurologic complications to both vaccines [3]. By 1982, the French yellow fever vaccine was discontinued because it was associated with higher rates of post-vaccination encephalitis. The 17D vaccine became the only WHO-approved vaccine to prevent yellow fever disease in individuals living in or traveling to areas at risk for yellow fever virus transmission (Fig. 34.1).

Transmission

Endemic to the tropical regions of Africa and South America, the yellow fever virus is transmitted to humans via the bite of infected *Aedes* (Africa) and *Haemagogus* or *Sabethese* (South America) species of mosquitoes. Humans have the highest level of

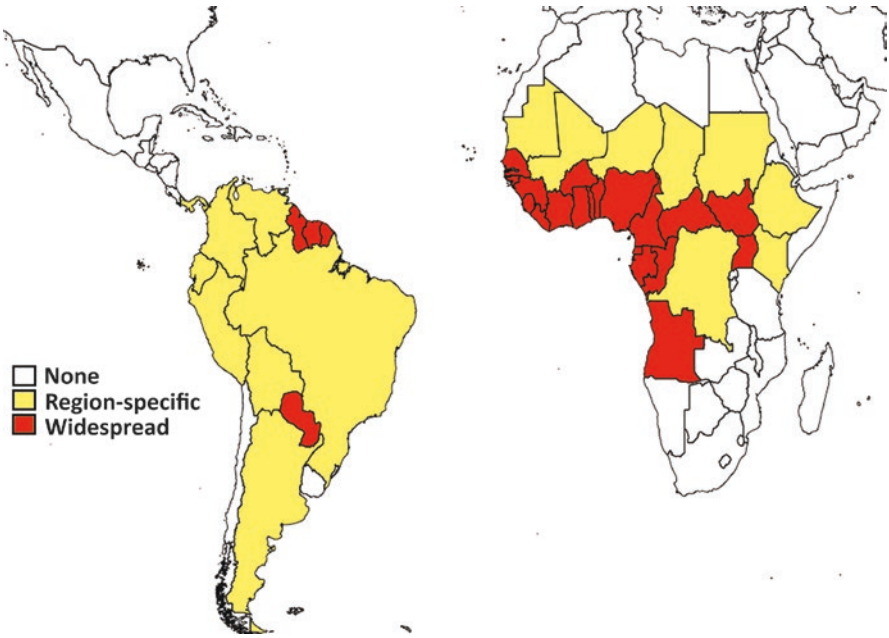

Fig. 34.1 Map depicting countries at risk for yellow fever virus transmission

viremia in the first few days of illness. It is during this time that humans can then transmit infection to mosquitoes. Once infected, mosquitoes remain infective for life and can go on to infect other humans and nonhuman primates. Transovarial transmission within mosquito populations and virus survival in desiccation-resistant mosquito eggs are additional maintenance factors. There are three transmission cycles for the yellow fever virus: the sylvatic cycle, the intermediate cycle, and the urban cycle.

Sylvatic (Jungle) Cycle In the jungles or tropical rainforests, monkeys are the primary reservoir for the yellow fever virus. Mosquitoes bite infected monkeys, acquire infection, and then transmit virus to susceptible monkeys. Transmission to humans from infected mosquitoes then occurs incidentally when humans enter the jungle for work or recreation, causing sporadic cases.

Intermediate (Savannah) Cycle Semi-domestic mosquitoes (those that breed both in the wild and around households) infect both monkeys and humans who are in the jungle border areas for work or recreation. This cycle can result in small-scale yellow fever epidemics, with outbreaks occurring in separate villages at the same time.

Urban Cycle Peri-domestic mosquitoes (those who breed around households) bite an infected human (usually one recently infected in the jungle or savannah), acquire infection, and then transmit infection to a susceptible human. When this infection is brought to an urban setting with high population density and low community immunity, large yellow fever epidemics can occur.

Several factors need to be present for yellow fever outbreaks to occur in a region. First, a competent mosquito vector that can efficiently acquire, disseminate, and transmit infection must infest the area. In addition, the environmental and climate factors must be such that the mosquitoes survive long enough for this process to occur. Lastly, the virus needs to be introduced into the regions with susceptible human population, whether it be from a traveler or nonhuman primates [4]. While yellow fever virus is not prevalent in Asia, the presence of competent mosquito vectors and susceptible communities leaves this population at risk of outbreak should virus be brought into the region. Most of these countries require yellow fever vaccination for travelers from endemic countries. Global warming, which is expanding the geographical range of competent mosquito vectors, raises the concerns for potential human disease risk in additional regions.

Clinical Presentation

Most commonly, yellow fever causes asymptomatic or mild infection. Symptomatic yellow fever infection manifestations start with a nonspecific illness, with symptoms of fever, chills, severe headache, myalgias, back pain, prostration, nausea, and vomiting. Infected individuals are typically ill during this viremic period. Relative

bradycardia for the degree of fever, Faget's sign, may also be present. While the majority of these infections self-resolve in 3–4 days, up to 15% of infections can progress to severe hemorrhagic disease after 48 hours of initial clinical improvement. Severe disease symptoms include jaundice (reason for the name "yellow fever"), hemorrhagic symptoms (hematemesis, melena, petechiae, epistaxis), shock, and multisystem organ failure. Mortality rates for severe infection range from 30% to 60%, with progression to death in 7–10 days. Survivors recover without permanent sequelae.

Management There is no antiviral therapy available for the treatment of yellow fever infection. Management of infection is supportive care, including rest, fluids, analgesics, and antipyretics. Aspirin and nonsteroidal anti-inflammatory medications should be avoided as they increase the risk of bleeding. Infected individuals should avoid mosquito exposures for 5 days after disease onset so as to not contribute to persistence of virus transmission.

Prevention Yellow fever prevention includes both vector control and vaccination. Preventing mosquito bites will prevent acquisition of yellow fever virus. Measures including the use of insect repellant and long-sleeved shirts and pants and control of mosquitoes both indoors (using screen windows and doors, air conditioning, bed nets) and outdoors (eliminate standing water) are effective in reducing mosquito bites. Vaccination of individuals traveling to areas in Africa or South America that are at risk for yellow fever virus transmission provides long-lasting protection from infection.

Yellow Fever Vaccine

Vaccine Characteristics

YF-Vax, manufactured by Sanofi Pasteur (USA), has been the only live attenuated yellow fever virus vaccine licensed and available for use in the United States. As of the time of this writing, YF-Vax stores have been depleted as Sanofi Pasteur is transitioning to a new production facility [5]. In the meantime, the FDA has approved the use of Stamaril, also manufactured by Sanofi Pasteur (France), in place of YF-Vax in the United States. While, in this country, Stamaril is currently available under an investigational new drug (IND) program, this vaccine has been routinely used in more than 70 countries since 1986 [5].

YF-Vax is indicated for persons of ages 9 months and older at risk of acquiring yellow fever infection. This vaccine is made using the 17D-204 yellow fever virus strain. Other vaccine ingredients include sorbitol, gelatin, egg proteins, chicken proteins, and sodium chloride.

Stamaril is indicated for persons of ages 6 months and older at risk for acquiring yellow fever infection. This vaccine is also made using the 17D-204 yellow fever

virus strain. Other vaccine ingredients include egg proteins, chicken proteins, sorbitol, L-histidine hydrochloride, L-alanine, sodium chloride, potassium chloride, disodium phosphate dihydrate, potassium dihydrogen phosphate, calcium chloride, and magnesium sulfate.

Vaccine Storage, Preparation, and Administration

YF-Vax is supplied as a lyophilized vaccine with a separate sterile diluent. Store vaccine refrigerated (2–8 °C). Do not freeze. Administer 0.5 mL dose subcutaneously. All leftover live vaccine product and delivery equipment must be disposed of following biohazard waste guidelines.

Stamaril is supplied as a lyophilized vaccine with a separate pre-filled syringe sterile diluent. Store vaccine refrigerated (2–8 °C). Do not freeze. Administer 0.5 mL dose subcutaneously. All leftover live vaccine product and delivery equipment must be disposed of following biohazard waste guidelines.

Vaccine Recommendations

Yellow fever vaccine is not part of the routine childhood immunization schedule in the United States. The most recent ACIP guidance states that yellow fever vaccine is only recommended for individuals 9 months of age and older who are traveling to or living in areas with risk of transmission of the yellow fever virus and laboratory workers at risk for occupational exposure to the virus. One's risk for being infected with yellow fever virus is determined by immunization status and travel destination, duration, season, and activities. When indicated, vaccine should be administered at least 10 days prior to travel departure. The CDC Travelers' Health Website (https://wwwnc.cdc.gov/travel/) provides vaccine requirements and recommendations based on travel destination. Some countries even require vaccination if transit includes more than 12 hours in an airport located in a country with risk of yellow fever virus transmission.

The International Health Regulations allow countries to require proof of receipt of a WHO-approved yellow fever vaccine prior to entry of a traveler to minimize importation and spread of yellow fever virus [6]. Yellow fever vaccine can only be given at designated vaccination centers (wwwnc.cdc.gov/travel/yellow-fever-vaccination-clinics/search). After vaccination, the traveler will be given an "International Certificate of Vaccination or Prophylaxis" (also known as the yellow card). If yellow fever vaccine is required for entry into the destination country, the traveler needs to have this card available as proof of vaccination. Travelers to a country with a yellow fever vaccine requirement who do not have their yellow card may be required to be vaccinated on site, quarantined for up to 6 days, or refused entry.

Yellow fever vaccine can be administered with inactivated vaccines. In general, the yellow fever vaccine can either be given at the same time as other live viral vaccines or separated by 30 days. Data suggest, however, that yellow fever vaccine and measles-mumps-rubella vaccine should be given at least 30 days apart (and not co-administered) so as to not interfere with the immune response to these antigens. A single primary dose of vaccine provides lifelong protection against yellow fever infection. As such, the ACIP no longer recommends vaccine boosters for most travelers. Those who may benefit from a booster vaccine include women who were initially immunized during pregnancy, individuals who have received a hematopoietic stem cell transplant after receiving yellow fever vaccine, and people who were infected with HIV when they were previously immunized. Also, people who are believed to be at higher risk for yellow fever infection, based on travel destination and duration, or because of occupational exposure to the virus may be eligible for booster vaccinations [6].

Contraindications to Yellow Fever Vaccine

Contraindications and precautions to the yellow fever are listed in Table 34.1. Medical exemptions to yellow fever vaccination require a waiver letter. The healthcare provider will also need to fill out the medical contraindications to vaccination

Table 34.1 Contraindications and precautions to administering yellow fever vaccine

Contraindications to yellow fever vaccine	
Severe reaction to prior dose of yellow fever vaccine	
Allergy to any vaccine ingredient	Eggs, egg products, chicken proteins, gelatin
Infants <6 months	Increased risk of encephalitis
Severe immunosuppression	Symptomatic HIV/AIDS, CD4 + <200/mm^3, persons receiving immunosuppressive therapy, primary immunodeficiency, malignant neoplasm, transplant recipients; family members of immunosuppressed individuals can be vaccinated
Thymic disorders (myasthenia gravis, DiGeorge syndrome, thymoma)	Increased risk for developing yellow fever vaccine-associated viscerotropic disease
Precautions to yellow fever vaccine	
Not recommended for infants 6–8 months or women breastfeeding infants <9 months of age except during epidemic	Increased risk of encephalitis in young infants
Pregnancy, unless during an outbreak	Theoretical risk because of live vaccine
Adults 60 years of age and older	Higher risk for severe adverse events
Persons with acute febrile illness	Vaccination should be postponed until illness resolves

section of the yellow card. The traveler should contact the embassy of the country of destination prior to departure.

Adverse Events

Common adverse events to yellow fever vaccination include headache, myalgia, low-grade fevers, and redness and pain at the site of the injection. Severe adverse events, more common with primary vaccination than with booster doses, include an anaphylactic reaction, yellow fever vaccine-associated neurologic disease, and yellow fever vaccine-associated viscerotropic disease.

Anaphylactic reactions to yellow fever vaccination occur in approximately 1 in 55,000 vaccinated individuals, most commonly in those with allergies to eggs or gelatin.

Yellow fever vaccine-associated neurologic disease (YEL-AND), previously termed post-vaccinal encephalitis, is either caused by direct vaccine virus invasion of the central nervous system or an autoimmune reaction to vaccination. Infants younger than 9 months old, adults older than 60 years old, and immunosuppressed individuals are at an increased risk of YEL-AND. The Vaccine Adverse Event Reporting System (VAERS) reported that YEL-AND occurs at a frequency of 4–5 cases per million vaccine doses, with a case fatality rate of <5%. Among infants younger than 4 months of age, the frequency of YEL-AND increases to 50–400 cases per million vaccine doses.

Yellow fever vaccine-associated viscerotropic disease (YEL-AVD), previously termed febrile multi-organ failure syndrome, is caused by replication and dissemination of vaccine virus resulting in symptoms consistent with severe yellow fever disease, including multisystem organ failure, liver disease, and hemorrhage leading to death. Adults older than 60 years are at an increased risk of YEL-AVD. VAERS reported that YEL-AVD occurs at a frequency of 3–4 cases per million doses, with a case fatality rate of 60%.

Impact of Vaccine on Disease Burden

There are three basic vaccination strategies utilized by the WHO: routine immunization for all persons older than 9 months of age living in yellow fever-endemic regions, mass vaccination campaigns in at-risk countries to maintain vaccination rates of 80% for outbreak prevention, and vaccination of all travelers to yellow fever-endemic regions. Mass immunization programs, beginning in the 1930s, led to a dramatic reduction in disease burden in both Africa and South America. In 1941, yellow fever vaccination was made mandatory in all French-speaking African regions, following which there was essentially elimination of disease in these regions. On the other hand, the countries without vaccine campaigns continued to

experience large epidemics during this same time. Similarly, mass immunization campaigns in Brazil, starting in 1937, along with mosquito vector control led to expected elimination of disease in the region. Since the 1980s, there has been a resurgence of disease, particularly with large outbreaks in African countries and Brazil. Declining population immunity, deforestation, urbanization, and global travel have all contributed to this rise in cases.

The early 2000s saw a significant increase in yellow fever activity in West Africa, with outbreaks in Cote d'Ivoire, Senegal, Guinea, and Burkina Faso. Outbreaks in different locations requiring mass vaccinations put a significant stress on the public health systems and the global vaccine supply. In 2006, the Yellow Fever Initiative, a partnership between the WHO, UNICEF, and GAVI Alliance, was established to reduce yellow fever outbreaks through securing global vaccine supply and increasing population immunity through vaccination in the 12 countries with the highest risk of virus transmission. More than 105 million people have been immunized through this program, with no outbreaks of yellow fever reported in West Africa after 2015.

Outbreaks of yellow fever continue to occur in the tropical regions. In December 2015, three cases of yellow fever were diagnosed in the Luanda province of Angola. This identified the start of the largest, most widespread yellow fever outbreak in Africa in over 20 years. The virus was also exported to other countries through occupational and recreational travel. By April 2016, the Democratic Republic of the Congo declared a yellow fever outbreak, with almost all of the cases and deaths occurring in a single province that bordered Angola, with high population traffic between the two countries. Mass immunization programs started in June 2016, with over 19 million individuals vaccinated. This large outbreak, however, suffered from supply and operational obstacles as global vaccine supplies were rapidly depleted, requiring a transition to fractional vaccine dosing to stretch out the remaining stocks. The WHO's Strategic Advisory Group of Experts on Immunization determined that a fifth of the standard dose (fractional dosing) provides full protection against disease for at least 12 months and can be used, if needed, to control outbreaks effectively.

Between 2016 and 2018, countries in South America reported cases of yellow fever in their regions, with the most number of cases in Brazil. In 2016, the reemergence of yellow fever in Brazil showed expansion of disease to the southeastern region of the country, an area previously declared risk-free. Over the next few years, this outbreak evolved to be the largest observed in the country in decades. During the 2017–2018 season, the fractional dose of yellow fever vaccine was used in the 77 municipalities with the greatest risk of virus transmission. This mass immunization campaign vaccinated over 20 million people in the states of Sao Paulo, Rio de Janeiro, and Bahia.

