

29. Immunization

Edina H. Moylett, MD,^a and I. Celine Hanson, MD^b *Houston, Tex*

The medical dictionary defines immunization as the “protection of susceptible individuals from communicable diseases by the administration of a living modified agent, a suspension of killed organisms, or an inactivated toxin.” This elegant description can be expanded to include twenty-first century approaches to immunization that include recombinant technology, reassortment virus techniques, live vectors, DNA vaccines, and the expansion of the field to encompass noncommunicable diseases such as Alzheimer’s disease, autoimmunity, and tumor immunogenetics. Integral to the success of immunization is our knowledge of the immune system’s memory of antigens, yet our understanding of this fundamental feature remains limited. On a global scale, communicable diseases remain the number-one cause of morbidity and mortality; hence Jenner’s pioneering work with its birth in 1796 still has a challenging and exciting future. (*J Allergy Clin Immunol* 2003;111:S754-65.)

Key words: Vaccine, immunoglobulin, immunization schedules

James Phipps and Joseph Meister, the respective recipients of the original smallpox and rabies vaccines, played key roles in the development of the science of vaccinology. In 1796, Dr Edward Jenner used material from cowpox lesions to vaccinate an 8-year-old boy and in 1885, Dr Louis Pasteur vaccinated a 9-year-old boy who had been bitten by a rabid dog. The impact of immunization on a global health scale is evidenced in the work of Salk and Sabin,^{1,2} creators of the inactive and live attenuated polio vaccines, respectively. Because of the ensuing dramatic decline in paralytic poliomyelitis, the development of the vaccine has rightfully been hailed as one of the great accomplishments of medical science. Universal polio immunization ultimately resulted in eradication of disease as the result of naturally occurring polioviruses in the United States by 1979 and in the entire Western Hemisphere by 1994. Polio-free status in the United States was certified by an independent commission in 1994. Global polio eradication is now a scientifically attainable feat, and, barring political disruption of health care delivery systems, the question soon to be addressed will be when to discontinue routine childhood immunization in the United States and globally.

Adverse events have hampered the development of certain important childhood vaccines. The initial respiratory syncytial virus (RSV) vaccine and, more recently, the rotavirus vaccine are two such examples. Administration

Abbreviations used

ACIP: Advisory Committee on Immunization Practices
CDC: Centers for Disease Control and Prevention
DTaP: Diphtheria, tetanus, and acellular pertussis
FDA: Food and Drug Administration
HIV: Human immunodeficiency virus
IG: Immunoglobulin
IPV: Inactivated polio vaccine
IVIG: Intravenous immunoglobulin
MMR: Measles, mumps, and rubella
OPV: Oral polio vaccine
RSV: Respiratory syncytial virus
VAERS: Vaccine Adverse Events Reporting System
VAPP: Vaccine-associated paralytic poliomyelitis
WHO: World Health Organization

of the alum-precipitated formalin-inactivated RSV vaccine developed in the 1960s resulted in an adequate level of protective antibodies but was followed by the unfortunate outcome of augmented disease in vaccinees during subsequent natural infection.³ RSV infection persists as one of the leading causes of morbidity in the pre-school age population. Rotavirus quadrivalent vaccine was licensed on August 31, 1998, for vaccination of infants. Owing to an apparent increase in the incidence of postlicensure intussusception among vaccine recipients, in July 1999, the Centers for Disease Control and Prevention (CDC) recommended that health care providers and parents postpone use of the rhesus rotavirus vaccine-tetavalent.⁴ Rotavirus continues as the most common cause of severe gastroenteritis among children worldwide.

In May 1980, the World Health Assembly certified that the world was free of naturally occurring smallpox.⁵ Controversy existed regarding destroying remaining laboratory strains of smallpox; however, recent political events, most notably those of September 11, 2001, have prompted the possibility of reintroducing routine immunization against this horrific disease for those previously vaccinated and for vaccine-naïve populations. The current US childhood immunization schedule recommends that children receive vaccinations against up to 13 different infectious agents from birth to the teenage years; the adult schedule recommends additional dosing throughout adult life and for special populations periodic influenza and pneumococcal vaccines.⁶ How many more vaccines are to be added will depend on scientific advancement and availability of resources for their distribution.

IMMUNIZATION

Protection against microbial infection may be provided passively or actively. Passive immunization follows the

From ^aBaylor College of Medicine and ^bTexas Department of Health, Houston, Tex.

Reprint requests: Edina H. Moylett, MD, Texas Children’s Hospital, Department of Allergy and Immunology, 6621 Fannin St (MC-FC330.01), Houston, TX 77030.

