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diffuse ground-glass opacities. Consolidation, predominantly in the lower lobes and peripherally, is a frequent finding. Mortality rates for patients requiring intensive care and mechanical ventilation have improved significantly over the course of the pandemic but remain ≥20% for patients who progress to that disease severity. Risk factors for severe disease and poor outcomes include age ≥65 years, morbid obe sity, diabetes, cardiovascular or cerebrovascular disease, hypertension, chronic obstructive lung disease, and chronic kidney disease. Severe disease and mortality is also increased in males and pregnant women.

Treatment currently includes supportive care, antiviral therapy, anti-inflammatory therapy, and anticoagulation prophylaxis or treat ment. Patients with respiratory distress are hypoxemic but maintain pulmonary mechanical functioning; thus, invasive mechanical ventila tion should be delayed until other interventions have been exhausted. In a meta-analysis, dexamethasone or other glucocorticoids reduced 28-day mortality in patients with severe COVID-19 disease compared with standard care: 32% and 40%, respectively (odds ratio, 0.66; 95% confidence interval, 0.53–0.82). Thus, dexamethasone (6 mg IV/PO daily) is indicated for patients with hypoxemia. IL-6 inhibitors such as tocilizumab may be indicated for patients with rapidly escalating oxy gen requirements. Secondary bacterial pneumonia in COVID-19 is not common, and antibacterial agents should not be routinely prescribed. With the availability of highly effective vaccines, prevention is the most important strategy to control COVID-19. Vaccination has reduced progression to severe disease and hospitalization. In addition, treat ment with antiviral agents such as nirmatrelvir/ritonavir or remdesivir can reduce risk of progression to severe disease and hospitalization for patients with mild symptoms. Hantavirus Pulmonary Syndrome (See also Chap. 215)

Hantavirus pulmonary syndrome has been documented in the United States since 1993 (primarily the southwestern states, west of the Mis sissippi River), Canada, and South America. Most cases occur in rural areas and are associated with exposure to rodents. Patients present with a nonspecific viral prodrome of fever, malaise, myalgias, nausea, vomit ing, and dizziness that may progress to pulmonary edema, respiratory failure, and death. Hantavirus pulmonary syndrome causes myocardial depression and increased pulmonary vascular permeability; there fore, careful fluid resuscitation and use of pressor agents are crucial. Use of venoarterial extracorporeal membrane oxygenation (ECMO) for severe Hantavirus pulmonary syndrome has been successful and should be considered. Aggressive cardiopulmonary support during the first few hours of illness

can be life-saving in this high-mortality syn drome. The early onset of thrombocytopenia may help distinguish this syndrome from other febrile illnesses in an appropriate epidemiologic setting. PART 5 Infectious Diseases SUMMARY Acutely ill febrile patients with the syndromes discussed in this chapter require close observation, aggressive supportive measures, and—in most cases—admission to intensive care units. The most important task of the physician is to distinguish these patients from other infected febrile patients whose illness will not progress to fulminant disease. The alert physician must recognize the acute infectious disease emer gency and proceed with appropriate urgency. ■ ■FURTHER READING Hasburn R: Progress and challenges in bacterial meningitis: A review. JAMA 328:2147, 2022. Hua C et al: Necrotising soft-tissue infections. Lancet Infect Dis 23:e81, 2023. Kollef MH et al: Timing of antibiotic therapy in the ICU. Crit Care 25:360, 2021. Theilacker C et al: Overwhelming postsplenectomy infection: A prospective multicenter cohort study. Clin Infect Dis 62:871, 2016. Wilder-Smith A et al: Dengue. Lancet 393:350, 2019.