Between 1970 and 2015, there were ten cases of yellow fever reported in unvaccinated US and European travelers to West Africa and South America. Eight of these infected individuals died from infection. Each year, millions of travelers from endemic regions arrive in non-endemic regions potentially bringing the virus into these susceptible populations. In 2016, nearly 2.8 million people entered the United

States from yellow fever-endemic countries without any requirement to show proof of yellow fever vaccination. *Aedes aegypti* mosquitoes are now prevalent in many cities across the Southern United States, particularly in areas of high poverty rates, poor urban housing, and worsening problems with mosquito infestation and standing water. While there are only a few US cities considered to be ecologically right to support transmission of yellow fever virus, over 9.5 million people reside in these areas.

In 2017, the Eliminate Yellow Fever Epidemics (EYE) strategy, an international collaborative strategy to support 40 at-risk countries, was launched to prevent, detect, and respond to suspected yellow fever cases and outbreaks. By 2026, this program aims to immunize over one billion people to protect at-risk populations, prevent international spread of yellow fever, and rapidly contain outbreaks. Still endemic in the tropical regions of Africa and South America, there are approximately 900 million people living in regions at risk for devastating yellow fever epidemics. Each year, there are 200,000 and 60,000 severe cases and deaths, respectively, associated with yellow fever. The WHO considers yellow fever to be a re-emerging disease of high importance. The evolving global situation underscores the importance of effective combination measures, including sustained mosquito control, vaccination, and surveillance. The expansion of vaccine manufacturing and strengthening of outbreak response campaigns are also paramount to re-controlling disease.

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Chapter 35
Combination Vaccines

Joseph Domachowske

Introduction

Combination vaccines are products containing multiple immunogens specifically designed to induce protective immune responses against different pathogens or multiple subtypes of the same pathogen. For example, the infant hexavalent vaccine that is used to immunize against diphtheria, tetanus, pertussis, polio, hepatitis B, and *Haemophilus influenzae* type b in many parts of the world is a blend of immunogens in a single syringe, administered as one injection during an office visit. This strategy avoids the unpleasant need to use separate injections to accomplish the same goal. Combination vaccines available in the United States that target more than one pathogen are listed in Table 35.1. Monovalent formulations, once available for nearly every vaccine-preventable illness, are no longer marketed in the United States as individual vaccines for measles, pertussis, diphtheria, mumps, or rubella. Diphtheria protection must be delivered as a combination vaccine with tetanus and can be delivered using even broader formulations with pertussis, polio, and either or both hepatitis B and *H. influenzae* type b. Similarly, monovalent pertussis vaccine is no longer available. Pertussis protection must be provided using vaccines that also include immunogens directed against diphtheria and tetanus. Measles, mumps, and rubella immunogens are currently only available as the trivalent MMR vaccine.

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Table 35.1 Examples of combination vaccines that target multiple pathogens

Vaccine [brand name(s)]	Diseases targeted for prevention	Notes
DT	Diphtheria Tetanus	For children less than 7 years of age who cannot receive pertussis vaccine
Td [Tenivac]	Tetanus Diphtheria	For individuals 7 years and older who are not eligible to receive pertussis vaccine
DTaP [Daptacel, Infanrix]	Diphtheria Tetanus Pertussis	For children 6 weeks to 7 years of age
TdaP [Adacel, Boostrix]	Diphtheria Tetanus Pertussis	For individuals 7 years and older
DTaP, hepatitis B, IPV [Pediarix]	Diphtheria Tetanus Pertussis Hepatitis B Polio	For children 6 weeks to 7 years of age
DTaP, IPV [Quadracel, Kinrix]	Diphtheria Tetanus Pertussis Polio	For children 4–6 years of age
DTaP, IPV, Hib [Pentacel]	Diphtheria Tetanus Pertussis *Haemophilus influenzae* type b	For children 6 weeks to 7 years of age
DTaP, IPV, hepatitis B, Hib [Vaxelis]	Diphtheria Tetanus Pertussis Polio Hepatitis B *Haemophilus influenzae* type b	For children 6 weeks to 5 years of age
Hepatitis A and B [Twinrix]	Hepatitis A Hepatitis B	For individuals 18 years and older
MMR [MMRII]	Measles Mumps Rubella	For individuals 12 months of age and older. First dose may be given as early as 6 months of age if risk for measles exposure is high
MMRV [ProQuad]	Measles Mumps Rubella Varicella	For children 12 months through 12 years. Use with caution in those less than 23 months of age

Combination Vaccines in Practice

During the first 2 years of life, children are recommended to receive vaccines to prevent 14 different infectious diseases. Optimal protection against each of these infections requires a primary series of two or more doses separated by appropriate

intervals. Booster doses are administered months to years later for most but not all childhood vaccines. The pediatric immunization schedule (Fig. 35.1) shows the ages when each dose of each vaccine is recommended. The recommended vaccine schedule is particularly busy for office visits that are scheduled at ages 6 months and 4–6 years. The development of different combination vaccines facilitates the timely delivery of all recommended immunogens that would otherwise require the administration of up to six injections during the same office visit.

The 6-Month Office Visit

During a routine healthy infant office visit, a 6-month-old who has previously received all recommended immunizations to date is due to receive vaccines for protection against diphtheria (D), tetanus (T), pertussis (aP), polio (IPV), hepatitis b (HepB), pneumococcus (PCV), and influenza (QIV). In addition, depending on the formulations of *H. influenzae* type b (HIB) and rotavirus vaccine (RV) used at 2 and 4 months of age, doses of each may also be required at this 6-month visit. Rotavirus vaccine is given orally. All of the other vaccines listed here are given by intramuscular

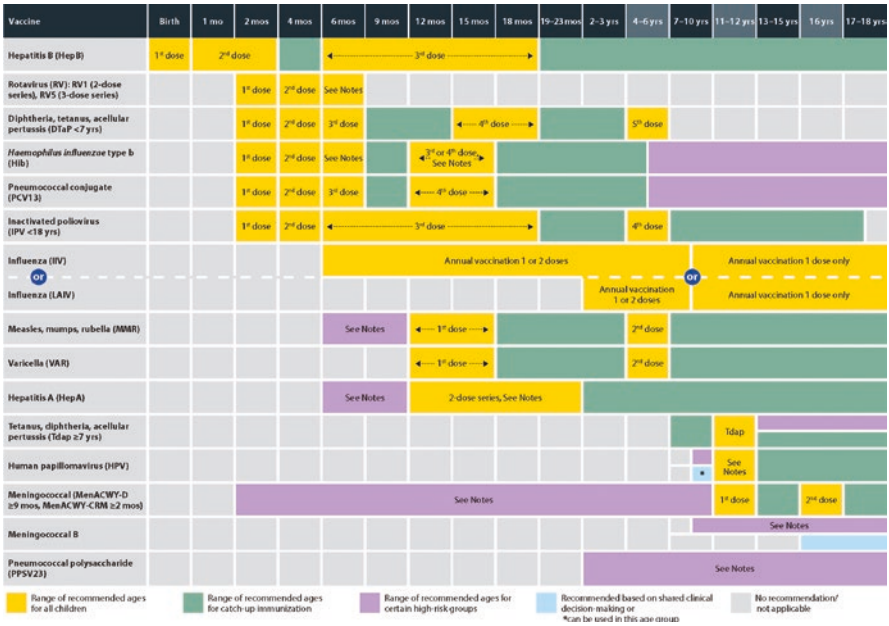

Fig. 35.1 2020 recommended immunization schedules for children and adolescents.(Source: Centers for Disease Control and Prevention. This material is available on the agency website at no charge: https://www.cdc.gov/vaccines/schedules/index.html. Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the US Government, Department of Health and Human Services, or Centers for Disease Control and Prevention)

injection. Available combination vaccine products present four different options to keep this infant fully up to date for all recommended vaccines at this visit. For illustration purposes, assume that this infant requires 6-month doses of both *H. influenzae* type b and rotavirus vaccines.

Option 1: DTaP, IPV, HepB, HIB, PCV, QIV, RV
Option 2: DTaP-IPV-HIB, HepB, PCV, QIV, RV
Option 3: DTaP-IPV-HepB, HIB, PCV, QIV, RV
Option 4: DTaP-IPV-HIB-HepB, PCV, QIV, RV

All four options include the administration of oral rotavirus vaccine. In addition, Option 1 requires six separate intramuscular injections. Options 2 and 3 both require four separate injections, and Option 4 requires three separate injections.

Diphtheria and pertussis are only available in combination vaccines, all of which include tetanus. Note that Option 1 makes use of DTaP vaccine, while each of the others uses a combination that includes a DTaP "backbone." Note also that Option 1 appears to otherwise make use of only monovalent vaccine products in the forms of IPV, HepB, HIB, PCV, QIV, and RV. On further inspection, while each of these vaccines is directed to prevent disease caused by a single pathogen, only HepB and HIB are truly monovalent. IPV is a trivalent vaccine that includes immunogens targeting poliovirus types 1, 2, and 3. PCV is a multivalent vaccine containing conjugated polysaccharide immunogens that target 13 serotypes of *Streptococcus pneumoniae*. QIV is a quadrivalent product directed against four strains of influenza, and the RV vaccine that requires a dose at age 6 months is the pentavalent formulation. These and other available combination vaccines that target multiple types or strains of the same pathogen are summarized in Table 35.2.

The 4- to 6-Year-Old Office Visit

During a routine healthy office visit, a 4- to 6-year-old who has previously received all recommended immunizations to date is due to receive vaccines to protect against diphtheria, tetanus, pertussis, polio, measles, mumps, rubella, varicella, and influenza. Beginning at the age of 2 years, influenza vaccination can be achieved with either the quadrivalent inactivated influenza vaccine (QIV, intramuscular injection) or the live attenuated quadrivalent influenza (LAIV, intranasal mist formulation). Available combination vaccine products present different options to keep this child fully up to date for all recommended vaccines at this visit.

Option 1: DTaP, IPV, MMR, varicella, quadrivalent influenza vaccine
Option 2: DTaP-IPV, MMR, varicella, quadrivalent influenza vaccine
Option 3: DTaP, IPV, MMRV, quadrivalent influenza vaccine
Option 4: DTaP-IPV, MMRV, quadrivalent influenza vaccine

All four options include quadrivalent influenza vaccine, which can be administered either as injection (QIV) or intranasal mist (LAIV). Depending on which influenza vaccine formulation is used, Option 1 requires the administration of either

Table 35.2 Examples of combination vaccines that target multiple types or strains of the same pathogen

Prevention target	Vaccine formulations	Brand name(s)	Pathogen types or strains included in the vaccine
Human papillomavirus	Bivalent	Cervarix	Types 6 and 11
	Quadrivalent	Gardasil	Types 6, 11, 16, 18
	Nine valent	Gardasil 9	Types 6, 11, 16, 18, 31, 33, 45, 52, 58
Influenza virus	Trivalent and quadrivalent	Many	Quadrivalent vaccines include 2 strains of influenza A and 2 strains of influenza B. Trivalent vaccines include 2 strains of influenza A and 1 strain of influenza B[a]
Neisseria meningitidis	Monovalent[b]	Bexsero Trumenba	Serotype B
	Quadrivalent	Menactra Menveo Menomune	Serotypes A, C, Y, W135
Streptococcus pneumoniae	7-valent	Prevnar	4, 6B, 9V, 14, 18C, 19F, 23F
	13-valent	Prevnar 13	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F
	23-valent	Pneumovax	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F
Polio virus	Trivalent	iPOL	Poliovirus types 1, 2, 3
Rotavirus	Monovalent	Rotarix	G1P8
	Pentavalent	RotaTeq	G1, G2, G3, G4, P1A

[a]Influenza strain modifications are made each year based on recommendations from the World Health Organization, the US Centers for Disease Control and Prevention, and other global stakeholders

[b]Monovalent meningococcal serotype A and serotype C vaccines are available outside the United States

four or five separate injections. Options 2 and 3 accomplish the same goal using three or four injections, and Option 4 requires two or three injections.

Advantages of Combination Vaccines

A major public health benefit of combination vaccines is the clear association between their use and improvements in both immunization coverage rates and in the timeliness of receiving recommended vaccines. Incremental improvements in both measures are described for each additional immunogen included in the combination vaccine being used. Combination vaccine products have also greatly reduced the total number of injections needed to fully immunize infants and young children against the same number of infectious diseases. The direct beneficiary is, of course, the child. Fewer numbers of injections also benefit the parent(s) by reducing the anxiety associated with observing their child receive multiple shots. Time-motion

studies show direct time savings associated with the preparation and administration of combination vaccines resulting in more efficient office workflow. Combination products also reduce the complexity of the office vaccine inventory.

Disadvantages of Combination Vaccines

While the advantages of incorporating the use of combination vaccines into routine office practice far outweigh the real and perceived disadvantages, there are some downsides.

Providers, nurses, and office staff involved in tracking vaccine inventory and entering data into state immunization registries all need to be knowledgeable about the specific immunogens included in each combination vaccine. Familiarity with the formulations used in the practice isn't sufficient given the frequency with which families and patients relocate and/or change providers. Patients that begin a vaccine series with one combination regimen can almost always complete their series with another, but it can be challenging to discern the number and types of immunogens already received and the specific antigenic components needed to keep their vaccination status up to date. Practice-wide, it's best to select a single combination regimen for all patients. With experience, familiarity becomes expertise. Decisions to switch from one combination to another should be considered carefully. On occasion, vaccine shortages force practice-wide changes in the combination regimen used. Re-training staff is key to facilitating the transition and to avoid vaccination errors.

Official ACIP guidance states that the use of combination vaccines that contain the necessary immunogens is recommended over the administration of two or more single-component vaccines in nearly all circumstances. The single exception is noted below. Occasionally, following these recommendations results in also administering vaccine immunogens that the patient does not otherwise need. These "extra" doses of vaccine immunogen are safe and well tolerated and do not represent a contraindication or precaution to receiving the combination vaccine.

The only exception to using a combination vaccine in preference to individual component vaccines relates to the recommendations for using MMRV. Immunization against measles, mumps, rubella, and varicella is recommended at 12 months and at 4–6 years of age. Early clinical vaccine trials showed antigenic competition between vaccine components when MMR was first tested in combination with varicella. An early formulation of investigational MMRV vaccine showed blunted immunogenicity of the varicella component when compared to administering MMR and varicella vaccines separately. Increasing the amount of varicella immunogen in MMRV solved the problem with immunogenicity, but the new formulation was more likely to cause fever when given as the first dose between 12 and 23 months of age. The increased frequency of fever was also associated with an increased frequency of febrile seizures from 2.2 per 10,000 vaccinated with MMR and varicella vaccine separately to 5.8 per 10,000 immunized with the MMRV combination vaccine. The

adverse reaction of 5.8 per 10,000 vaccinated with MMRV is quite uncommon, but because of the difference in risk between the two groups, the Centers for Disease Control and Prevention recommends that children under 4 years old get their first doses of MMR and varicella vaccines separately. There is not an increased risk of fever or seizure in second-dose recipients or in those who receive the vaccine at age 4 or older.

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Part III
Maintaining a Culture of Vaccine Confidence

Chapter 36
Vaccine-Preventable Disease Outbreaks

Manika Suryadevara

Definitions

Eradication	*global* reduction of disease incidence to zero as a result of deliberate efforts, with no need for further preventive measures [1]
Elimination	*regional* reduction of disease incidence to zero as a result of deliberate efforts, still requiring continued interventions to maintain status [1]
Vaccine-preventable outbreaks	occurrence of disease cases greater than what would normally be expected in a defined community, geographic area, or season [2]
Primary vaccine failure	failure to mount an immune response after vaccination
Secondary vaccine failure	waning immunity over time after vaccination

Introduction

Vaccine programs have successfully reduced global disease burden. In addition to preventing up to three million deaths each year, the use of vaccinations has contributed to the global eradication of smallpox and polioviruses 2 and 3 and the regional elimination of specific infectious diseases around the world [3]. In the United States, alone, morbidity associated with nine pathogen-specific diseases has declined by nearly 100% since the initiation of immunization programs [4] (Table 36.1). Despite the protection offered from vaccines to the immunized individuals and the

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Table 36.1 Diseases for which there have been a dramatic decline in morbidity through use of vaccine [4]

Smallpox
Diphtheria
Pertussis
Tetanus
Poliomyelitis
Measles
Mumps
Congenital rubella syndrome
Haemophilus influenzae type b

Table 36.2 Factors contributing to vaccine-preventable disease outbreaks

Factors	Pathogen-specific example
Importation of disease from foreign countries	Measles
Incomplete protection despite vaccination	Mumps
Waning immunity to vaccination	Pertussis
Vaccine hesitancy	Measles

community, vaccine-preventable disease outbreaks continue to occur. The reasons for this are multifactorial and include the ease of global travel, vaccine-related factors, and pockets of under-immunization due to lack of access to medical care and vaccine hesitancy [5] (Table 36.2).