© 2003 by Mosby, Inc. All rights reserved.

0091-6749/2003 \$30.00 + 0

doi:10.1067/mai.2003.83

administration of pooled human plasma rich in antibodies directed against certain pathogens. These products may be formulated for intramuscular immunoglobulin (IG) or intravenous IG (IVIG) administration; additionally, they may contain high titers of antibody against a specific pathogen, hyperimmune globulin. Traditionally, IG was indicated as prophylaxis after measles or hepatitis A infection. Intravenous or intramuscular formulations with high titers against certain infections are also available, such as RSV-IVIG (Respigam; Medimmune Inc, Gaithersburg, Md), varicella zoster immunoglobulin (VZIG), hepatitis B immunoglobulin (HBIG), and cytomegalovirus-IVIG (Cytogam; Medimmune Inc). These therapies may be given as preexposure prophylaxis, Respigam, Cytogam, or as postexposure prophylaxis, most notably HBIG, VZIG, tetanus-IG and rabies-IG. The advantage of this form of intervention is the immediate acquisition of humoral immunity in the recipient; conversely, the disadvantage is that no memory is inferred and therefore long-lasting protection is not provided. An additional concern with passive immunizations relates to potential risk for transmission of infectious agents, considering the human origin of these products. Although modern sterilizing techniques and additional virucidal steps make this an unlikely event, infectious transmission has occurred often before routine accessibility of serologic testing for a specific pathogen.⁷

In addition to Respigam as prophylactic therapy against RSV infection, Palivizumab (Synagis; Medimmune Inc) is a humanized monoclonal antibody licensed for use in a defined population of "at-risk" pediatric patients. The product contains humanized monoclonal antibody directed against the F protein of RSV that exhibits neutralizing activity. It is administered monthly by intramuscular injection and has been shown to reduce RSV-associated hospitalizations by 55%.⁸ Protective immunity after this mode of therapy is immediate but short-lived because regular administration is required during the RSV season.

Outside of therapy for specific infectious diseases, IG, or more frequently, IVIG, has been used to provide humoral immunity to patients with underlying defects in antibody production or infection, for example, severe combined immunodeficiency, common variable immunodeficiency, or specific antibody deficiency states. A higher dose of IVIG (2 g/kg) is indicated for immunomodulating therapy, as in patients with certain autoimmune or inflammatory conditions.

Passive immunization may also be provided as antitoxin in therapy of equine or human origin. Antitoxins immediately neutralize circulating toxins, allowing the adaptive arm of the immune system a chance to provide antigen specific neutralizing antibodies. Within the United States, equine botulinum antitoxin may be used as an alternative to human-derived product when clinically necessary. Outside of the United States, equine-derived product is available as adjunctive therapy for tetanus, rabies, and diphtheria infections. There are strict guidelines regarding the administration of equine antiserum therapy, owing to the significant risk of developing serum sickness.

TABLE I. Features of effective vaccines

Safety	Vaccine must not result in infection in the recipient
Protective	Vaccine must protect the recipient against illness resulting from exposure to the live pathogen
Provides prolonged protection	Protection against illness should be long-lasting if not life-long
Induces neutralizing antibody	Neutralizing antibody which plays a key role in defending the host against invading pathogens (especially true for preventing virus entry into host cells) should be generated for vaccine recipients
Induces protective cellular response	Cellular host response, an important mode of defense especially against intracellular pathogens, eg, mycobacteria, should be produced
Practical considerations	Acceptable side-effect profile Low cost of production Ease of storage Ability to produce large quantities Ease of administration

Active immunization depends on two primary factors: an antigenic vaccine and an intact immune system in the recipient. Several requirements are necessary for vaccines to be effective (Table I). A variety of different antigenic vaccine components are available and will be discussed in the subsequent review.

VACCINE TYPES

Table II outlines vaccines that are suggested by the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians for routine delivery to children and adults in the United States. Many more vaccines are licensed in the United States and have indications for use in special clinical settings. Table III outlines the 25 organisms for which vaccines exist, the vaccine type, their potential for adverse events, and clinical setting for contraindications. Vaccine types vary and include attenuated live viral or bacterial vaccines, killed (subunit, toxoid or conjugate) vaccines, and recombinant, DNA, or vector vaccines. Each of these uses varying methods of promoting an immune response and will be discussed below.