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Principles of

Immunization The birth of vaccinology is often ascribed to Edward Jenner’s obser vation in the 18th century that infection of milkmaids with cowpox, termed vaccinia and hence the term vaccination, conferred protection against smallpox. This discovery catalyzed a sequence of events that ultimately led to the eradication of smallpox, one of the most disfigur ing and lethal infections of humans. Vaccination programs are among the most impactful and cost-effective health interventions. Consid ered to be one of the greatest achievements in public health, vaccines are estimated to have averted more than 37 million deaths globally between 2000 and 2019. This represents a 45% reduction in deaths compared with a scenario of no vaccination. Vaccines are defined as inactivated or attenuated pathogens or com ponents of a pathogen (nucleic acid, protein) that, when administered to the host, stimulate a protective response by the cells of the immune system (Table 128-1). Adjuvants may be added to vaccines to nonspe cifically boost the immune response. Vaccination is the act of introduc ing a vaccine into the body to induce protection from a specific disease. Immunization is a process by which a person becomes resistant to a particular infectious disease or pathogen, usually by vaccination. How ever, immunity may also be conferred passively. ■ ■IMMUNE RESPONSES TO VACCINES While Chapter 360 provides an overview of immune responses, a few additional concepts are relevant to vaccines. Vaccines targeted for new infectious pathogens, such as SARS-CoV-2 at the onset of the pandemic, or vaccines given to infants and young children without prior expo sure to a pathogen, will trigger a primary immune response with peak antibody titers achieved several weeks after administration. It may take several doses of a vaccine to induce a priming response, particularly if the vaccine is inactivated or a toxoid. Live, attenuated vaccines gener ate more robust responses and generally only require one or two doses. Subsequent booster doses of vaccines trigger a secondary response with rapid induction of antibody within several days to a week. Vaccines administered against common pathogens, such as influenza, will trigger secondary booster responses since all older children and adults would have encountered influenza virus and/or will have received past influ enza vaccines. Immune responses to vaccines are generally measured in terms of serum antibody levels, but mucosal antibodies, cellular responses, and memory cells also are stimulated after vaccination and function to prevent disease and sustain immunity. Passive Immunity Vaccines stimulate active immunity—inducing an immune response by the host to the vaccine antigen—and

will be the focus of most of this section. Passive immunity also serves an impor tant role in prophylaxis. Passive immunity results from the exogenous introduction of antibodies. Originally, such antibodies came from another person or animal and were relatively short-lived. Examples included hepatitis A, tetanus, and rabies immunoglobulins. The more recent capability to generate monoclonal antibodies to infectious pathogens, along with methods to extend the half-life of antibodies, has expanded their prophylactic use. Monoclonal antibodies targeted to SARS-CoV-2 strains were beneficial during the pandemic, par ticularly in populations who did not mount robust immune responses to vaccines. Currently, monoclonal antibodies are routinely used in infants and young children for the prevention of respiratory syncytial virus (RSV) infections, and their use in adults will likely continue or increase in the years ahead. These agents are evaluated for their safety and efficacy using similar methodology as in vaccine studies but will not be discussed extensively in this chapter. Another type of passive antibody protection is maternal immu nization, whereby vaccines are given to the pregnant person and the