Importation of vaccine-preventable disease from another country, with regional spread among unvaccinated individuals, has been the most frequently described factor contributing to measles outbreaks [6–8]. In fact, the majority of measles cases in the United States are either directly or indirectly related to international travel of an un- or under-immunized individual, particularly to areas in Europe, Africa, and Asia where measles remains endemic or outbreaks are occurring [6, 9]. If these travelers acquire measles abroad and return home to a highly vaccinated community, the risk of transmission is typically low. However, if they return home to a community with low measles vaccine coverage for any reason, transmission of infection can be substantial leading to outbreaks that escalate to epidemics [9–11].

On the other hand, outbreaks of domestically acquired vaccine-preventable diseases, such as mumps, have been reported in populations with high immunization rates [12–15]. Currently, in the United States, individuals are immunized against mumps infection with a two-dose series of the measles-mumps-rubella (MMR) vaccine administered during childhood. The median effectiveness of two doses of MMR vaccine for the prevention of mumps is estimated at 88%, with reports of increasing risk of acquiring mumps infection over time since vaccination. Taken together, incomplete protection despite vaccination and substantial waning immunity over time explain why mumps outbreaks continue to occur in highly immunized populations [15]. Similarly, pertussis outbreaks, which are more likely to occur in the un- or under-immunized populations, have been described in

communities with high immunization coverage. Pertussis vaccines are highly effective, but immunity wanes over time. Without regular boosting doses of vaccine, such outbreaks will continue to be observed [16–18].

Measles

Measles is an acute febrile illness, with symptoms of cough, coryza, and conjunctivitis followed by a diffuse, maculopapular rash which starts on the face and spreads to the trunk and extremities. Koplik spots, lesions on the buccal mucosa, may be present during the prodromal period and are considered pathognomonic for measles infection. Individuals who survive measles infection retain lifelong immunity; however, up to 30% of those infected will develop at least one complication during the infection. Acute complications of measles infection include otitis media, diarrhea, pneumonia, seizures, and encephalitis [19]. Pneumonia and encephalitis are the most common causes of measles-related deaths in children and adults, respectively [19]. Until the late 1950s, nearly all children acquired measles infection before their 15th birthday. During the pre-vaccine era in the United States, measles affected between three and four million people, resulting in 48,000 hospitalizations, 1000 encephalitis cases, and 400–500 deaths [20] (Fig. 36.1).

During the 1950s, John F. Enders, PhD, a virologist and microbiologist who was awarded the Nobel Prize in Physiology or Medicine for the cultivation of poliomyelitis virus in tissue culture, and Thomas C. Peebles, a pediatrician and virologist working with Enders, sought to isolate the measles virus by obtaining blood and throat samples from infected boarding school students during a measles outbreak near Boston, Massachusetts. Using a blood sample from 13-year-old David

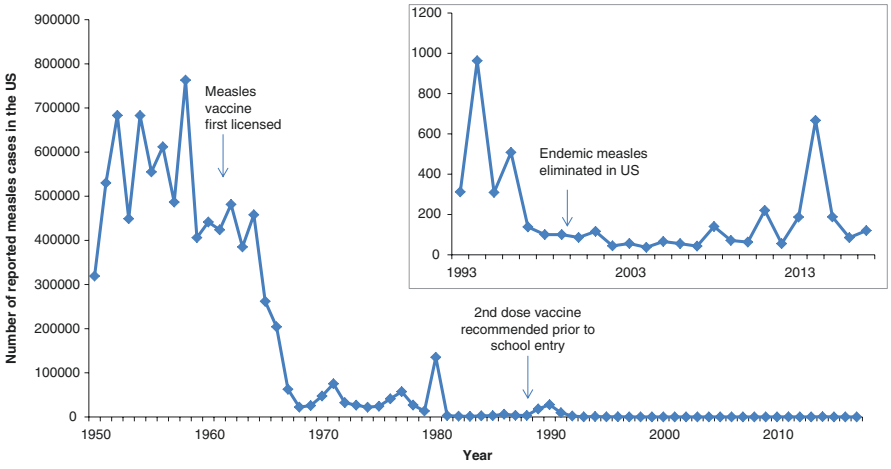

Fig. 36.1 Disease incidence of measles between 1950 and 2018. (Data adapted from CDC)

Edmonston, Enders and Peebles were the first to successfully isolate the measles virus in human and monkey kidney cell culture, giving rise to the Edmonston strain of measles virus. The isolate would ultimately be used to develop the attenuated measles vaccine strain that is still used in the United States today [21].

In 1963, the first two measles vaccines were licensed for use in the United States: (1) a live attenuated vaccine (using the Edmonston B strain attenuated in chick embryo cell culture) and (2) a formalin-inactivated whole virus vaccine [22]. The live attenuated vaccine resulted in a robust immune response in almost all susceptible recipients but was so reactogenic that co-administration of gamma globulin was required to reduce the likelihood of high fevers and rash. Alternatively, the formalin-inactivated vaccine was well tolerated following administration, but vaccinated individuals who contracted measles developed enhanced measles disease. The inactivated vaccine was discontinued in 1967 after being deemed unsafe and ineffective [22]. With the goal of producing a better-tolerated live attenuated measles vaccine, Maurice Hilleman, PhD, a leading virologist and vaccinologist, further attenuated the Edmonston B strain in chick embryo cell cultures and developed a less reactogenic Moraten ("more attenuated Enders"), also known as Enders-Edmonston strain vaccine, which was licensed for use in the United States in 1968 and is still used in measles-containing vaccines today [23].

The 1960s also saw advances in the development of the rubella and mumps vaccines. In 1963, Hilleman obtained a throat swab from his 5-year-old daughter, Jeryl Lynn, when she was infected with mumps. He brought the sample back to the lab, isolated the mumps virus, and passed the virus through chick embryo cell cultures to develop the live attenuated Jeryl Lynn strain mumps vaccine which was licensed for use in 1967 and is still used in mumps-containing vaccine.

In 1941, an Australian ophthalmologist, Norman Gregg, noted an increase in infants born with cataracts. After discussions with the young mothers and consultations with other ophthalmologists in the region, he linked these neonatal cataract cases to congenital rubella syndrome [24]. Between 1962 and 1965, a global epidemic led to 12.5 million cases of rubella infection that was associated with 13,000 fetal or neonatal deaths and 20,000 infants born with congenital rubella syndrome [25]. Using a strain of rubella virus obtained from the Division of Biologics Standards, Hilleman developed a live attenuated rubella vaccine that was licensed for use in the United States in 1969.

The combination measles-mumps-rubella (MMR) vaccine was licensed in 1971. This vaccine incorporated the Moraten measles strain, the Jeryl Lynn mumps strain, and Hilleman's attenuated rubella strain. In 1979, Hilleman's rubella vaccine strain was replaced by the Wistar RA 27/3 attenuated rubella virus strain developed by the leading vaccinologist Stanley A Plotkin, MD.

As one of the most highly contagious infectious diseases, >90% of susceptible individuals exposed to measles will become infected; therefore, 95% of the population needs to be immune in order to stop transmission of infection beyond an index case [26]. Nationwide efforts to eliminate measles in the United States resulted in a substantial decline in the number of reported measles infections in the years following vaccine licensure. However, in 1969, as the nation's focus shifted to the

prevention of congenital rubella syndrome, federal funding to support measles vaccination ended [27]. By 1970, measles vaccine coverage rates for children between 1 and 4 years of age had yet to exceed 63%, and measles cases were, once again, on the rise (Callout Box 36.1).

Callout Box 36.1
Sub-optimal vaccine use low vaccination rates measles outbreaks.

By the 1970s, less than half of the states in the United States had developed public health laws that included school immunization requirements. The majority of annual measles outbreaks were occurring in school settings. On April 6, 1977, the US Department of Health, Education, and Welfare announced a nationwide Childhood Immunization Initiative to increase and maintain childhood immunization rates for all vaccines at or above 90%. Through this program, over 28 million immunization records were reviewed to identify and vaccinate immunization-delayed children. By the fall of 1980, measles vaccine coverage rates among children entering school reached 96% [28]. The success of this program led the CDC to initiate a measles elimination program, announcing a three-pronged approach: (1) maintain high rates of a single-dose measles vaccination, (2) enhance disease surveillance, and (3) initiate prompt and aggressive outbreak control [29].

During the mid- to late 1980s, annual measles outbreaks continued to occur. The majority of the outbreaks occurred in school-age children; others were reported from university campuses. Nearly 65% of those diagnosed with measles during this time period had appropriately received a single dose of measles vaccine. Analysis of the findings concluded that 4% of vaccine recipients failed to mount a protective immune response. With the goal to eliminate measles from communities, schools, and colleges, the ACIP updated their recommendation from one dose of measles vaccine given at 12 months of age to a two-dose series of vaccine given at 12 months and 4–5 years of age so that all children received a second dose prior to school entry. All children 18 years and younger who had received one dose were recommended to receive a second dose at least 4 weeks after the first [22, 29–31]. Gradually, many states and universities introduced policies requiring that all attendees be immunized with two doses of measles vaccine (Callout Box 36.2)

Callout Box 36.2
Primary vaccine failure among vaccinated school-aged children measles outbreaks.

Between 1989 and 1991, there was a resurgence in measles cases, with over 55,000 cases and more than 120 deaths. Ninety percent of the deaths occurred in unvaccinated individuals [19, 29]. In 1989, the overall incidence of measles was

800% greater than the median incidence over the prior 10 years [32]. Unlike the outbreaks of 1985–1988, which were more commonly seen among vaccinated school-age children, the outbreaks of 1989–1991 involved unimmunized pre-school-age children, where only 19% of individuals were appropriately immunized [32]. While there was an increase in measles cases across all age groups, the highest increases were seen in children younger than 5 years old, particularly unimmunized black and Hispanic children living in inner city regions. Surveys of these areas found that only half of the children in these communities had received the measles vaccine by 2 years of age [19]. These findings led to intense efforts to increase vaccination rates among pre-school-age children by emphasizing that the first dose of vaccine should always be given at or as close as possible to 12 months of age, with a second dose prior to kindergarten entry [29, 31] (Callout Box 36.3).

Callout Box 36.3
Sub-optimal vaccine use low vaccination rates measles outbreaks.

The year 1993 marked the end of the measles resurgence with interruption of endemic transmission within the United States. In this same year, the Omnibus Budget Reconciliation Act (OBRA) created the Vaccines for Children (VFC) program, a national program to provide vaccine at no cost to eligible children through enrolled public and private providers. This federal entitlement program was launched to ensure that un- and under-insured children receive vaccines at no cost in their medical home [33]. While measles outbreaks declined in all age groups, the most notable decline seen occurred among pre-school-age children. By 1996, vaccination rates in this previously unimmunized cohort had exceeded 90% demonstrating the impact of and potential for the newly established VFC program.

By the late 1990s, all 50 states required documentation of measles immunity prior to school entry. However, resistance to mandatory school immunization requirements was already building. The strength of enforcement of these school vaccine laws varied by state. All states but West Virginia and Mississippi allowed for religious exemption to otherwise required vaccinations, and nearly half of US states permitted personal belief/philosophical exemptions. The effect of vaccine exemptions can be seen in the epidemiology of measles outbreaks. Exempted school children are 22–35 times more likely to be infected with measles than their vaccinated peers [11, 34]. Vaccinated children infected with measles are likely to have acquired the infection from an exempted student [11], and the frequency of exemptors within a county is directly associated with the incidence of measles in the area [11].

In 1994, a multi-state measles outbreak began when a 14-year-old student attending Christian Science High School in Missouri acquired measles while skiing in Colorado. She transmitted the infection to unimmunized individuals in both her home Christian Science community in Illinois and at her boarding school in Missouri. The single index case ultimately led to an outbreak of 200 cases [35]. The high levels of measles immunity in areas surrounding the outbreak coupled with a

rapid public health response to identify cases and track exposed contacts prevented further spread. By 2000, the absence of endemic virus transmission in the United States for more than a 12-month period led to the declaration that measles had been eliminated from the United States [36] (Callout Box 36.4).

Callout Box 36.4
WHO definition of measles elimination: the absence of endemic measles transmission in a defined geographical area for over a 12 month period.

Between 2001 and 2008, there were a total of 557 confirmed measles cases in the United States, with an annual incidence of less than one case per million population. The majority of these cases were associated with importation of infection from countries where measles was endemic or where outbreaks were occurring (initially the WHO Western Pacific Region (2001–2004) and then the WHO European Region (2005–2008)), with lack of vaccination being the primary factor for transmission of imported disease domestically [9, 37, 38]. The annual proportion of infected persons who were unvaccinated or had an unknown vaccine status during this period ranged from 73% to 95%. Of those infected, 68% had not been vaccinated because of personal beliefs [37]. Over this time period, nonmedical exemption rates for school attendance were on the rise, with higher rates of nonmedical exemption rates seen in states allowing philosophical belief exemptions [39]. Using an agent-based transmission model, Whittington et al. found that states with easy nonmedical vaccine exemption policies were 190% more likely to have a measles outbreak than states with more rigorous exemption policies [40].

Between January and July 2008, 135 measles cases had been reported to the CDC, the highest number of year-to-date cases since 1996. The cases occurred mainly in people who were unvaccinated or had an unknown vaccine status. This spike in disease was not a result of more imported measles cases, but instead due to increased transmission of imported infection within unvaccinated communities in the United States. In Washington and Illinois, 41 school-age children were diagnosed with measles, all of whose parents opted to not have them immunized for philosophical or religious beliefs [41] (Callout Box 36.5).

Callout Box 36.5
Nonmedical vaccine exemptions among school children contributed to measles outbreaks.

In 2011, more than 30,000 cases of measles were reported in Europe predominantly from France, Italy, Romania, Spain, and Germany [42, 43]. France, alone, reported 15,000 measles infections and 6 deaths that year. The primary factor contributing to the large European outbreaks was the failure to vaccinate susceptible

populations. WHO vaccine coverage data show that five million European children aged 2–12 years had not yet received a measles-containing vaccine [43]. Reasons for this likely included poor medical access in certain regions, reduced perception of disease risk and severity, the ease with which the anti-vaccine movement was able to widely spread vaccine misinformation via the Internet, mistrust of the government and healthcare providers, misdirected religious and/or philosophical ideologies, and vaccine safety concerns related to immune overload, "toxic" vaccine ingredients, or the risk for developing autism [42–44].

Concerns regarding MMR vaccine and autism stemmed from a study published in 1998, by the former British physician, Andrew Wakefield. The publication and the methods used were subsequently discredited and retracted [45, 46]. Multiple media outlets ran stories supporting Wakefield's hyperbole despite the significant problems with his report, further fueling mistrust in the healthcare system [47]. Review of MMR-related articles in UK newspapers and the Internet during this time found that more articles mentioned the alleged link between the MMR vaccine and autism than refuted it, and of all the articles that mentioned Wakefield, only half discussed the limitations of his report [48]. Following Wakefield's publication, a reduction in measles vaccine uptake was seen worldwide, with MMR vaccination rates in the United Kingdom dropping to less than 80% by 2004 [47, 49, 50]. Parents declining the MMR vaccine, including the parents and caregivers of unimmunized children infected with measles during an outbreak in England, continued to cite vaccine safety concerns, particularly related to the development of autism, as the most common reason for non-vaccination [51–53]. Even parents who understood that Wakefield's study was inaccurate still stated that they believed the publication reflects that he must have had serious concerns about the vaccine [52]. Wakefield's actions were determined to be fraudulent and in violation of medical ethics in the United Kingdom. His medical license was revoked, yet despite the evidence from numerous published studies, UK parents who reject MMR vaccine are still less likely than vaccine acceptors to believe that there is no scientific evidence linking MMR vaccine and autism [54–61] (Fig. 36.2). Winston Churchill is quoted having said "A lie gets halfway around the world before the truth has a chance to get its pants on." More than 20 years later, the world continues to see the negative impacts of Wakefield's false claims.