Killed or inactivated

A killed or inactivated vaccine, as the name implies, consists of a killed preparation of the pathogen, bacterial or viral, eliminating the chance of reversion to the "infectious" wild type. Traditionally, chemicals such as formalin are used in the deactivation process. Determinants of antigenicity remain intact, permitting an immune

TABLE II. Recommended and minimum ages and intervals between vaccine doses*

Vaccine and dose number	Recommended age for this dose	Minimum age for this dose	Recommended interval to next dose	Minimum interval to next dose
Hepatitis B1†	Birth–2 mo	Birth	1–4 mo	4 wk
Hepatitis B2	1–4 mo	4 wk	2–17 mo	8 wk
Hepatitis B3§	6–18 mo	6 mo¶		
Diphtheria and tetanus toxoids and acellular pertussis (DTaP)1	2 mo	6 wk	2 mo	4 wk
DTaP2	4 mo	10 wk	2 mo	4 wk
DTaP3	6 mo	14 wk	6–12 mo	6 mo¶¶
DTaP4	15–18 mo	12 mo	3 y	6 mo¶¶
DTaP5	4–6 y	4 y	—	—
Haemophilus influenzae, type b (Hib)1†††	2 mo	6 wk	2 mo	4 wk
Hib2	4 mo	10 wk	2 mo	4 wk
Hib3§§	6 mo	14 wk	6–9 mo	8 wk
Hib4	12–15 mo	12 mo	—	—
Inactivated poliovirus vaccine (IPV)1	2 mo	6 wk	2 mos	4 wk
IPV2	4 mo	10 wk	2–14 mo	4 wk
IPV3	6–18 mo	14 wk	3.5 y	4 wk
IPV4	4–6 y	18 wk	—	—
Pneumococcal conjugate vaccine (PCV)1††	2 mo	6 wk	2 mo	4 wk
PCV2	4 mo	10 wk	2 mo	4 wk
PCV3	6 mo	14 wk	6 mo	8 wk
PCV4	12–15 mo	12 mos	—	—
Measles, mumps, and rubella (MMR)1	12–15 mos	12 mo	3–5 y	4 wk
MMR2	4–6 y	13 mo	—	—
Varicella***	12–15 mo	12 mo	4 wk***	4 wk***
Hepatitis A1	≥2 y	2 y	6–18 mo	6 mo¶¶
Hepatitis A2	≥30 mo	30 mo	—	—
Influenza†††	—	6 mo	1 mo	4 wk
Pneumococcal polysaccharide (PPV)1	—	2 y	5 y§§§	5 y
PPV2	—	7 y§§§	—	—

*Combination vaccines are available. Use of licensed combination vaccines is preferred over separate injections of their equivalent component vaccines (Source: CDC. Combination vaccines for childhood immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP). MMWR 1999;48:5). When administering combination vaccines, the minimum age for administration is the oldest age for any of the individual components; the minimum interval between doses is equal to the greatest interval of any of the individual antigens.

†A combination hepatitis B-Hib vaccine is available (Comvax, manufactured by Merck Vaccine Division). This vaccine should not be administered to infants <6 weeks of age because of the Hib component.

§Hepatitis B3 should be administered ≥8 weeks after Hepatitis B2 and 16 weeks after Hepatitis B1, and it should not be administered before age 6 months.

¶Calendar months.

**The minimum interval between DTaP3 and DTaP4 is recommended to be ≥6 months. However, DTaP4 does not need to be repeated if administered ≥4 months after DTaP3.

††For Hib and PCV, children receiving the first dose of vaccine at age ≥7 months require fewer doses to complete the series (see CDC. Haemophilus b conjugate vaccines for prevention of Haemophilus influenzae, type b disease among infants and children two months of age and older: recommendations of the ACIP. MMWR 1991;40:1–7, and CDC. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2000;49:1–35).

§§For a regimen of only polyribosylribitol phosphate-meningococcal outer membrane protein (PRP-OMP, PedvaxHib, manufactured by Merck), a dose administered at age 6 months is not required.

¶¶During a measles outbreak, if cases are occurring among infants <12 months of age, measles vaccination of infants ≥6 months of age can be undertaken as an outbreak control measure. However, doses administered at age <12 months should not be counted as part of the series (Source: CDC. Measles, mumps, and rubella — vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 1998;47:1–57).

***Children 12 months to 13 years of age require only one dose of varicella vaccine. Persons ≥13 years of age should receive two doses separated by ≥4 weeks.

†††Two doses of inactivated influenza vaccine, separated by 4 weeks, are recommended for children 6 months to 9 years of age who are receiving the vaccine for the first time. Children 6 months to 9 years of age who have previously received influenza vaccine and persons ≥9 years of age require only one dose per influenza season.