TABLE 128-1 Categories and Characteristics of Approved Vaccines and Adjuvants EXAMPLES OF APPROVED VACCINES ADVANTAGES DISADVANTAGES TECHNOLOGY DESCRIPTION Live attenuated Weakened or attenuated form of the pathogen that causes disease Measles, mumps, rubella, varicella, oral poliomyelitis, nasal influenza vaccine, oral rotavirus Inactivated Pathogens or toxins rendered nonreplicating through heat or chemical processes (may be entire pathogen or parts of it) Inactivated poliomyelitis, hepatitis A, whole-cell pertussis, tetanus and diphtheria toxoids Purified protein-based (split or subunit) Specific parts of the pathogen are produced in culture Influenza, acellular pertussis, recombinant shingles Polysaccharide– protein conjugates Type of subunit vaccine that combines a polysaccharide antigen with a protein carrier to improve immune responses Pneumococcal, meningococcal, typhoid, Hib Virus-like particles One or more proteins arranged to closely resemble viruses Hepatitis B, HPV Broad and robust immunity Noninfectious Replicating viral vector Replicating, nonpathogenic viruses deliver nucleic acid to host for in vivo production of antigen Vesicular stomatitis virus– based Ebola vaccine Nonreplicating viral vector Replication-deficient nonpathogenic viruses deliver nucleic acid to host for in vivo production of antigen Chimp adenovirus–based COVID-19 vaccine Nucleic acid (DNA, RNA) Lipid nanoparticles deliver nucleic acid to host for in vivo production of antigen COVID-19 mRNA vaccines Rapid development and manufacturing timelines Effective and safe for majority of population TECHNOLOGY EXAMPLES CURRENT USE MECHANISM OF ACTION Alum Aluminum hydroxide or aluminum phosphate Multiple vaccines—e.g., HPV, hepatitis A, DTaP Oil-in-water emulsion AS03, MF59 Influenza Increases recruitment of innate immune cells and enhanced antigen uptake Toll-like receptor (TLR) agonists Monophosphoryl lipid A (MPL) Cytosine-phosphate-guanine (CpG) HPV (AS04—MPL and alum) Shingles (MPL and QS21) Hepatitis B (CPG) Saponins QS-21, Matrix-M Malaria vaccines (MPL, QS21, and Matrix-M) COVID-19 (Matrix M) Delivery platforms Lipid nanoparticle (LNP) COVID-19 mRNA vaccines Improved lymphatic transport enhances antigen uptake and presentation antibody generated by their immune system is transferred to the fetus through the placenta. Examples of vaccines given to the pregnant person, largely for the protection of the baby, include tetanus, acellular pertussis, and RSV vaccines. Other vaccines given to pregnant persons for protection of both the mother and the baby include influenza and COVID-19. ■ ■VACCINE FORMULATIONS Vaccine formulations have evolved over time (Fig. 128-1). In the late 19th to mid-20th century, methods to inactivate whole bacteria and detoxify bacterial toxins led to early whole-cell typhoid and cholera vaccines, as well as diphtheria and tetanus toxoids. The discovery that repeated passage of organisms in unnatural hosts could select for avirulent strains

provided the foundation for Bacille Calmette-Guérin (BCG) vaccine for tuberculosis and yellow fever vaccines. The abil ity to grow viruses in cell culture informed the development of live

VACCINES Mimics natural infection Effective priming with durable immunity Large-scale manufacturing capabilities Single or two doses often sufficient Difficult to reach desired level of attenuation Safety concerns for certain populations (e.g., pregnant women, immunocompromised patients) Stability Induces broad immune response to multiple antigens Large-scale manufacturing capabilities Reactogenic Multiple doses needed May require adjuvant Highly specific immune response Noninfectious Low reactogenicity Ease of production Multiple doses may be needed May require adjuvant Limited cross-protective immunity Conjugate protein may also provide immunity (e.g., tetanus) Strong immune responses in all ages, including infants Technically difficult and costly to produce Individual conjugate required for each vaccine serotype Technically difficult to produce Lower stability Induces broad immune response High manufacturing scalability Immunity to vector may dampen immune response Safety of vector—may not be suitable for certain immunocompromised populations CHAPTER 128 Induces broad immune response High manufacturing scalability Immunity to vector may dampen immune response Principles of Immunization May require several doses/boosters to maintain immunity Reactogenic ADJUVANTS Possible depot effect; increases antibody production Activates TLR to enhance antigen presentation and enhance adaptive immune responses Prolongs antigen bioavailability and enhances antigen signals attenuated vaccines against poliomyelitis, measles, mumps, rubella, and varicella viruses between 1950 and 1980. During the next three decades, the fields of biotechnology and molecular genetics burgeoned. New vaccines that circumvented poor immune responses to bacterial polysaccharides by their conjugation to proteins included pneumococ cal, Haemophilus influenzae type b, and meningococcal vaccines. The development of recombinant DNA technology allowed antigens to be expressed in cell lines, leading to hepatitis B and human papillomavirus (HPV) vaccines. With the COVID-19 pandemic, a new generation of vaccines and platform technologies emerged with unprecedented speed. While many of these new technologies had been in development for years, the public health need and the influx of government resources pro pelled these technologies through the approval and deployment phases at an accelerated pace. The gene-based (e.g., mRNA) and vectorbased technological advancements have been most visible. For years,