The impact is still seen globally, including in Hennepin County, Minnesota, home of the largest Somali community in the United States. Somali families began to reject the MMR vaccine around the same time they started expressing concerns regarding rates of autism in the children in the community [62]. It was noted that anti-vaccine activists, including Wakefield himself, personally met with families of Somali children with autism in this community [62, 63]. Over the course of a decade, MMR vaccine coverage rates among Somali children in Hennepin County decreased from 91% in 2004 to 54% in 2010 and 36% in 2014 [62, 64]. Community-wide measles outbreaks were reported in 2011 and 2017. During 2017 outbreak, 75 cases of measles were identified, 81% were in the Somali community, 91% were unvaccinated, and 28% of infected individuals were hospitalized [65]. Vaccination rates have improved since 2017, but only marginally.

On January 5, 2015, the California Department of Public Health was notified of seven cases of suspected measles, involving California and Utah residents, all of

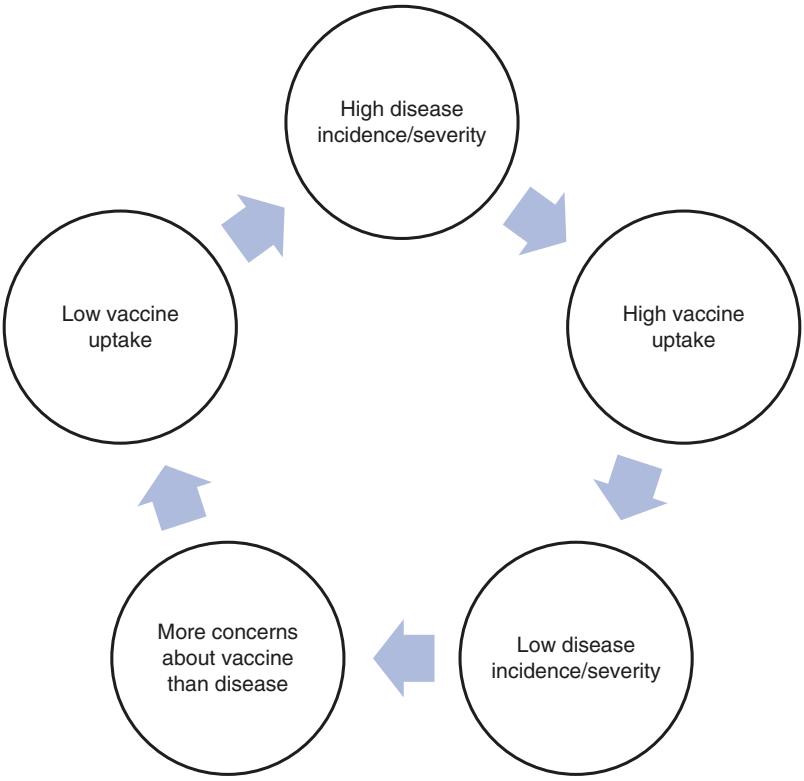

Fig. 36.2 Relationship between disease incidence and public vaccine confidence

whom had recently returned from the Disneyland Resort Theme Parks located in Orange County, California. By the end of the next month, a total of 147 epidemiologically linked cases were reported from 7 states, Mexico, and Canada, with the majority of infected individuals having been previously unvaccinated [66, 67]. Of the vaccine-eligible yet unimmunized individuals infected with measles, 67% intentionally declined the MMR vaccine for personal, religious, or philosophical reasons [66]. Recognizing the contribution of philosophical belief exemptions to the measles outbreak in Disneyland, the California State Legislature, led by Senator Dr. Richard Pan, wrote, sponsored, and passed a bill into law to no longer permit nonmedical exemptions to school vaccination requirements. In the years that followed, New York and Maine passed similar legislation.

Pockets of unimmunized individuals are a set up for large vaccine-preventable disease outbreaks. In 2019, there were 1249 measles cases in the United States from 22 separate outbreaks, the highest number of cases reported in a single year since 1992 and the second highest number of reported outbreaks since the elimination of measles in 2000. Approximately 75% of these cases occurred in the Orthodox Jewish communities of New York City. The outbreak extended into New York State, with ongoing transmission of disease for 364 days, 1 day short of

no longer meeting criteria for elimination status in the United States. Factors contributing to the prolonged duration of such outbreaks include the high population density and close social nature of large, close-knit unvaccinated communities with repeated importations of measles among unvaccinated travelers [68]. The rapid and robust public health response, consisting of administering 60,000 doses of MMR vaccine in the affected communities, widespread awareness campaigns, and development of partnerships between religious leadership, health systems, and advocacy groups, was effective in controlling the outbreak prior to the 1-year time mark [68].

Measles is a highly contagious infection for which we have a safe and effective vaccine. While measles has been eliminated from the United States, transmission of infection is driven by measles vaccine coverage rates [38]. Suboptimal vaccination rates increase the likelihood that an index case of infection will spread throughout the community, resulting in outbreaks.

Pertussis

Pertussis, or whooping cough, manifests as a protracted illness with paroxysmal coughing fits. Young infants are at the highest risk for acquiring complications of pertussis, including apnea, pneumonia, respiratory failure, seizures, and death [69, 70]. In the pre-vaccine era, pertussis was known to be an endemic disease with cyclical epidemics occurring every 3–5 years. In the United States, alone, there were between 115,000 and 270,000 cases associated with 5000 to 10,000 deaths from pertussis each year [71]. Ninety-five percent of these infections occurred in children younger than 5 years of age. In the year 1910, 10% of children with pertussis died from infection [72, 73].

In 1900, Jules Bordet, a Belgian physician, observed an ovoid gram-negative bacterium in the sputum of his 5-month-old daughter during a cough illness, but he was unable to grow this bacterium in standard culture media. By the time his son Paul contracted whooping cough, 6 years later, Bordet and Belgian bacteriologist, Octave Gengou, had created an enriched bacterial culture broth, known today as Bordet-Gengou (BG) media. They incubated Paul's sputum on the newly developed BG media, Bordet and Gengou, and successfully isolated the bacterium. The pathogen was named *Bordetella pertussis*, in honor of Dr. Bordet [74].

Following the initial isolation of *B. pertussis*, scientists around the world went to work on developing a vaccine to protect vulnerable infants from this infection. Using a whole cell killed vaccine preparation, it was quickly noted that inactivated *Bordetella pertussis* vaccine induced a robust antibody response, but the naturally occurring endotoxin in the vaccine was associated with substantial reactogenicity. In the 1920s, Danish scientist, Thorvald Madsen, was among the first to report the potential efficacy of a whole cell pertussis vaccine in the prevention of severe

disease [75]. He was also among the first to report serious adverse events related to pertussis vaccination when he noted two neonatal deaths within 48 hours of receiving whole cell pertussis immunization [74].

During the 1930s, whole cell pertussis vaccines continued to be modified and studied, but efficacy was variable among these vaccines. In 1932, after a virulent strain of *B. pertussis* spread through the pediatric community in Grand Rapids, Michigan, Drs. Pearl Kendrick and Grace Eldering, of the Michigan Department of Health (DOH), began their own pertussis research program [76]. They modified the BG medium to produce faster and more significant growth of the bacteria. Together, they visited infected children in the community, collected consecutive respiratory samples, and used their media to grow the bacteria to identify the most infectious period of illness, thereby changing the guidelines for isolation of infected individuals [76].

At the time, the Michigan DOH was one of the few public health departments working on vaccine development. Despite the limited resources available during the Great Depression, Kendrick and Eldering designed their own inactivated whole cell pertussis vaccine, which was then combined with tetanus and diphtheria toxoids to form the diphtheria-tetanus-whole cell pertussis (DTwP) vaccine used in the national immunization program [76, 77]. In 1948, the DTwP vaccine, with 70–90% effectiveness after four doses, was recommended for universal use among infants [70]. Contrary to the US experience, the UK clinical trials failed to show consistent effectiveness of their whole cell pertussis vaccine counterpart. It took an additional 10 years, and new clinical trials, for pertussis vaccination to become routine in Britain. Universal use of whole cell pertussis vaccines in other countries followed.

Following widespread use of DTwP vaccine in the United States, the incidence of reported pertussis cases declined dramatically from 115,000–270,000 cases per year to a low of 1010 cases in 1976, with national DTwP vaccine coverage rates at the time of 72.7% [78] (Fig. 36.3). Disease incidence in the United States remained low (1200–4000 cases per year) through the 1980s. Similarly, routine use of DTwP

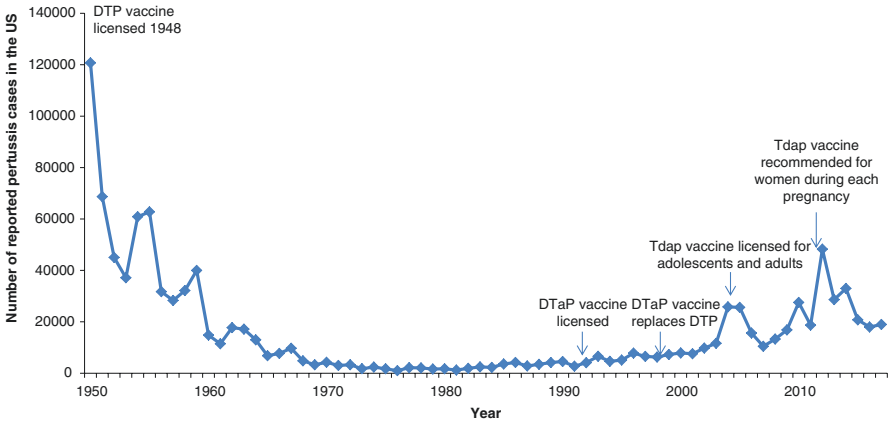

Fig. 36.3 Disease incidence of pertussis between 1950 and 2018. (Data adapted from CDC)

vaccine in England and Wales resulted in a decline in disease notifications and pertussis-associated infant mortality, from 106.1 per million infants (1954–1957) to 13.1 per million infants (1970–1973) [79]. As the incidence of pertussis infection dropped, more attention was drawn to the adverse effects of vaccine. Local reactions, including transient redness, swelling, and pain at the site of injection, were the most common reactions reported [80]. Systemic reactions, including fevers, febrile seizures, hypotonic-hyporesponsive episodes, protracted uncontrollable crying, and whole limb swelling, although transient and rare, were also reported and were frightening to families [81, 82].

By 1974, reports from London describing temporally associated neurologic complications following pertussis vaccination further fueled public concern [83, 84]. In the United Kingdom, public campaigning by groups, such as the Association of Parents of Vaccine Damaged Children, in addition to television programs and newspaper articles highlighting pertussis vaccine safety concerns and questioning the need for pertussis vaccine, contributed to widespread vaccine hesitancy across the country [79, 85]. This negative vaccine publicity was followed by a rapid decline in pertussis vaccination rates among UK children from 79% in 1973 to 31% just 5 years later. As vaccine uptake was falling, cases of reported pertussis infections were on the rise. The UK pertussis epidemic of 1977–1979, when vaccine coverage was at its lowest, saw 102,500 cases, 5000 hospitalizations, and 38 deaths [79] (Fig. 36.2).

A similar course was taking place in Japan. After the introduction of the whole cell pertussis vaccine in 1947, disease incidence in Japan declined, and public concern regarding vaccine safety increased [86]. In 1975, the Japanese Ministry of Health and Welfare suspended use of the pertussis vaccination after two pediatric deaths occurred within 24 hours of DTwP vaccine receipt [86]. As a result of vaccine discontinuation, pertussis cases in Japan increased from 206 cases (1971) to 13,105 cases (1979) [73] (Fig. 36.2) (Callout Box 36.6).

Callout Box 36.6
Vaccine safety concerns low vaccine uptake increase in disease incidence.

Meanwhile, in the United States, the DTwP vaccination program continued. However, concerns regarding vaccine safety spread through the public leading to an increase in vaccine-related litigation [87]. By 1984, 73 DTwP vaccine-associated lawsuits were filed, with an average of $46 million sought per claim, for a total $1.3 billion (more than 20 times the value of all DTwP vaccine sales for the same year) [87]. There seemed to be no end to the litigation, forcing several manufactures to withdraw from DTwP vaccine production. As fewer DTwP vaccines were produced, vaccine costs increased, and ultimately the United States had a DTwP vaccine shortage. In an effort to ensure vaccine supply, stabilize vaccine cost, and establish a mechanism by which individuals injured by vaccines can be

compensated, the National Childhood Vaccine Injury Act of 1986 created the National Vaccine Injury Compensation Program (VICP), a federal "no-fault" compensation program for vaccine-related injuries funded by the addition of an excise tax on vaccines [88].

In 1992, the Institute of Medicine reported that the available evidence did not indicate a causal relation between the DTwP vaccine and infantile spasms, hypsarrhythmia, Reye's syndrome, or sudden infant death syndrome and that the range of excess risk of acute encephalopathy was consistent with prior reports of 0–10.5 per million vaccinated [89]. With the lack of public confidence in DTwP vaccine, increasing vaccine litigation, decreasing vaccination rates, and increasing disease incidence, it was clear that a newer, less reactogenic vaccine was needed.

Acellular pertussis vaccines, consisting of purified antigenic components of *B. pertussis* instead of the whole organism, were already being studied. In the early 1990s, there were 13 acellular pertussis vaccines, in combination with diphtheria and tetanus toxoid (DTaP), in active clinical trials in the United States. Each of these vaccines was immunogenic and had less frequent and less severe reactions compared to the prior whole cell pertussis vaccines [90, 91]. Multiple formulations of DTaP vaccine were approved for use by the US FDA. In 1997, DTaP vaccine was recommended for routine use in place of DTwP vaccine for children at ages 2, 4, 6, 15–18 months, and 4–6 years [92]. By 2002, DTwP vaccine was no longer available for use in the United States.

Since reaching a historic low in pertussis cases during the mid-1970s, the number of reported pertussis cases has been on the rise. During the 1990s, following widespread use of DTaP vaccine, there was a shift in pertussis epidemiology with an increasing proportion of infections identified in adolescents [70]. Between 1990 and 2003, there was a tenfold increase in pertussis incidence among this age group, accounting for almost 30% of the infections across the country [93, 94]. With vaccination rates at 96% in 2003, it seems unlikely that under-vaccination contributed to the rising disease incidence in the teens [95]. Subsequent data revealed that the more time that passed from receipt of the fifth dose of DTaP vaccine, the higher the likelihood of acquiring pertussis infection, demonstrating substantial waning immunity to the acellular pertussis vaccine over time [16, 17]. As years passed, middle and high schools, full of students with waning immunity to pertussis since their last pertussis-containing vaccine was administered prior to kindergarten entry, became a common site for pertussis outbreaks to occur [94]. In 2006, it was recommended that adolescents (11–18 years) receive a booster dose of Tdap vaccine to optimize their protection from disease and reduce school outbreaks [94] (Callout Box 36.7).

Callout Box 36.7
High infant vaccination rates plus waning immunity over time leads to increase in disease incidence during adolescence.

Despite the increasing proportion of disease occurring in adolescents, infants continued with the highest rates of disease incidence, hospitalizations, and deaths [96]. Efforts to identify the source of infection for these babies found that when a source could be identified, a household member was nearly always responsible for transmitting infection to the infant. The infant's mother was the most common source. Fathers, grandparents, and siblings were implicated less commonly [97, 98]. Since neonates, at highest risk for morbidity and mortality from infection, were too young to be vaccinated, the strategy of cocooning was adopted. Cocooning refers to the practice of vaccinating infants' close contacts, thereby providing indirect protection. In 2006, the recommendations were expanded to also include a dose of Tdap (1) for adults younger than 65 years anticipating close contact with an infant and (2) immediately postpartum for women who had not yet received a dose of acellular pertussis vaccine [99].