§§§Second doses of PPV are recommended for persons at highest risk for serious pneumococcal infection and those who are likely to have a rapid decline in pneumococcal antibody concentration. Revaccination 3 years after the previous dose can be considered for children at highest risk for severe pneumococcal infection who would be <10 years of age at the time of revaccination (see CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 1997;46:1–24).

Adapted from MMWR 2002;51(RR-2):1–35.

TABLE III. Vaccines currently licensed in the United States

Organism	Disease	Vaccine type(s)	Specific contraindications*	Specific adverse events
Bacteria				
<i>Bacillus anthracis</i>	Anthrax	Inactivated		
<i>Bordetella pertussis</i>	Whooping Cough	Inactivated, Subunit	Encephalopathy within 7 days of receipt of a previous dose	Febrile seizures Hypotonic-hyporesponsive state Fever >104.8°F Prolonged crying All of the above are significantly less frequent after acellular pertussis
<i>Borrelia burgdorferi</i>	Lyme disease	Inactivated		
<i>Clostridium tetani</i>	Tetanus	Toxoid		
<i>Corynebacterium diphtheriae</i>	Diphtheria	Toxoid		
<i>Haemophilus influenzae B</i>	Meningitis, Epiglottitis, Pneumonia	Inactivated protein conjugate		
<i>M tuberculosis</i>	Tuberculosis	Live attenuated	Pregnancy Immunodeficiency†	Disseminated <i>Mycobacterium bovis</i> (immunodeficiency)
<i>Neisseria meningitidis</i>	Meningitis	Inactivated‡		
Serogroup A, C, Y and W	Sepsis			
<i>Salmonella typhi</i>	Typhoid fever	Inactivated Live	Pregnancy (live vaccine)	
<i>Streptococcus pneumoniae</i>	Meningitis	Inactivated		
	Sepsis	Polysaccharide, Protein conjugate		
	Pneumonia			
	Otitis media			
<i>Vibrio cholerae</i>	Cholera	Inactivated		
<i>Yersinia pestis</i>	Plaque	Inactivated		
Viruses				
Adenovirus	Respiratory disease	Live attenuated	Pregnancy Immunodeficiency	
Hepatitis A	Liver disease	Inactivated		
Hepatitis B	Liver disease	Inactivated (DNA recombinant)	Anaphylaxis to Baker's yeast	Anaphylaxis (approx one event per 600,000 vaccine doses distributed)
	Liver cancer			
Influenzavirus	Respiratory disease	Inactivated, whole virus or subunit		(Table continued on next page)

*Anaphylactic reaction to a vaccine or vaccine component contraindicates future use of that vaccine or vaccine constituent.

†Hematologic and solid tumors, congenital immunodeficiency, and long-term suppressive immunotherapy.

‡Protein conjugate vaccine (serogroup C) licensed in the United Kingdom.

§SSPE, Subacute sclerosing panencephalitis

§CRS, Congenital rubella syndrome.

¶HIV-infected children without evidence of immunosuppression (CDC class 1) may receive the Varicella zoster virus vaccine.

In general, neither OPV nor IPV should be given to pregnant women unless immediate protection is needed, in which case OPV is the vaccine of choice.

response to develop. Examples of this type of vaccine include inactivated whole organisms (eg, cholera, pertussis), detoxified exotoxin (eg, diphtheria and tetanus toxoids), soluble capsular material either alone (eg, pneumococcal polysaccharide), or covalently linked to carrier proteins (eg, *Haemophilus influenzae* type B conjugate vaccines) or purified extracts of some component or components of the organism (eg, subunit influenza and subunit acellular pertussis vaccines). Figure 1 provides a schematic of interactions between a polysaccharide-protein conjugate and the host's immune system, specifically antigen presenting cells, type 2-helper cells, cytokines, and B cells, to produce specific antibody.⁹ Immunity after the administration of inactivated vaccines is typically humoral and may be assessed by measuring postimmunization neutralizing antibodies. Neutralizing antibodies (IgG) are produced on reexposure to the immunizing antigen resulting from the rapid expansion of memory B cells and subsequent control of the infection. Inability of a killed vaccine component to replicate

in the host minimizes triggering the arm of the immune system responsible for eliciting cytotoxic cellular responses. An additional component of protection afforded by live attenuated vaccines, which is lacking with inactive vaccines, is the ability of certain live viral vaccines to induce production of secretory IgA at mucosal barriers. Increased safety is an obvious feature of killed vaccines. However, life-long protection is not inferred after inactivated vaccine administration, necessitating repeat or "booster vaccines."