Major Conceptual and Technological Advances Vaccinology Era: Concept of immunity Immunology Virology Production: Eggs Animals Chikungunya

SARS-CoV-2 RSV

Ebola (VSV) HPV Rotavirus Varicella Jpn. Enceph. Hepatitis A Hepatitis B Rubella Mumps Adenovirus Measles Poliovirus Influenza Yellow fever Rabies Smallpox

Viral Vaccines

1820 1840 1860 1880 1900 1920 1940 1960 1980 2000 2020 2040 2060 2080 2100 FIGURE 128-1 Major conceptual and technological advances for viral vaccines in the vaccinology era. (Reproduced with permission from Barney Graham.) mRNA technology was limited by its instability and inefficiency of in vivo transfection, until the lipid nanoparticle (LNP) delivery system improved

the RNA-based vaccine delivery. Further, new adjuvants and structure-guided antigen design of the SARS-CoV-2 spike protein transformed the field. These technological advances were accompanied by innovations in trial design, real-time safety surveillance and effec tiveness evaluations at a massive scale, transmission modeling, and sophisticated analysis of immunologic correlates of protection. PART 5 Infectious Diseases Adjuvants Adjuvants are substances that are added to vaccines to enhance the immune responses to the antigen. Replicating viral vaccines generally do not need adjuvants, but they are often needed in inactivated or protein-based vaccines. Early emulsions, such as Freund’s adjuvant, stimulated humoral and cellular responses but were very reactogenic. Alum, the oldest adjuvant formulated as aluminum hydroxide or phosphate, has been in use for more than 90 years. It pro motes humoral immune responses, has an excellent safety record, and is included in many of the vaccines administered to infants and young children. As the understanding of molecular mechanisms involved in immune responses progressed, new adjuvants were developed. Oilin-water emulsions, including MF59 and AS03, contain squalene as a vehicle and enhance innate and adaptive immune responses. They are approved in combination with certain influenza vaccines. As Toll-like receptors were discovered, adjuvants were developed to combine with the newer, more purified protein and subunit vaccines. The Toll-like receptor agonists TLR4 and TLR9 have been included in licensed vac cines. These include monophosphoryl lipid A (MPL) with alum (AS04) for HPV and cytosine-phosphate-guanine (CpG) for hepatitis B. More recently, MPL has been combined with a natural saponin component, QS-21, for use in the recombinant shingles vaccine and the RTS,S malaria vaccine. Likewise, a saponin-based adjuvant, Matrix-M, is approved for use in the recombinant COVID-19 vaccine and the R21 malaria vaccine. In addition to enhancing delivery of mRNA vaccines, LNPs induce inflammation and have an adjuvanting effect. Additional adjuvants are being studied in experimental vaccines, and others will likely be included in licensed products in the future. ■ ■VACCINE DEVELOPMENT The pathway from vaccine discovery to population impact encom passes a broad set of components summarized in Fig. 128-2. These steps include understanding of the burden of the pathogen to be prevented and the immune factors involved in protection; antigen dis covery; preclinical animal studies advancing to human trials assessing immune responses, safety, and efficacy; vaccine licensure and policymaking; implementation; and finally monitoring of vaccine uptake, impact, and safety after implementation. Well-established systems and processes, both pre- and postlicensure, ensure that vaccines are safe and effective.