Nationally, pertussis outbreaks continued to occur in cycles every 3–5 years, as it did in the pre-vaccine era. In 2010, a large outbreak in California resulted in 9154 pertussis cases (more reported disease in this state than in any year since 1947), 809 hospitalizations, and 10 deaths. Almost three quarters of those hospitalized were younger than 6 months of age, and all deaths occurred in infants younger than 3 months of age [100]. While waning immunity to acellular pertussis vaccine contributed to this outbreak, it was not the only factor. Nonmedical exemptions to vaccines in California were on the rise. In 2010, 2% of students across the state claimed a philosophical belief exemption to vaccines otherwise required for school attendance [101]. As nonmedical exemptions tend to cluster in specific geographic areas, some schools reported nonmedical exemption rates as high as 80% [102]. Census tracts with a cluster of nonmedical exemptions were 2.5 times more likely to also be in a cluster of pertussis infection, with more cases of infection occurring within exemption clusters [102].

This was not the first time that an association between nonmedical exemptions and pertussis incidence was noted. In 2000, exempted students were 5.9 times more likely to acquire pertussis than their vaccinated peers, with the frequency of exempted children in a county directly correlating with pertussis incidence in vaccinated children [11]. Similarly, schools with pertussis outbreaks had higher rates of vaccine exemptions than schools without outbreaks [11]. Not only was the allowance of nonmedical exemptions important, but the ease with which this happens determines how frequently the exemptions are sought. At this time, a philosophical belief exemption in California required a parent signature on a preprinted affidavit on the back of the child's school immunization record [103]. It is well described that easier granting of exemptions and use of personal belief exemptions is associated with incidence of pertussis infection [39]. Ultimately, in 2016, California became the third US state to completely eliminate the use of nonmedical exemptions (Callout Box 36.8).

Callout Box 36.8
Clustering of nonmedical vaccine exemptions increase incidence in pertussis infection.

By this time, the cocooning programs to prevent neonatal pertussis infection showed limited success due to their logistical and financial challenges. Following the implementation of Tdap vaccination to postpartum women, the most likely source of pertussis in infants shifted from the mother to the siblings [104]. With the source of infection less likely to be an adult contact, cocooning became even more difficult to justify putting in place. Newer strategies for infant protection were needed. Vaccinating pregnant women would allow for transplacental transfer of maternal antibodies to the fetus, with direct protection to newborns when they are the most vulnerable. This strategy proved to be between 80 and 90% effective in preventing neonatal pertussis infection. In 2011, recommendations from the ACIP were updated to include a dose of Tdap vaccine for all pregnant women, ideally administered between 27 and 36 weeks' gestation [105]. Due to rapidly waning antibody levels following a booster dose of Tdap, vaccine recommendations were updated again in 2012 to state that a dose of Tdap vaccine should be administered during each pregnancy to optimize neonatal protection [106].

In 2014, a second pertussis outbreak occurred in California, with 9935 cases reported in the first 11 months of the year. Disease incidence was highest in infants younger than 1 year of age, followed by 14–16-year-old adolescents, most of whom had received Tdap vaccine at least 3 years prior to infection. Of the 211 infants younger than 4 months whose mothers' vaccination status was available, only 17% reported receiving Tdap vaccine during their most recent pregnancy [107]. Adolescents with longer time from Tdap vaccine receipt were more likely to test positive for disease, suggesting that waning immunity occurs after the booster doses as well [18].

In addition to the continued problems with waning immunity among vaccinated children and adolescents, there has also been persistence of groups refusing vaccinations. In one large religious community in Columbia County, Florida, with a high level of vaccine hesitancy, an unimmunized child was diagnosed with pertussis. At the time, only 15% and 5% of the kindergarten and seventh grade students, respectively, at the local charter school were fully immunized against pertussis. The most common reason for non-vaccination was religious exemption. Ultimately, 109 pertussis cases were diagnosed in the community, including 30% of the students attending the charter school [108]. In a review of five large statewide pertussis epidemics, 24–45% of the infected population were un- or under-vaccinated, with the majority of these individuals intentionally declining vaccine.

Between 2000 and 2016, 339,420 cases of pertussis were reported in the United States. Infants continue to have the highest incidence of disease and account for 88% of pertussis-related deaths [96]. Pertussis continues to cause cyclical epidemics, as it had in the pre-vaccine era, yet there continues to be an increase in both baseline and epidemic disease [96]. Nationwide epidemics in 2004 and 2010, each with over 25,000 cases, paled in comparison to the outbreak in 2012 when more than 48,000 cases were reported. This was the largest number of cases reported during any calendar year since 1955 [5]. The cycle is likely to continue. The problem is multifactorial including vaccine hesitancy and refusals, secondary vaccine failure from waning immunity, and challenges to source identification and contact tracing. Optimizing vaccine effectiveness, durability, and acceptance is needed to protect

infants and other vulnerable groups in our community from this life-threatening, vaccine-preventable infection.

Conclusion

Maintaining high vaccination rates is crucial to the control of vaccine-preventable diseases. Yet, largely due to the success of vaccines, parents and providers no longer have experience with the diseases, their potential severity, or their complications. Many now perceive vaccines to pose greater risks than the infections they are meant to prevent. This focus on vaccine concerns, rather than prevention of life-threatening illness, contributes to large pockets of unimmunized and under-immunized individuals, breaks in herd immunity, and the disease outbreaks that follow. Future efforts to optimize the effectiveness of vaccines and re-establish confidence in our safe and highly effective vaccine programs are needed.

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Chapter 37
Vaccine Mandates

Manika Suryadevara

Definitions

Herd immunity A situation in which a sufficient proportion of a population is immune to an infectious disease so that an index case of infection is unlikely to lead to a cluster or outbreak [1]
Medical exemption to vaccines Legal permission to *not* be immunized with an otherwise mandated vaccine because of an existing medical contraindication to receiving the vaccine
Nonmedical exemption to vaccines Legal permission to *not* be immunized with an otherwise mandated vaccine because of nonmedical reasons such as personal, philosophical, or religious beliefs

Introduction

Widespread implementation of national vaccination programs has reduced the morbidity of ten infectious diseases by more than 95%. When immunization rates are high enough to achieve herd immunity, vaccine benefits extend beyond the individual to the entire community. Herd immunity provides essential protection for those who cannot be immunized because of a contraindication to receiving the vaccine and for those who are immunized but failed to mount a robust protective response.

Within the community, transmission of infection occurs commonly in schools and healthcare facilities. Maintaining high vaccination rates in those attending and working in these facilities will reduce the potential for transmission or outbreaks of

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vaccine-preventable illnesses. In an effort to ensure high rates of immunity in these settings, state laws have established vaccination requirements for children attending school, day care centers, colleges, and universities, healthcare workers (HCW), and patients or residents of healthcare facilities [2]. Vaccine mandates are designed to reduce vaccine complacency and improve vaccine access, thereby increasing vaccine coverage and protection of attendees of these settings. Yet, mandates for vaccination have been met with resistance, from those who oppose vaccines for religious or philosophical reasons and from individuals who believe in vaccines but are opposed to forced legislation.

Resistance to vaccine mandates is not new to society. During a smallpox outbreak in the early 1900s, the Cambridge, Massachusetts, board of health mandated that all adult residents be vaccinated or re-vaccinated against the disease or be fined $5. Henning Jacobson refused vaccination, stating he had adverse reactions to his first vaccination, so he was fined $5. Refusing to pay, Mr. Jacobson appealed his case all the way up to the Federal Supreme Court of the United States. He argued that vaccine mandates infringe on individual liberty and are therefore in violation of the 14th Constitutional Amendment. The Supreme Court, however, ruled in favor of the State of Massachusetts emphasizing that states have the authority to implement vaccine mandates to maintain public health, a collective right of the community.

> The police power of a State embraces such reasonable regulations…as will protect the public health and safety…The liberty secured by the Constitution of the United States does not import an absolute right in each person to be at all times, and in all circumstances, wholly freed from restraint [3].

Less than 20 years later, the city of San Antonio, Texas, required documentation of smallpox vaccination or immunity prior to entering school. Rosalyn Zucht refused vaccination and had no certificate of immunity, so she was excluded from attending school. The Texas state court system denied her claim that mandating vaccine deprived her of personal liberty. Like Mr. Jacobson before her, she appealed to the US Supreme Court. The Supreme Court justices upheld the precedent stating that *Jacobson v Massachusetts* had already determined the authority of the state to mandate immunizations [4].

School Vaccine Mandates

Gradually, all 50 states developed and implemented immunization requirements for school attendance. By the 1980s, it was clear that state immunization laws for school attendance were highly effective in reducing outbreaks of vaccine-preventable disease, most notably from measles. State laws act as incentives for parents to immunize their children and for school districts and nurses to track childhood immunizations, benefiting the community as a whole [5]. Exemptions to state-mandated vaccines are included in the public health laws of all 50 US states. Three general exemption categories are used: (1) medical, (2) religious, and (3)

philosophical or personal belief. Differences in vaccine laws lead to variability in the vaccines required for school entry and the process for obtaining vaccine exemptions among the states.

All states allow for medical exemptions. Medical exemptions are granted appropriately to children who have a valid contraindication to receiving the otherwise required vaccine(s). Depending on individual state law, the healthcare provider or the family (with healthcare provider documentation) submits a request for medical exemption to either the school nurse, the representative for the school district, or the local department of health. While some states require retaining a single medical exemption form on file during the entire period of education, other states require resubmission of medical exemption documents each school year. Some states distinguish between temporary and permanent medical exemptions, requiring that providers provide a date when the medical exemption should be re-evaluated. Most states make it clear that exempt students will be excluded from school during an outbreak. Mean national estimates of medical exemptions to vaccination at kindergarten entry are low (0.3%) and vary little from state to state. Arizona and Arkansas report the lowest medical exemption rate nationwide at 0.1%, while California reports the highest rate at 0.6%. Medical exemptions are few in number and scattered widely across each state. The small numbers and random distribution of children with medical exemptions do not interfere with efforts to provide the herd immunity that such patients rely on for protection [6]. Currently, the five US states that limit vaccine exemptions to medical contraindications only include California, Maine, New York, West Virginia, and Mississippi. Exemptions based on religious beliefs are allowed in the remaining 45 states. Of these, 15 also allow the most permissive category for exemption based on philosophical or personal beliefs [7]. National mean estimate for all categories of nonmedical vaccine exemptions during the 2018–2019 school year was 2.3%, nearly eight times the rate of medical exemptions for the same school year. Nonmedical exemption rates are also more variable from state to state ranging from a low of 0.9% in Alabama to a high of 7.4% in Idaho. Not surprisingly, states with more permissive exemption processes have higher vaccine exemption rates. For example, Alabama, with the lowest rate of nonmedical exemptions, does not allow for personal belief exemptions. Moreover, to be approved for a Certificate of Religious Exemption, parents must receive education regarding the risk of not immunizing their child and submit a written objection to their county health department. In contrast, obtaining an exemption to a mandated vaccine in Idaho requires only that parents submit a form to the school indicating that they are claiming the exemption.

Significant local and regional variability in nonmedical vaccine exemption rates is also seen within some states. Geographic clustering of children with nonmedical vaccine exemptions is not uncommon, particularly in large metropolitan areas in states with more lenient exemption policies [8]. Private schools consistently report higher rates of nonmedical exemptions when compared to public schools. Between 2000 and 2014, the average personal belief exemption rate across Waldorf schools, alone, in California was 45%, 19 times higher than that of regional public schools [9]. High rates of unimmunized children living in the same community and

attending the same school put the community at risk for the vaccine-preventable disease outbreaks [10–12].

The link between nonmedical vaccine exemptions, pockets of low immunization rates in school-age children, and outbreaks of vaccine-preventable diseases has not escaped the attention of legislators. In 2015, California State Senator Dr. Richard Pan and colleagues wrote, sponsored, and passed a bill into law no longer permitting nonmedical exemptions statewide. Since then, similar legislation was passed in both New York State and Maine, while a change in Washington state law focused on removing the personal belief exemption only for the measles, mumps, and rubella vaccine. Other states passed legislation adding rigor to their exemption process, such as requiring parents to provide an annual, notarized statement detailing reasons for their exemption request or submitting details regarding religious objections to local school authorities for approval [7].

While a more stringent exemption process results in more immunized children attending school, there may be a replacement effect leading to an unimmunized cohort across the state. In the year after California removed all nonmedical exemptions to school-mandated vaccines, the percentage of kindergarteners that were not up-to-date with required vaccines only dropped from 7.2% to 4.4%, due to increases in both medical exemptions and in the number of children enrolled in homeschooling [13].

Vaccine Requirements in the Healthcare Setting

Healthcare workers (HCW), defined as all persons working in healthcare settings with the potential for exposure to patients and/or infectious materials, are at risk of acquiring and transmitting vaccine-preventable diseases to and from their patients [14]. The Advisory Committee on Immunization Practices (ACIP), therefore, recommends that HCW be immunized against potentially life-threatening infections to protect the health and safety of their patients and co-workers [14]. Vaccine laws for the HCW are initiated at the state level and can be further detailed in individual healthcare facility policy. One example to highlight is vaccination for influenza. During the 2015–2016 influenza season, 18 states had laws in place for influenza vaccination of hospital-based HCW, which included assessment of vaccination status (10 states), requiring HCW to demonstrate proof of vaccination (8 states), and/or requiring unimmunized HCW to wear surgical masks for the duration of the influenza season (3 states) [15].

Outbreaks of influenza infection in healthcare settings lead to HCW absenteeism and increased patient morbidity and mortality. In an effort to reduce absenteeism and influenza-related illness and deaths, the ACIP has recommended an annual influenza vaccine for all HCW since 1981 [16]. However, influenza vaccination rates among HCW remained less than 50% through the mid-2000s. A variety of interventions to improve influenza vaccination at the healthcare facility level have been studied. Multi-component immunization campaigns, particularly those that

improve vaccine access and include a required declination statement, are most likely to increase vaccine uptake, while the use of education alone results in minimal, if any, improvement [17–19].

Similar to the effect of school vaccine mandates, employer mandates for influenza vaccination, particularly with consequences for noncompliance (termination, voluntary resignation, mandatory masking), also have a significant impact on vaccine coverage rates [20]. In the absence of state law, employer vaccine requirement was found to be associated with the largest increases in mean influenza vaccination coverage [15]. During the 2018–2019 influenza season, while nationwide vaccine coverage rate among HCW was 81.1%, the highest rates of vaccination were seen in settings where immunization was required (97.7%) [21].

Despite endorsement of employer influenza vaccine mandates by various medical organizations, there has been a steady increase in litigation challenging hospital policy to require the influenza vaccine for HCW. Of interest, the Equal Employment Opportunity Commission (EEOC) initiated several lawsuits, resulting in hospital fines, alleging that healthcare facility mandates for influenza vaccine violate the Title VII of the Civil Rights Act of 1964, which prohibits employment discrimination on the basis of religious beliefs [22]. Healthcare institutions implementing mandatory influenza vaccines for their HCW should understand the legal and ethical implications in order to optimize the success of their vaccination policy.

Conclusion

High vaccine coverage results in herd immunity and prevention of vaccine-preventable disease outbreaks, and is especially important in areas where transmission of infection is high. Vaccine mandates, developed and implemented at the state level, exist to ensure that the population attending schools or working at healthcare facilities are immune to vaccine-preventable diseases which could spread rapidly through these settings.