Structure-based design Mol Bio Cells Chemical synthesis Bioreactors Structural biology Gene-based delivery High-throughput sequencing Rapid manufacturing Rapid gene synthesis Single cell analysis including B cell lineages Human mAb isolation Nanoparticle display Custom animal models Multi-omics glycobiology Cell biology Imaging Establishing the Need for an Immunization Generally, before extensive resources are expended to formulate and develop vaccines, it is important to establish the burden of disease, the population at risk for the disease, and the mechanisms involved in protection. Much of this can be done through existing surveillance systems, such as those at the Centers for Disease Control and Prevention (CDC), that measure the burden of disease and the population at risk. In certain situations, vaccines are developed before their potential benefit is fully known, based on the theoretical risk to the population. Examples of these vac cines are those directed against potentially pandemic influenza strains or other pandemic threats. Phases of Vaccine Development Like the development of phar maceutical agents, vaccine development progresses through preclinical and three distinct clinical stages: phases 1, 2, and 3. Under specific circumstances where phase 3 trials may be delayed or challenging, controlled

human infection models (CHIM) may be part of the devel opment pathway. Initially, research focuses on the identification of an antigen or antigens with the potential to stimulate a protective immune response that will prevent disease upon encounter with the pathogen. For most vaccines the generation of an antibody directed to an important com ponent of the pathogen is associated with protection. Examples are vaccines directed against the attachment proteins such as the spike in SARS-CoV-2 vaccines or against toxins such as the tetanus or diph theria vaccines. These proposed vaccines are administered in preclini cal studies to small animals, often mice; their immune responses are measured, and safety established. Generation of immunity against the pathogen must be demonstrated, or the vaccine will not undergo fur ther testing. Toxicity studies are conducted in animals to detect safety signals, and some vaccinated animals are challenged with wild-type pathogens after vaccination to establish protection. Phase 1, 2, and 3 Clinical Trials When preclinical studies in animals demonstrate that the vaccine stimulates an immune response and there are no toxicity concerns, vaccines then undergo phase 1 clini cal trials. In the United States, prior to the onset of phase 1 studies, the vaccine manufacturer must submit an Investigational New Drug (IND) application to the U.S Food and Drug Administration (FDA) that outlines the vaccine approach prior to the start of the study. When the IND is approved, phase 1 trials can begin. These trials enroll limited numbers of healthy participants, usually fewer than 100 individuals and generally between the ages of 18 to approximately 55 years, pri marily to test the safety of the new experimental vaccine, although immunogenicity also is measured. Subjects enrolled in phase 1 studies are well informed about the risks and the potential benefits of the vac cines and are screened for their ability to be monitored closely and to adhere to rigorous safety assessments. These assessments include daily

BURDEN OF ILLNESS STUDIES TO INFORM PUBLIC HEALTH NEED/MARKET NEED ASSAY and PROCESS DEVELOPMENT, FORMULATION AND MANUFACTURING PRECLINICAL STAGE PHASE I PHASE II PHASE III/HUMAN CHALLENGE STUDIES DISCOVERY & EXPLORATORY STAGE • PATHOGENESIS • IMMUNE RESPONSES • ANTIGEN DESIGN • ADJUVANTS • ANIMAL MODELS • ORGANOID SYSTEMS • TRIAL DESIGN, EXECUTION, ANALYSIS • IMMUNOGENICITY AND CO-ADMINISTRATION • SAFETY AND EFFICACY • CORRELATES OF PROTECTION AND SYSTEMS BIOLOGY • MICROBIOME AND -OMICS BIOINFORMATICS, STATISTICS, COMPUTATIONAL BIOLOGY FIGURE 128-2 Vaccine development: a continuum from antigen discovery to population impact. (Figure created by Kathleen M. Neuzil, MD, MPH.) monitoring of local and systemic adverse events with measurement of temperature and size of redness and swelling at the injection site, and with detailed assessments of systemic reactions that may result in limitations of normal activities after vaccine administration. Phase 1 studies often involve a dose-ranging component such that the first enrolled subjects are administered the lowest doses of vaccine, and, if tolerated, the doses are increased. Many phase 1 studies have indepen dent Data Safety and Monitoring Committees (DSMCs) composed of vaccine- and pathogen-specific experts, independent of the study site investigators and sponsors of the study, who assess the reactions and approve the advancing of the dose level based on the safety profile of the administered vaccines. Phase 1 studies have halting rules such that if severe reactions are seen, the study will be stopped. These halting rules might include hospitalization for a vaccine-related adverse event, or a severe reaction attributed to the vaccine in several participants. All participants in the phase 1 trials will have immunologic studies per formed as well to determine the magnitude of the antibody responses and, in some situations, the function of the antibody generated and/or T lymphocyte responses to the vaccines. At the conclusion of the phase 1 trial, the safety and immunogenicity data are reviewed and