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Chapter 38
Vaccine Confidence and Vaccine Hesitancy

Manika Suryadevara

Definitions

Vaccine hesitancy Delay in acceptance or refusal of vaccines despite availability of vaccination services [1]

Vaccine confidence Level of trust that people have in recommended vaccines, in the providers who administer vaccines, and in the process that leads to vaccine licensure and the recommended vaccination schedule [2]

Vaccine acceptance Timely receipt of all childhood vaccines as recommended by the Advisory Committee on Immunization Practices (ACIP) when vaccines and vaccine services are available [2]

Epidemic Sudden increase in the number of cases of disease beyond what is normally expected to occur sporadically in a given geographic area [3]

Pandemic An epidemic that has spread across several countries, continents, or the entire globe affecting a large number of people [3]

Antigenic drift of influenza virus Mutations in influenza virus genes that leads to changes in the surface proteins, hemagglutinin and neuraminidase; results in need to review influenza vaccine composition annually [4]. Occurs regularly in both influenza A and influenza B viruses

Antigenic shift of influenza virus An abrupt change in one or more genetic segments of influenza A virus resulting in the expression of novel hemagglutinin and/or neuraminidase proteins; responsible for influenza pandemics [4]

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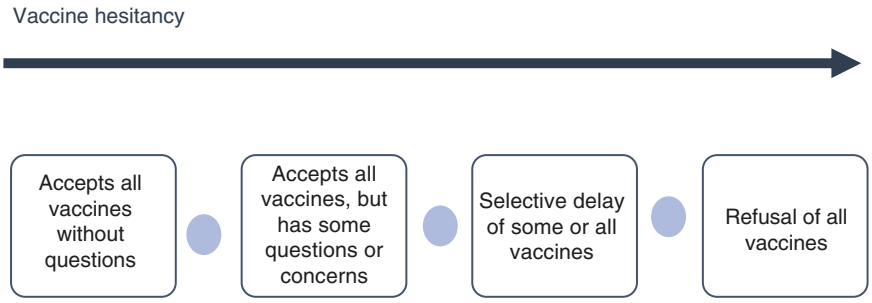

Fig. 38.1 Spectrum of vaccine attitudes

Introduction

Under-immunization, or the lack of receipt of all recommended vaccines, has a number of underlying causes including but not limited to parental vaccine hesitancy, lack or suboptimal access to medical care, vaccine shortages, and/or low public health support for vaccination programs. Parental vaccine attitudes represent a continuum of vaccine beliefs, from complete acceptance to complete refusal of all vaccines. The parental level of confidence in vaccine safety and efficacy influences their decision-making (Fig. 38.1) [2]. Factors associated with higher levels of vaccine confidence include personal experience with one or more vaccine-preventable diseases, receipt of vaccine information from a trusted source, and a strong relationship with one's healthcare provider [5].

The term "vaccine hesitancy" is defined by the 2014 report from the Strategic Advisory Group of Experts (SAGE) on Immunization of the World Health Organization (WHO) as the "delay in acceptance or refusal of vaccines despite availability of vaccination services. Vaccine hesitancy is complex and context specific, varying across time, place, and vaccines. It is influenced by factors such as complacency, convenience, and confidence" [1]. While the majority of parents fall on the vaccine acceptance side of the spectrum, there are an increasing number who are declining all vaccines and even more who are requesting that their providers use an alternative to the ACIP-recommended vaccine schedule [6] (Fig. 38.1).

Factors Contributing to Vaccine Hesitancy

An individual's personal experiences, in combination with input from various social, cultural, and political influences, guide his/her attitude toward vaccinations [7]. As such, there is no single factor associated with developing vaccine hesitancy, nor is there a single approach to counter the various causes. Themes that have been consistently identified among vaccine-hesitant groups include a perception that risks of vaccination outweigh their benefits, concerns regarding the adverse effects

Table 38.1 Factors contributing to vaccine hesitancy

Perceived risk versus benefit of vaccination
Concerns regarding the adverse effects of vaccinations
Mistrust in institutions
Desire for autonomy

of vaccines, mistrust in institutions, and desire/demand for autonomy in making decisions about receiving vaccines (Table 38.1) [6, 8–10].

Perception that Risks Outweigh Benefits of Vaccination

Medical decisions for oneself and/or one's children take into account the perceived benefits and risks of a given intervention. Vaccine-related decision-making is somewhat dependent on the real or perceived incidence of the preventable disease. In general, when the incidence of a vaccine-preventable disease is high, confidence in the vaccine targeted to prevent the disease is also high. High levels of vaccine acceptance lead to a reduction in disease. Slowly, concerns about disease shift to concerns related to real or perceived side effects of the vaccine. As concerns about vaccine safety increase, the associated vaccine hesitancy results in lower vaccination rates (Fig. 36.2). Furthermore, some parents incorrectly believe that living a healthy lifestyle, using only "natural" products, and/or eating only fresh, organic food reduces risks for developing disease, so they avoid vaccines because they perceive them to be unnatural [11, 12]. Many parents perceive the risks of vaccines to be higher than they actually are, particularly those prone to make causal associations between vaccines and unrelated childhood health issues that typically appear around the same age that most vaccines are administered [8, 11]. This is especially true since vaccinations are administered during times of good health, when the benefits of preventing a disease with low incidence, despite the potential for high severity, may not be well-recognized.

Concerns Regarding the Adverse Effects of Vaccinations

Concerns about adverse effects of vaccinations quite often reflect misperceptions. Some of these misperceptions are so pervasive they are shared by large segments of the population. For example, a substantial portion of the population that decline influenza vaccine each year state that each time they get a "flu shot," it gives them the "flu." "Flu shots" are, of course, inactivated vaccines incapable of transmitting influenza disease, yet this misperception endures. Despite evidence to the contrary, parents still cite beliefs that vaccines cause the diseases they are designed to prevent or that vaccines cause autism, neurologic disability, or other chronic illnesses. Some parents incorrectly believe that too many vaccines administered simultaneously can

overwhelm the immune system, and others continue to insist that acquiring natural infection is a safer way to develop immunity. A vocal few continue to bemoan the presence of "toxic ingredients" present in vaccines, specifically listing aluminum, mercury, embalming fluid, and antifreeze as items of concern (see Chap. 4) [9, 13].

The Food and Drug Administration Modernization Act of 1997 required the FDA to review and assess the risk of all mercury-containing food and drugs, including vaccines [14]. Thimerosal, an ethylmercury-containing preservative used in some vaccine since the 1930s to prevent bacterial contamination of multi-dose vials of vaccine, has been studied extensively and never shown to be unsafe at the concentrations used. However, as part of the efforts to modernize vaccine formulations, the US Public Health Service, the American Academy of Pediatrics, and vaccine manufacturers all agreed to switch to unit dose vaccines where feasible, so preservative would no longer be necessary. Thimerosal remains FDA approved as a preservative. It is included only in multi-dose vaccine vials used to immunize non-pregnant adults. On the global scale, thimerosal-containing vaccines remain the norm for all ages as the World Health Organization recognizes its long-standing safety profile. On a global scale, converting the use of multi-dose vaccine vials to individual unit doses of preservative vaccine would incur a level of cost that would jeopardize the ability for most established vaccination programs to continue their efforts. The resulting drop in vaccine coverage rates across the globe would be disastrous.

Social Norms

Social norms play a significant role in determining parental vaccine attitudes. When parents perceive that vaccine confidence is the norm within their social group, they tend to share the same level of confidence in vaccines. Similarly, when parents believe that vaccine hesitancy is the norm within their social group, they are more likely to express concerns regarding vaccinations [2]. On the other hand, there are some groups of vaccine refusers who believe that vaccinators are a marker of parental conformity to societal norms, perceiving that their caregiving practices are superior to those of vaccinators and that "natural" practices eliminate the need for vaccinations [12].

Mistrust in Institutions

Trust, or the willingness to rely on someone else's expertise or advice, in information sources is an important component in making medical decisions for one's child [2]. With regard to vaccines, this trust involves a complex web of entities, including the pharmaceutical companies that produce vaccines, the healthcare system that delivers vaccines, the providers who recommend and administer vaccines, the scientific organizations which study vaccine safety and efficacy, and the policy makers

that decide which vaccines are needed and when they should be given [2]. High levels of trust in one's healthcare provider are associated with vaccine acceptance, while low levels are associated with vaccine hesitancy and refusal [2].

Individuals who mistrust governmental institutions are generally skeptical regarding their motives in vaccine promotion. Some people do not trust the relationship between the government and the pharmaceutical companies, suspecting financial motives which ultimately impact vaccine research and the credibility of scientific evidence [10, 11]. Those inclined to extend this belief to providers have suggested that the physicians and pharmacists who are administering the vaccines are influenced and incentivized by the vaccine manufacturers [11].

Desire for Autonomy

Parents report a strong sense of responsibility in making medical decisions for their child, particularly with regard to vaccines [11]. Some are concerned that their decision to vaccinate, a decision to act in the moment that cannot be changed later, may result in harm to their child. Those who choose not to vaccinate are making a passive decision, one that could be changed later should their perceptions about the risks for acquiring the preventable disease change [11]. In both situations, the vast majority of parents view their decisions as caring best for their child [11].

The desire for autonomy in medical decision-making for oneself or one's child contributes to the opposition for mandated vaccines. This argument against vaccine mandates in the United States dates back as far as 1902 during a smallpox outbreak in Cambridge, Massachusetts. In response to the outbreak, the local board of health mandated that all city residents be vaccinated against smallpox to curb the spread of the disease. Noncompliant citizens were subjected to a $5 fine. Minister Henning Jacobson refused vaccination and would not pay the fine. The Massachusetts Supreme Judicial Court found that Jacobson was within his rights to refuse vaccination but was legally obligated to pay the $5 fine. Jacobson refused and appealed to the US Federal Supreme Court. The action is one of the first legal cases in the United States whereby a citizen challenged the authority of the state to prioritize public health over an individual's freedoms. The Supreme Court sided with the State of Massachusetts upholding the state's authority to mandate vaccination during an epidemic [15]. Since that time, state-directed vaccine mandates have become standard practice. Today, most public health laws mandating vaccines list the immunization requirements for children to attend public school. In most states that permit them, nonmedical (philosophical or religious) vaccine exemptions are on the rise.

While hesitancy can be seen with vaccines in general, there are also specific vaccines associated with very high levels of hesitancy. The two vaccines associated with the most hesitancy are influenza and the human papillomavirus (HPV). Opposition to receiving an annual seasonal influenza vaccine is multifactorial, stemming from each of the vaccine hesitancy factors discussed above.

Influenza Vaccine Hesitancy

ACIP recommends annual administration of influenza vaccine to all eligible persons 6 months of age and older [16]. Yet, influenza vaccine hesitancy throughout the community, even among those with high likelihood of exposure (healthcare workers) and those at risk for severe disease or complications from influenza infection, has resulted in suboptimal vaccine uptake. More than 70 years after the licensure of the first influenza vaccine, only 62% of children aged 6 months–17 years and 45% of adults received a dose of the 2018–2019 seasonal influenza vaccine [17]. Providers who report that they recommend all standard vaccines to eligible patients also report that they do not routinely recommend the influenza vaccine [18–20]. The discordance between the two responses strongly suggests that those providers do not consider influenza vaccination standard despite the clear Category A recommendation from ACIP to immunize everyone starting at 6 months of age. Similarly, in a study of low-income families in Central New York, 93% of parents reported that their children were up to date for all recommended vaccines; however, only 39% reported that their children had received an influenza vaccine [21].

Healthcare workers (HCWs), defined as any personnel with patient contact working in a healthcare facility, can acquire influenza infection from and transmit infection to their patients. Until very recently, the culture of workplace presence meant that many HCWs would continue to work during illnesses [22–24]. Higher-risk patients visit healthcare settings frequently for care related to the comorbidities that put them at increased risk for severe influenza infection. Individuals who are 65 years and older, those with chronic medical conditions, pregnant women, and children younger than 2 years old are particularly susceptible to the complications of influenza infection, including the development of bacterial pneumonia, myocarditis, encephalitis, myositis, and multi-organ dysfunction, which may lead to hospitalization or death. Median mortality rates from nosocomial influenza infection in acute care facilities and geriatric hospitals are reported to be approximately 16% and even higher at 33–60% among transplant and intensive care unit patients [24]. Reductions in nosocomial influenza infection can be accomplished by ensuring consistently high HCW vaccination rates [25]. Annual influenza vaccination has been routinely recommended for HCW since 1981 to reduce nosocomial transmission of infection, yet influenza vaccine acceptance among this group has plateaued.

Pregnant women represent another under-immunized high-risk population. Women who acquire influenza infection during pregnancy are at higher risk for severe disease and complications, including death. Between 2010 and 2018, pregnant women accounted for 24%–34% of influenza-associated hospitalizations [26]. Influenza vaccine is recommended for all pregnant women as an intervention proven to reduce severity of disease and improve maternal-fetal outcomes, yet only half of the surveyed pregnant women received an influenza vaccine before or during their pregnancy during the 2018–2019 season [26].

Perceived Risk Versus Benefit of Vaccination

- "The flu vaccine doesn't work! You still get the flu."
- "I never get the flu, I don't need the vaccine."
- "The flu is just like getting a cold."
- "I am healthy, the flu is no big deal."

There are three influenza types, A, B, and C, known to infect humans. Influenza types A and B both cause annual seasonal epidemics, but only influenza A viruses undergo antigenic shifts that lead to pandemics. The most lethal global pandemic known, referred to as the "Spanish flu of 1918," infected more than 500 million people representing ~1/3 of the world's population at the time, killing more than 50 million [27]. The Spanish influenza pandemic caused more deaths among American military personnel during World War I than those killed by enemy fire [28].

It took another 25 years before the first inactivated influenza vaccine was licensed for use in the United States. During the seasonal influenza epidemic of 1947, scientists first discovered mutations in the circulating influenza virus, known as antigenic drifts, that reduced the efficacy of the vaccines that were being used. Antigenic drifting of influenza A and B viruses occurs continuously highlighting the importance of ongoing surveillance and characterization of circulating viruses. These data are used to instruct vaccine composition for the upcoming influenza season [29].

Influenza vaccine efficacy depends on multiple factors, including the age and immune status of those vaccinated and the degree of similarity between the vaccine virus and the circulating viruses each year. Annual influenza disease burden is influenced by seasonal influenza vaccine uptake, vaccine efficacy, and timing of outbreaks. Between 2014 and 2018, influenza vaccine effectiveness (VE) ranged from 19% to 48% [30]. Even during the 2014–2015 influenza season, when VE was estimated to be 19%, vaccination was estimated to have averted 1.4 million infections, 700,000 medical visits, over 38,000 hospitalizations, and ~4000 deaths [31]. Influenza vaccines prevented an estimated 40,000 deaths in the United States between 2005 and 2014 [32] (Callout Box 38.1).

Callout Box 38.1
The influenza vaccination is the best way to prevent severe disease and complications from influenza infection.

The perception that an individual is at low risk for acquiring infection or developing severe disease or complications from influenza is often cited as a reason for non-vaccination. However, during the 2018–2019 influenza season, there were an estimated 35 million influenza illnesses in the United States, equivalent to 1 in 11 individuals nationwide infected during this season, alone. Figure 38.2 shows the annual influenza disease burden in the United States between the 2014–2015 and

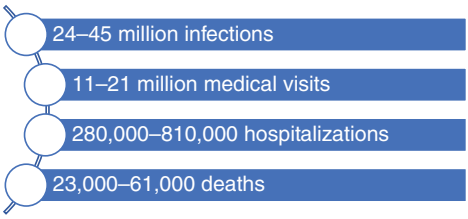

Fig. 38.2 Estimated number of infections, medical visits, hospitalizations, and deaths attributed to influenza infection in the United States annually between 2014 and 2019

2018–2019 influenza seasons. During the 2017–2018 influenza season, 43% of children hospitalized with influenza infection had no known underlying complications [33]. Therefore, while there is a focus on influenza prevention among those individuals at higher risk for developing complications from infection, it is recommended that otherwise healthy individuals 6 months of age and older also receive an annual influenza vaccine.

Concerns Regarding the Adverse Effects of Vaccinations

- "The flu shot gives you the flu."
- "The flu shot makes me sick."
- "The flu shot doesn't work, I still get the flu."

All formulations of "flu shots" are formulated with inactivated influenza viruses. They do not contain active virus and cannot transmit influenza infection. The most commonly reported side effects from the inactivated influenza vaccines include redness or tenderness at the site of injection, headaches, nausea, or fevers, all of which self-resolve within 48 hours.

The development of an influenza-like illness following influenza vaccination can occur for multiple reasons:

1. Influenza season is more accurately referred to as "cold and flu" season. Several respiratory viruses co-circulate. Symptoms of infection caused by each respiratory virus overlap. Individuals who acquire infections with human metapneumovirus, parainfluenza virus, rhinovirus, adenovirus, or respiratory syncytial virus, for example, may develop fevers, congestion, and cough and deem the influenza vaccine ineffective even though their infection was caused by a different pathogen.
2. It takes 2 weeks to develop protective antibodies following immunization. If influenza is circulating in the community at the time of vaccination, it is possible to acquire influenza infection before the protective effect of the vaccine develops.
3. Influenza vaccine effectiveness varies based on the vaccine virus-circulating virus match and the host's ability to mount a robust immune response to vaccine. While vaccinated individuals may become infected with influenza, their symptoms tend to be less severe compared with those who are unimmunized. Benefits of influenza vaccination include reductions in influenza-associated hospitaliza-

tions among healthy adults and among those with underlying conditions, better outcomes among adults hospitalized with influenza infection, fewer hospitalizations among infants born to mothers who were immunized during pregnancy, and lower risks for life-threatening infection among children [34–37].