presented to the FDA for approval to advance to phase 2 studies. Phase 2 studies involve several hundred subjects and often have a larger age range than that evaluated in phase 1. They expand the safety profile and assess immune responses in larger numbers of subjects. Again, meticulous attention to safety assessment is included in these studies, often with independent DSMCs to assess the reaction profile. Finally, if phase 2 studies confirm safety and immunogenicity in the expanded populations and with approval of the FDA, phase 3 trials can begin. Phase 3 trials are designed to determine whether the vaccines will prevent a predefined endpoint, generally the prevention of laboratory-

confirmed disease with the vaccine-directed pathogen. Subjects enrolled in phase 3 studies are randomized and blind to the receipt of either another irrelevant vaccine or a control agent, usually consisting of a placebo. Subjects and investigators are blind to group assignment and remain so throughout the phase 3 trial. After administration of the vaccine, study participants are followed closely, and if they develop predefined symptoms of disease they are tested for the presence of the pathogen. The determination of the primary endpoint of the study and the level of vaccine efficacy is the study goal. When feasible, one of the additional outcomes of the phase 3 trial is the determination of a serologic correlate of protection. For example, a correlate could be an antibody level associated with protection from disease. This

would facilitate evaluation of additional vaccines in population groups not involved in the original trial and would not require assessment of actual protection from disease. While this is a highly sought-after end point, it is often not possible to determine. Prior to submission of the vaccine for licensure there will need to be lot-consistency assessments that determine that several lots of the vaccines can be made that are consistent in their safety and immunogenicity endpoints. Controlled Human Infection Models (CHIMs) CHIMs may be part of the development pathway of a vaccine. Such models involve intentionally infecting healthy participants with a pathogen and fol lowing them carefully for development of disease. The evaluation of vaccines in these models may provide unique immunologic insights into correlates of protection, may establish a rapid pathway for downse lection of candidates to move to later-phase trials or to endemic areas, and may inform vaccine approval. For example, an oral cholera vaccine for travelers in the United States was approved by the FDA based on a controlled human challenge study that established efficacy against clinical cholera. The determination to use CHIM is made in consulta tion with the FDA and based on the premise that the size, complexity, and expense of a study—for example, a study of a cholera vaccine with a disease endpoint in travelers—would render a phase 3 trial infeasible and significantly delay the approval of the vaccine. Other well-established CHIMs that are used to assess vaccines include those for influenza, typhoid fever, shigellosis, and malaria. CHAPTER 128 Principles of Immunization Vaccine Licensure At the conclusion of the phase 3 efficacy trials and consistency lot testing, data are presented to the national regula tory authorities who ultimately will decide whether the vaccine will be licensed. In the United States, the FDA will require that the product be labeled for how it will be used, based on the data generated in the phase 3 clinical trial. They will seek the guidance of a standing advisory group of experienced clinicians, vaccine experts, epidemiologists, and other subject matter experts, called the Vaccine and Related Biological Prod ucts Advisory Committee (VRBPAC), to advise whether the vaccine should be

licensed. The FDA poses specific questions to the VRBPAC that relate to both vaccine efficacy and safety. All the adverse events reported in clinical trials are comprehensively presented and discussed with the committee. Any significant safety concerns raised may delay licensure, and additional safety studies may be proposed. Ultimately, although the FDA will seek the guidance of the VRBPAC, it will decide independently whether to license the vaccine and what requirements will be placed on that license. The inclusion of children and pregnant women in vaccine licensure will generally not occur unless the vaccines