Social Norms

- "None of my friends get the flu vaccine."
- "The other moms were saying that I should not give my child the flu vaccine."

Influenza vaccine uptake is lower when the perception of social pressure to be vaccinated is lower [38]. Along those lines, individuals are more likely to have received the influenza vaccine when they reported that the majority of their group want to be vaccinated [39–41]. Social norms should be utilized by vaccine-confident people to promote influenza vaccination in their community.

Mistrust in Institutions

- "The pharmaceutical companies want me to get vaccinated so they can make more money."
- "The government made those recommendations and we don't trust them."
- "I don't trust those doctors."

Trust, whether in the healthcare provider's recommendation, the influenza vaccine production process, or the vaccine, itself, is significantly associated with an increase in vaccine uptake [42]. Studies reveal that lack of trust in pharmaceutical companies and the government varies by race. Whites were more likely to trust governmental institutions but doubt their competency, whereas African Americans were less trusting of the government altogether [43, 44]. This difference in institutional trust may contribute to the disparities in influenza vaccine uptake.

Desire for Autonomy

Despite the ACIP recommendation for HCW to be vaccinated against influenza annually, between 1997 and the mid-2000s, vaccination rates among HCW remained at 40%. Even among this subpopulation at high risk of acquiring and transmitting infection, the most commonly cited barriers to vaccination included fear of developing an influenza-like illness after vaccination, perceived ineffectiveness of vaccine, perceived low likelihood of contracting disease, and inconvenience of having to find a place to get vaccinated [23, 25, 45]. Hospital employees also stated that they

would be more likely to receive the influenza vaccine if they were informed about the importance of influenza vaccination in the healthcare setting and if the vaccine was easily accessible at work [23, 46].

In response, institutions adopted interventions including peer education, promotional campaigns, convenient access to vaccine at no cost, and mandatory declination. Together these interventions lead to only modest increases in HCW vaccine uptake [45]. Further improvements have been gained by institutions that have been successful in mandating influenza vaccination as a condition of employment. Noncompliance consequences vary by institution, ranging from no consequences, to a requirement to wear a mask during influenza season, and, in rare cases, to termination of employment. Healthcare facilities with mandatory influenza vaccination programs have achieved influenza vaccination rates exceeding 90% [47, 48]. In the 2018–2019 influenza season, over 81% of HCW reported receiving an influenza vaccination, with the highest coverage (97.7%) among those with workplace vaccination requirements and the lowest (42.1%) among those without mandates [17].

Despite the duty of HCW to protect the patients, particularly those vulnerable to influenza complications, the argument that mandatory vaccination programs infringe on the autonomy of HCWs has led to increases in litigation. The Equal Employment Opportunity Commission (EEOC) has led multiple lawsuits involving the denial of religious exemptions from influenza vaccination requirements by healthcare facilities, citing violation of Title VII of the Civil Rights Act of 1964 which prohibits discrimination against employees on the basis of sex, race, color, national origin, and religion [49].

Multiple factors contribute to influenza vaccine hesitancy. Interventions to improve influenza vaccine uptake should be tailored to the rationale provided by the hesitant individual or group.

Vaccines and the Media

Vaccine attitudes are influenced, in part, by the health information sources used by an individual. While healthcare providers remain the most trusted source, there is an increasing reliance on online media for medical information. In 2019, it was reported that more than 90% of American adults use the Internet, for convenient, easy, and immediate access to a wide variety of information and misinformation [50]. This access allows for widespread exchange of ideas, often with limited ability to distinguish opinion from expertise, hyperbole from balanced, or fiction from fact. A 2018 Pews study found that 14% of Americans changed their mind about an issue because of something they viewed on social media [51]. While social media has been used to help with smoking cessation and weight loss, these outlets have also been used to disseminate false information, particularly with regard to vaccines [52].

Recent studies have shown that more people list the Internet as the first place they obtain health information, even above family/friends, healthcare professionals, and traditional media [53]. Up to 72% of Internet users look online for health

information [54]. For example, parenting blogs are used by mothers as a major source of health information, being perceived as an authority for online information. Mothers report satisfaction with the availability of unlimited information to them, which they view to be generally trustworthy, and with the ability to gather multiple viewpoints when making a decision about their child [55]. Mothers also appreciated the immediacy of the affirmation and support found on these sites, preferring advice from social media than their healthcare providers [55]. In addition to parenting blogs, pediatrician blogs are also viewed by parents for guidance regarding decision-making, with blogs written in the third-person objective voice considered to be more accurate and reliable than blogs written using personal or mixed voices [56].

A recent study found that 67% of all vaccine-related blogs expressed pro-vaccine sentiments, while 22% were classified as anti-vaccine. Not surprisingly, the majority of comments to the pro-vaccine blogs were pro-vaccine, while the majority of the comments to the anti-vaccine blogs were anti-vaccine, one-quarter of which contradicted CDC vaccination guidelines [57]. Facebook, and other social media outlets, similarly allows for echo chambers to emerge resulting in further polarization of their users [58]. Of interest, spending even just 5–10 minutes on vaccine-critical websites increased perception of risk of vaccination and decreased intention to vaccinate among users [59].

The media has been shown to influence vaccine attitudes and vaccine uptake in both positive and negative ways. Understanding these influences will allow providers to have a deeper understanding of the contributing factors in their patients' decision-making process and to offer avenues to disseminate accurate messages consistent with organizational recommendations.

Examples of Media Influence on Vaccine Uptake

US HPV Vaccine Experience

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States, causing an estimated 14 million new infections each year, half of these occurring in the adolescent and young adult population. While the majority of HPV infections are asymptomatic and self-limiting, a proportion of infected people go on to develop HPV-related complications, including genitourinary and oropharyngeal cancers. Each year, there are approximately 35,000 new genitourinary and oropharyngeal cancer diagnoses attributable to HPV infection in the United States [60].

The HPV vaccine is safe and effective in the prevention of vaccine-type infection and the development of HPV-associated complications. Current recommendations for the HPV vaccine series, either a two- or three-dose series depending on individual's age and immune status, are for universal administration of vaccine to adolescents starting at 11 years old. Despite the availability, safety, and efficacy of this cancer prevention vaccine, national coverage rates remain suboptimal, with about half of the nation's adolescent population still vulnerable to acquiring HPV infection.

In February 2006, the Merck's investigational cervical cancer vaccine was considered eligible for priority review from the US Food and Drug Administration. This expedited process allows for the evaluation of drugs that, if approved, could offer significant benefit with regard to disease treatment, prevention, or diagnosis, with a goal of completion of review and determination of action within 6 months instead of the typical 10-month time period [61]. This review pathway, however, does not change the scientific and quality rigor required for approval. On June 8, 2006, the US Food and Drug Administration, through their review of data from studies of ~21,000 females, approved the quadrivalent HPV vaccine for females 9–26 years of age to protect against genitourinary cancers and genital warts [62].

Later in 2006, the ACIP followed with recommendations which included a three-dose HPV vaccination series for girls 11–12 years of age, with catch-up vaccination for females 13–26 years [63]. The ACIP determined the age of vaccination (11–12 years old) based on the robust immune response to vaccine in this age group, the need to administer vaccine prior to sexual debut, and the benefit in administering this vaccine at a medical visit where other vaccines are also recommended [63].

Mass media coverage during this time framed the HPV vaccine as a cervical cancer vaccine, with fairly neutral news content focused on the public health and medical implications of vaccine, describing the link between HPV and cervical cancer but without much background information [64, 65]. The main concerns during this time included the risk that the HPV vaccine would promote promiscuity after vaccination [66]. Despite an abundance of evidence showing that the receipt of HPV vaccine does not influence sexual behavior, articles that discussed sexuality are more than two times more likely to contain conflict than those without [67–69].

Several states began considering the implementation of a bill requiring HPV vaccine for middle school-age girls. However, in 2007, Republican Texas Governor Rick Perry went so far as to issue an executive order for an opt-out HPV vaccination program for girls prior to entering sixth grade. After facing backlash from conservative and religious groups, he reversed this decision to put through a vaccine mandate using executive orders. This political incident resulted in a significant increase in both public attention, as seen with an increase in Google searches related to HPV vaccine, and news media attention [66]. The focus of coverage, however, shifted from public health and science to politics, highlighting reasons for and opposition to mandating HPV vaccine, referencing "conflict" and "controversy" in association with the HPV vaccine, and citing concerns of promoting promiscuity, in addition to autonomy in parental decision-making and the potential for side effects that were not yet known [66, 70].

In October 2009, following FDA approval of use of HPV vaccine in males, the ACIP issued a "permissive recommendation" stating that the HPV vaccine may be administered to males aged 9–26 years [71]. Differing from the routine recommendation for all adolescent females, this permissive recommendation led to provider confusion regarding if and how they should be recommending vaccine to their male adolescents. The early presentation of this vaccine as cervical cancer prevention, in an effort to avoid the stigma associated with prevention of a sexually transmitted infection, implied that females were the only target population to benefit from vaccine and further led to the difficulties in understanding and accepting

male vaccinations. It was not until 2 years later that the ACIP routinely recommended vaccinating all males 11–21 years of age and high-risk males (men who have sex with men and HIV-infected males) aged 21–26 years to protect males from the development of HPV-associated genitourinary or oropharyngeal cancers [72]. By this time, providers and public, alike, had to change their understanding about the target population benefiting from this vaccine, yet the HPV-related news articles during this time failed to provide information regarding HPV and noncervical cancers [73].

As the release of these recommendations coincided with the 2012 US presidential campaign, it was inevitable that the vaccine would get pulled into the political arena. In September 2011, during the US Republican presidential debate, and on national news the following day, Minnesota Representative Michele Bachman stated that the HPV vaccine was a "potentially dangerous drug" that can lead to "mental retardation," referencing a story one woman had told her [74, 75]. The number of Google searches related to HPV reached its second highest number in the time following these comments [76]. Despite response from the American Academy of Pediatrics that "there is absolutely no scientific validity to this statement," HPV-related online content continued to link the HPV vaccine with Bachman's incorrect statements, with a shift from HPV-associated news covering vaccine dosing, duration, and protection to HPV and politics [54]. During this time period, almost half of all HPV-related news articles were more focused on political events than science or public health, with only a quarter even acknowledging that boys are now vaccine eligible [66]. Surveyed parents of adolescent boys who were aware of Bachman's comments had larger increases, compared to the parents who were not aware, in their belief that the vaccine may cause short-term health problems [76].

Over the next 3 years, continued changes in the recommendations for HPV vaccine may have added to confusion of vaccine eligibility, both on the part of the providers and parents. In 2014, HPV-9 was approved for use, with recommendations to replace quadrivalent HPV vaccine, to protect against infection with an additional five HPV types. The following year, the FDA expanded Gardasil 9 to include males up to 26 years old. In December of 2016, the recommendations changed again to include a two-dose vaccine series of healthy individuals who receive the first dose of HPV vaccine before their 15th birthday.

Anti-HPV vaccine messaging continues to have a social media presence. In the years following vaccine approval, vaccine safety is continuously monitored. With over 120 million doses of HPV vaccine administered, the most common side effects reported include redness and pain at the site of injection, fever, headache, and dizziness. Yet, anti-HPV vaccine messages tend to focus on unproven side effects [52]. In addition to vaccine safety, social media reports of conspiracy theories between the government and pharmaceutical industry, and misinformation spread through use of personal stories of harm are widely found [52]. A review of over 258,000 HPV-related tweets between 2013 and 2015, with potential exposure to over 291 million US users, found that the tweets were varied among positive, neutral, and negative messages [77]. Lower vaccine coverage was found in states with higher proportion of exposure to negative tweets, whereas there was no association between positive messaging and vaccine coverage [77].

These trends still occur. A recent study found that 45% of surveyed parents of adolescents reported having heard a story, whether positive or negative, about the HPV vaccine. Information about vaccine harms were more likely to occur through traditional and social media, while stories about vaccine benefits were more likely to be recalled from personal conversation. Parents who were only exposed to stories about vaccine harms were more likely to delay or refuse HPV vaccine [78]. While positive HPV vaccine messages are also seen on social media, specifically using facts and numbers to show vaccine benefit, social media users are more likely to remember the reported harms than the benefits [52]. Similarly, a review of HPV-related Facebook posts and their comments found that mothers who refused the HPV vaccine for their children stated concerns of vaccine safety, lack of trust in the organizations making recommendations, and concerns relating to sexual activity [79]. On the other hand, mothers in support of the HPV vaccine simply stated they vaccinated their daughters, without any reasons or explanations which may not be enough to counter the spread of the anti-vaccine messages posted [79].

Israel Polio Outbreak

Poliovirus infections can result in asymptomatic infection, nonspecific febrile illness, a nonparalytic polio manifesting with viral meningitis, or acute flaccid paralysis (paralytic poliomyelitis). There are two types of poliovirus vaccines available, a bivalent oral polio vaccine (bOPV) and an inactivated polio vaccine. While OPV is very safe and effective in prevention of paralytic poliomyelitis, it has the potential to rarely cause vaccine-associated paralytic polio (VAPP). Inactivated polio vaccine (IPV) protects against paralysis from poliovirus but does not prevent fecal shedding and transmission of virus. Therefore, most countries transitioned from universal use of bOPV to IPV when the risk of VAPP was higher than the risk of wild poliovirus-associated acute flaccid paralysis.

Widespread use of polio vaccine has led to eradication of disease from the majority of the world. Currently, polio remains endemic in only three countries (Afghanistan, Nigeria, and Pakistan) [80]. In response to a polio outbreak in Israel, in 1989, a routine environmental surveillance program was set up to allow for monthly testing of sewage samples from designated sites across the country, covering almost 40% of the population, in addition to surveillance for acute flaccid paralysis among children younger than 15 years of age [81]. In 2002, the WHO certified Israel to be polio-free. Exclusive use of IPV for polio prevention in Israel started in 2005.

In April 2013, despite no clinical cases of acute flaccid paralysis, the environmental surveillance program detected wild poliovirus type 1 from the sewage samples obtained in two cities in southern Israel [81]. Following this finding, stool surveys, conducted in areas where the wild poliovirus was found in the sewage, found that the majority of positive fecal samples were collected from children younger than 10 years of age, the birth cohort that received only IPV for polio prevention [81]. IPV vaccination rates were above 90% in these communities;

however, IPV does not prevent shedding and transmission of the virus. In addition, the residents of these cities were of low socioeconomic status, living in areas of overcrowding and poor sanitation.

In an effort to interrupt viral transmission, the Israel Ministry of Health and the WHO led an immunization initiative to vaccinate all eligible children under 10 years old with the bivalent oral polio vaccine. As part of this campaign, the Ministry turned to the media, including web-based platforms, social media outlets, electronic journalism, and print media, to disseminate information regarding hygiene and vaccination. This media campaign first started in southern Israel and then expanded to include the whole country. Between August 4 and September 16, 2013, the Ministry of Health campaign website, alone, received almost 850,000 visitors. By mid-October, more than 900,000 children of the targeted 1.2 million had received vaccine [82]. There was a significant association between positive media exposure and OPV vaccine uptake. Of note, negative media exposure was not associated with a change in vaccine uptake [83]. By April 2015, the WHO officially declared Israel to be polio-free again.

Mass media campaigns have been found to contribute to increases in vaccination rates in a variety of circumstances worldwide. Daily influenza-related media coverage was associated with increased influenza vaccination rates among those over 65 years of age [84, 85]. Similar campaigns were associated with increase in measles-mumps-rubella vaccinations in Finland [86]. After negative media led to lower vaccine uptake and a resurgence in polio cases in Nigeria, the implementation of the Journalists' Initiatives on Immunization Against Polio, emphasizing the importance of immunization in the region, resulted in increased acceptance of polio vaccine in northern Nigeria [87].