Vaccine development and testing Submission to FDA for a Biologics License Application FDA licensure Vaccines and Related Biological Products Advisory Committee Advises Advisory Committee on Immunization Practices Advises CDC consideration ACP's Board of Regents consideration Recommendations for use published in MMWR Insurance or Medicare coverage Uptake and financing PART 5 Infectious Diseases Public sector FIGURE 128-3 Development and dissemination of vaccine recommendations and policies for adults. ACP, American College of Physicians. (From Annals of Internal Medicine, JC Smith et al: Immunization Policy Development in the United States: The Role of the Advisory Committee on Immunization Practices, Vol. 150, No. 1. Copyright © 2009 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.) have been specifically studied in those populations for their safety and immunogenicity. This process is outlined in Fig. 128-3. The Advisory Committee on Immunization Practices (ACIP) Process Following licensure of vaccines by the FDA, the group that has played the major role in determining recommendations for vaccina tion in the United States is the Advisory Committee on Immunization Practices (ACIP) of the CDC. The ACIP provides recommendations for the use of vaccines in children, adolescents, and adults and issues a yearly vaccination schedule for all age groups and clinical conditions. Since 1995, the ACIP, American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians, American College of Obstetricians and Gynecologists, and other professional organizations have worked together to coordinate vaccine schedules and policies. Members of the ACIP have expertise in a variety of disciplines related to the charge to the committee, including clinical medicine, epidemiology, vaccinology, public health, implementation science, and economic evaluations. The ACIP charter states, "Committee delib erations on use of vaccines to control disease in the U.S. shall include consideration of disease epidemiology and burden of disease, vac cine efficacy and effectiveness, vaccine safety, the quality of evidence reviewed, analyses and implementation issues." The committee may revise or withdraw their recommendation(s) regarding a particular vaccine as new information on disease epidemiology, effectiveness or safety, economic considerations, or other issues becomes available. Once approved by the CDC Director, the ACIP recommendations are published in the Morbidity and Mortality Weekly Report (MMWR) and become official CDC immunization use policy. Among the responsi bilities of the ACIP is prioritizing use in settings where there are short ages of vaccines so that the highest-priority groups for whom vaccine might be recommended can receive them. The immunization delivery system in the United States consists of both public and private providers. Since 1993 the Vaccines for Children

Advises ACP's Adult Immunization Initiative Physician Advisory Board Recommendations for use published in Annals Private sector (VFC) Program provides vaccines to children whose parents or guard ians may not be able to afford them. Serving as one of the nation's most important contributors to health equity, the program helps ensure that all children have a better chance of getting their recommended vaccinations on schedule and staying healthy. In contrast, most vaccines for adults are delivered by private healthcare providers, although many of the vac cines

are purchased using federal or other government funds. This may contribute to the relatively low coverage of adult vaccines compared with childhood vaccines. The Affordable Care Act requires private insurers to cover ACIP-recommended vaccines at in-network providers. Vaccine Policy and Postlicensure Surveillance Once a vac cine is licensed for use in the United States and recommendations are made by the ACIP, systems need to be put in place to provide access to vaccines and to remove barriers to access, such as cost. Ongoing monitoring of vaccine effectiveness and safety are critical to evaluate issues such as waning immunity, to identify groups at heightened risk for vaccine failure, and to determine adverse events following vaccina tion that are causally related, especially rare events that could not be detected in prelicensure trials. Estimations of the burden of causally vaccine-related adverse events can then be weighed against the benefits of the vaccine to determine if any changes in recommendations are warranted. Disease surveillance is crucial to determine who continues to acquire disease, risk factors for disease, and the role of vaccine fail ure versus failure to vaccinate in disease prevention. After Vaccine Implementation Prelicensure clinical trials usually enroll thousands of participants. However, there are questions that can not be answered in these studies. These questions include (1) What is the duration of protection from disease, and is there a need for boosters? (2) What is the effectiveness of the vaccine in population groups not evalu ated in the clinical trials? Effectiveness can be measured in observational studies post-licensure by comparing disease incidence in vaccinees

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