Conclusion

Vaccine hesitancy is a wide-ranging spectrum of attitudes that result from personal experiences and external influences. Approaches to vaccine hesitancy need to be tailored individually and may benefit from strategic use of external sources, such as traditional and social media, in order to be successful. Understanding one's underlying concerns to vaccination is crucial to improving vaccine uptake and maintaining immunity against vaccine-preventable disease.

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Chapter 39
Communicating with Parents About Vaccines

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Introduction

Vaccines are safe and effective in preventing an array of moderate and severe infections that can be life-threatening. In fact, vaccines have been so effective that many healthcare providers and parents have never seen some of these diseases that were once so prevalent and devastating. When disease incidence and severity is high, vaccines are more widely accepted within the community. With high vaccination rates, disease incidence goes down, so the infections and their complications become less familiar. As new providers and parents become less aware of the potential for disease severity, more focus is placed on the risk of vaccination rather than on acquiring the infection itself. As vaccine hesitancy increases, vaccination rates drop, and the incidence of the vaccine-preventable infection begins to rise again. Maintaining high immunization rates in the community is the key to optimize protection of individuals from vaccine-preventable infections. Protection at the community level is achieved through individual immunization, and when vaccine rates are high enough, herd immunity prevents index cases from spreading to cause outbreaks.

Most parents believe that vaccines are important to their child's health, have confidence in vaccine safety and efficacy, and agree to fully immunize their child as recommended. However, there are an increasing number of families who are refusing or delaying vaccination and/or insisting on following immunization schedules that do not conform to current recommendations [1, 2]. A large reason for vaccine delay is that parents feel they do not have sufficient information to make vaccine-related decisions. Without confidence in their own ability to weigh the benefits and risks of

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vaccination, some begin to develop distrust in the vaccination program [3]. While parents refer to a variety of sources for healthcare-related information, including the Internet, books, television, newspapers, and/or family and friends, it is the healthcare provider who is consistently reported by parents as the most credible source for vaccine information [4–7]. The importance of established, trusting relationships between providers and parents in optimizing vaccine uptake cannot be understated.

A trusted provider, one who has confidence in their vaccine knowledge, is consistently able to identify with the child and parent as individuals, and listen to and address their concerns in a comprehensive manner, plays a crucial role in influencing medical decisions made by parents [8]. Each provider-patient-parent encounter involves a unique set of vaccine attitudes and concerns that stem from personal experience, trust in the healthcare system, and understanding about vaccines and vaccine-preventable diseases. Parents generally expect that communication with their healthcare provider offers open discussion about vaccine topics, without judgement. Parents expect providers to be receptive to their concerns and to provide clear answers to their questions [3]. Providers, on the other hand, report decreased job satisfaction specifically related to increases in parental vaccine hesitancy and the associated need to spend an additional 10–20 minutes or more per visit [2, 9].

Effective provider-parent communication can motivate parents toward vaccination, yet providers receive little training as to how to best deliver this information [8, 10]. Not only is the quality of information being relayed important, but the manner with which it is delivered requires careful consideration. Providers should avoid using a confrontational, dismissive, or rushed approach, pay close attention to their use of body language, and make efforts to minimize distractions while answering questions and providing vaccination advice [8].

Initiating Vaccine Discussions

1. *Providers should be confident in the process of vaccine development and testing for safety and efficacy in disease prevention. Providers should be able to effectively communicate this information to their patients and parents.*

Vaccine information should be delivered in lay term avoiding medical jargon that is specifically tailored to address the questions and concerns expressed by the parents. It is especially important to present the known benefits and risks of the vaccine(s) in question. A brief summary of the disease being prevented can be helpful. All providers should be prepared to respond to the most common immunization concerns voiced by parents (see Table 39.1) [2, 6, 11, 12]. Providers who are able to convey authoritative vaccine information in a straightforward manner are viewed by parents as confident and trustworthy.

Educational material should be readily available to parents as a supplement to any information provided during the encounter (Table 39.2). Written materials can be provided prior to the vaccine encounter so that parents have time to review and

Table 39.1 Most commonly reported parental vaccine concerns

Parental vaccine concerns
Pain associated with multiple injections at one visit
Belief that child receives too many vaccines in the first 2 years of life
Misperception that vaccination may lead to learning disability or autism
Concern regarding unsafe vaccine ingredients
Belief that vaccines are not thoroughly tested for safety prior to approval
Belief that vaccines are given for diseases the children would not get anyway
Belief that vaccines are more dangerous than the diseases they prevent

Table 39.2 Online vaccine education materials

Vaccine education materials for parents
cdc.gov/vaccines/hcp/conversations/resources-parents.html
Immunize.org/handouts/discussing-vaccines-parents.asp
Healthychildren.org/English/safety-prevention/immunizations/pages/default.aspx
How to create a culture of immunization slide deck
cdc.gov/vaccines/hcp/conversations/your-practice.html

ask questions before the vaccination appointment. Distributing written vaccine information to parents during the prenatal encounter and at the newborn's office visits at 1–2 weeks and 1 month of age invites proactive discussions of the importance of immunizations prior to the first outpatient encounter for vaccine administration around 2 months of age [13].

2. *Build a proactive, office-wide culture of immunization confidence* [14].

Inconsistent vaccine messages within a practice negatively affect vaccine uptake. It is critical that all office staff members, from the front office staff to the providers in the examination rooms, understand the importance of vaccines in disease prevention. Mixed or discordant messages about vaccines from those working in the office lead to confusion and promote vaccine hesitancy.

A. Educate all office staff on the importance of supporting immunization recommendations, the current practice-specific vaccination rates, and the role of each member of the practice in creating this office-wide philosophy. Resources to assist in this effort are available from agencies such as the Centers for Disease Control and Prevention and the American Academy of Pediatrics. Materials are designed so they can be customized to the needs of the end users.
B. Develop a single practice-wide immunization policy and share it with the staff and parents of the practice.
C. Assign an immunization champion to keep the team current on new or evolving vaccine recommendations.

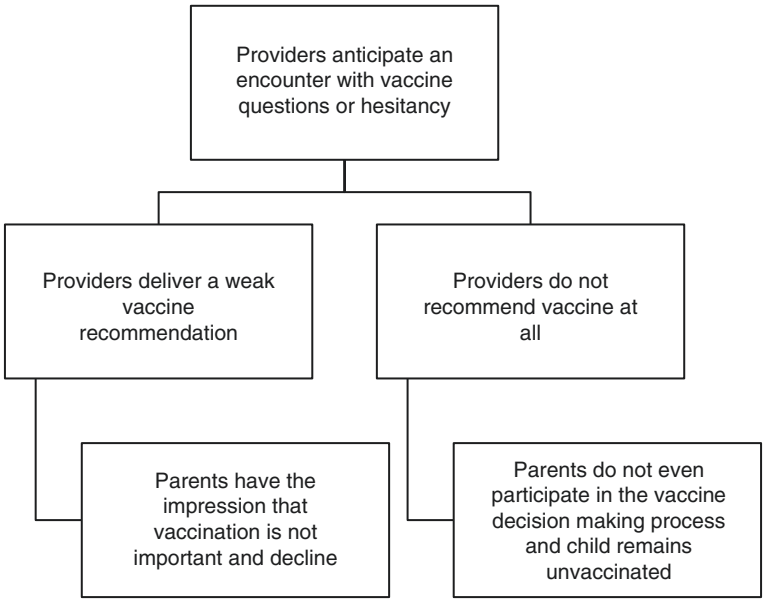

Fig. 39.1 Effects of overestimating parental vaccine hesitancy in medical encounters

D. Encourage and be prepared to answer parents' vaccine questions.
E. Be mindful to make vaccine education material, such as vaccine schedules and vaccine information sheets, easily accessible to parents.

3. *Provide strong and consistent vaccine recommendations to all eligible patients.*

Provider recommendation is the single most commonly cited factor associated with vaccine acceptance. The strength of that vaccination recommendation further influences vaccine uptake [15, 16]. In general, providers tend to overestimate parental vaccine concerns [17], which can impact the frequency and quality of their vaccine recommendations and ultimately the vaccine decisions made by the parents (Fig. 39.1). Parents and patients report that they are more likely to accept vaccines if their doctors state that the vaccination is important to their child's health [15].

Presumptive Versus Participatory Vaccine Recommendations

Providers typically convey their vaccine recommendations in one of two ways (Table 39.3) [16, 18]. The preferred technique is a presumptive recommendation. This approach is a direct statement of the vaccines recommended and presumes that the parents are ready to accept vaccines for their child. This strategy presents vaccination as the accepted medical norm. In contrast, the participatory approach adds question or uncertainty to the parents' vaccine motivations and offers them a choice

Table 39.3 Presumptive versus participatory vaccine recommendations

Presumptive vaccine recommendation	Participatory vaccine recommendation
Assumes the parents will accept vaccines	Questions whether parents will accept vaccines
Makes statement of vaccines in need	Offers the possibility of vaccination
First-person recommendation (I recommend)	Third-person recommendation (The AAP recommends)
Uses words such as "strongly recommend" or "is important to health"	Offers the possibility of vaccination at a later date or mentions vaccine without recommendation
Examples of initiating the vaccine discussion	
Your child is due for 3 vaccines today	Do you want vaccines for your child today?
I strongly recommend your child get these vaccines today	Have you thought about shots for your child?
The vaccines we will give today are important to protect your child from life-threatening infections	Do you want to think about the shots your child needs and come back on another day to get vaccinated?

to accept or decline vaccine. Initiating the vaccine discussion with a presumptive recommendation is more likely to result in vaccine acceptance than the use of a participatory recommendation [16]. Maintaining this strong vaccine recommendation despite a parent's initial hesitance is also associated with increased vaccine acceptance.

For some patients, it may be beneficial to combine the strong recommendation with an anecdote emphasizing vaccine benefits or successes [19]. Even stating that the provider's children have been vaccinated sends the message that the provider strongly believes in the importance of vaccines. Physicians report greater success in achieving vaccine acceptance using messages of their own personal choices and experiences [2].

Continuing Vaccine Discussions with Hesitant Parents

1. *Maintain strong vaccine recommendations.*

Standing by the strong recommendation in a non-confrontational manner emphasizes the importance of vaccines to the child's health. Parents are more likely to accept vaccinations when providers maintain a strong vaccine recommendation, even despite initial parental resistance [16].

Examples

He really needs these vaccines today to protect him from these serious infections.

I still strongly recommend that she get these shots today. I am worried that she may get one of these preventable infections.

Vaccine Questions Do Not Equal Vaccine Refusal

Parents who have questions about vaccines are asking because they consider their provider to be a credible source for the information. Having a vaccine question does not equate to vaccine resistance or vaccine refusal. Listening to and acknowledging the parent's questions, without judgment, builds trust in the provider-parent relationship and opens discussions for deeper concerns that need to be addressed. Ask about sources of the concerns, paraphrase what the parents asked, and repeat back to the parents to ensure understanding of the questions to be answered. Acknowledge their fears and their desires to do what is best for their children. A disconnect between the parents' expectations and the providers' assumptions may result in a counterproductive encounter with little room for discussion [8].

A key is to provide answers to the parents' questions in easy to understand language (Tables 39.4 and 39.5). If the parents are concerned about pain with injections, discuss strategies to minimize pain, including but not limited to breastfeeding or administering sweet-tasting solution to infants or using distracting techniques for an older child while vaccines are administered [21, 22]. Discussions should include both the benefits and risks of vaccination as well as the risks associated with remaining unimmunized and vulnerable to vaccine-preventable diseases. Nearly half of parents who are initially vaccine hesitant ultimately accept vaccines after hearing the rationale for vaccination [16]. If a parent asks a question that cannot be answered at that visit, it is appropriate to inform them that you need to review the information and postpone the discussion to a later date. Most often, initially hesitant parents who go on to accept vaccines state that the change in vaccine intention was due to information provided by the child's healthcare provider [23]. Vaccine education resources should be on hand and readily available, in case they may be of further help to the parents (Table 39.2).

Table 39.4 Examples of provider responses to parent vaccine questions [20]

Parent question	Provider response (CDC tip sheet)
Are vaccines safe for my child?	Yes. Millions of children receive vaccines each year. We have a vaccine safety monitoring system that ensures vaccines are as safe as possible
Isn't natural immunity better than immunity from vaccines?	Babies may get some temporary immunity from mom during pregnancy. This immunity doesn't last very long. After the protection is gone, your baby may get one of these diseases if not vaccinated
Why do vaccines start so early?	We vaccinate babies because their young age put them at the highest risk of being hospitalized or dying from these infections
Is it safer to come up with an alternate vaccine schedule so they are not getting too many shots at one time?	Alternate vaccine schedules have not been studied to see if they are as safe and protective against these diseases. It is best to continue with the standard recommended vaccine schedule

Table 39.5 Key points to highlight during communication tailored to address specific parental vaccine concerns

Vaccines protect from infections that can make individuals very sick. Sometimes infected people need to be hospitalized, and some die from infection
Vaccines are tested over many years before they are licensed for use. Vaccine safety continues to be monitored after licensure
Vaccines are very safe. The most common reactions to vaccines are mild and include redness and tenderness at the site of injection
There is no link between MMR vaccine or thimerosal and autism
Vaccines do not overload the immune system. Even when receiving multiple vaccines in a single visit, the baby only receives a small proportion of antigens they encounter on daily basis
There is no known benefit to altering or delaying the vaccination schedule. Not following the recommended schedule leaves the baby vulnerable to these severe diseases
Young children are at a high risk of complications to infections that lead to hospitalizations and death. Vaccinating at a young age protects these babies from this severe disease
The ingredients in vaccines help to keep them safe, without contamination, and are effective in preventing disease
While immunity from natural infection may be better for some diseases, there is also a risk of serious complications from infection that can be prevented by vaccination

Persistent Vaccine Hesitancy

Keeping the conversation open with vaccine-hesitant parents is essential to allowing the opportunity for vaccine acceptance in the future. Asking open-ended questions and listening to and acknowledging parental concerns will allow the provider to more deeply understand parental vaccine attitudes. Further vaccine discussion should be tailored to the parents' needs, expectations, and experiences leading to their concerns, understanding that some parents may be motivated by science, while others may be more influenced by personal stories. For example, one study found that using information from the Centers for Disease Control and Prevention corrected vaccine misperceptions but reduced vaccine intent among families with the least favorable vaccine attitudes [24].

Motivational Interviewing

Originally developed in an effort to reduce substance abuse, motivational interviewing has been shown to also be effective in changing behaviors in other health-related fields, including vaccinations among the vaccine hesitant [25]. Motivational interviewing is a patient-centered, collaborative approach, based on building rapport and trust, focused on understanding and strengthening an individual's motivation for and commitment to changing behaviors [25]. The process of motivational interviewing involves:

A. Asking open-ended questions

It seems like you have concerns about the vaccines due today. Would it be ok for us to discuss this?

You seem like you have questions about the vaccines your daughter needs. Would you mind sharing your concerns?

B. Reflective listening and affirmation

For parents who are unsure about vaccinations, repeat back both the concerns they have stated followed by the reasons they would accept vaccines. For parents who are not ready to accept vaccinations, repeat back and affirm ("I understand why you feel this way") the vaccine concerns they have stated.

C. Informing and advising if permission is given by the parent

May I share some information with you that may ease some of your concerns?

D. Making a strong recommendation

This is why I strongly recommend that your daughter receive these vaccines today. What do you think?

Patients appreciate being listened to and having their concerns acknowledged without confrontation or judgment. Using the technique of motivational interviewing helps the provider to identify the parent's vaccine concerns or misperceptions and gear their education to what the parent is willing and ready to hear.

Conclusion

It is important to remember that a single method to counter vaccine hesitancy will not apply to everyone. Communication strategies need to be tailored to individual parents' vaccine attitudes and behaviors. There will be patients who, despite the use of these communication strategies, will still decline or delay vaccinations. It's important to keep lines of communication open for further vaccine conversations. Parents should be informed that discussions about vaccines will continue during future visits. Each medical encounter offers a new opportunity for discussion. Many parents who initially decline a vaccine will eventually accept a strong, consistent recommendation.

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