Conjugate vaccines

Many bacteria, including *Haemophilus spp* and *Streptococcus pneumoniae*, have an outer capsule composed of polysaccharides and are of particular pathogenic importance in children younger than 2 years of age. The most effective defense against these microorganisms is opsonization of the polysaccharide coat with antibody. The aim of vaccination, therefore, is to elicit antibodies against the polysaccharide capsule of the bacteria. Unlike

TABLE III. Continued

Organism	Disease	Vaccine type(s)	Specific contraindications	Specific adverse events
Japanese encephalitis virus	Encephalitis	Inactivated		
Measles virus	Respiratory tract, SSPE	Live attenuated	Pregnancy Immunodeficiency Anaphylaxis to neomycin or gelatin	Fever ($\geq 103^{\circ}\text{F}$) 6 to 12 days after vaccination in 5% to 15% Simple febrile seizures Thrombocytopenia Encephalopathy (<1 per million doses)
Mumps virus	Parotitis Orchitis Meningitis	Live attenuated	Pregnancy Immunodeficiency	Orchitis Parotitis
Poliovirus	Poliomyelitis	Inactivated (Salk) Live attenuated (Sabin)	Pregnancy (live) Immunodeficiency (live) Immunodeficient house hold contact (live) Anaphylaxis to neomycin or streptomycin (inactivated)	Vaccine associated paralytic poliomyelitis has been reported after administration of the live virus vaccine
Rabies virus	Rabies	Inactivated		
Rubella virus	CRS§	Live attenuated	Pregnancy Immunodeficiency	Arthralgia (25%) Transient arthritis (10%)
Vaccinia virus	Smallpox	Live attenuated	Pregnancy Immunodeficiency	
Varicella zoster virus	Chickenpox	Live attenuated	Pregnancy Immunodeficiency Anaphylaxis to neomycin or gelatin	
Yellow fever virus	Yellow fever	Live attenuated	Pregnancy Immunodeficiency Egg allergy	

the thymus-dependent response observed with protein antigens (second signal for B-cell proliferation provided by helper T cells), polysaccharide antigens alone mount a T-cell-independent immune response resulting in low-affinity high-avidity IgM production. This response is sub-optimal in young patients because of the immaturity of the immune system. To overcome this, *Haemophilus* and *Streptococcus pneumoniae* have successfully been conjugated to carrier proteins to which the immune system has already been exposed (eg, tetanus and diphtheria toxoids). The subsequent immune response to these particular polysaccharide-protein antigens becomes T-cell-dependent with generation of immunologic memory (Fig 1).⁹ Conjugated *Haemophilus influenzae* B vaccines, licensed since 1987, have resulted in a dramatic reduction in pediatric infection related to this organism¹⁰; additionally, the pneumococcal conjugate vaccine, licensed for use in 2000, has had significant impact on disease prevalence secondary to the serotypes contained in the vaccine.¹¹

Subunit vaccines

Subunit vaccines are frequently made with the use of recombinant DNA technology. The currently available subunit hepatitis B vaccine was developed by cloning the hepatitis B surface antigen (HBsAg) gene into yeast, leading to synthesis of HBsAg within the yeast cell.¹² Similar recombinant DNA technology is applied to the recently licensed subunit *Borrelia burgdorferi* vaccine against Lyme disease.¹³ The immunogenicity of peptide

vaccines may be augmented through the formation of aggregates such as immunostimulating complexes, virus-like particles, antigen-coated beads, or lipid-encapsulating antigen under various conditions.

Live attenuated

One of the key components of a successful vaccine is its ability to mimic natural infection in eliciting a complete immune response. Attenuated live vaccines have the ability to induce limited viral replication of adequate amplitude to elicit a protective immune response without resulting in significant clinical infection. The majority of antiviral vaccines currently in use in the United States are live attenuated vaccines. Traditionally, attenuation is achieved by passage of the virus in nonhuman cell lines. Attenuated virus strains used in vaccines are selected for their instability or difficulty in growing in human cells. Other mechanisms of attenuation include passage of virus in conditions (temperature, pH, and so forth) not favorable for replication in normal human host conditions. An example is the candidate intranasal cold-adapted influenza virus vaccine,¹⁴ which, although not yet licensed for use, has been documented as safe and efficacious in clinical trials to date.¹⁵ Because live attenuated vaccines mimic natural infection, the immune response achieved is usually life-long, eliminating the need for booster series. Moreover, mucosal immunity and cellular responses can be achieved, improving immunity against natural infection. The duration of immunity after live

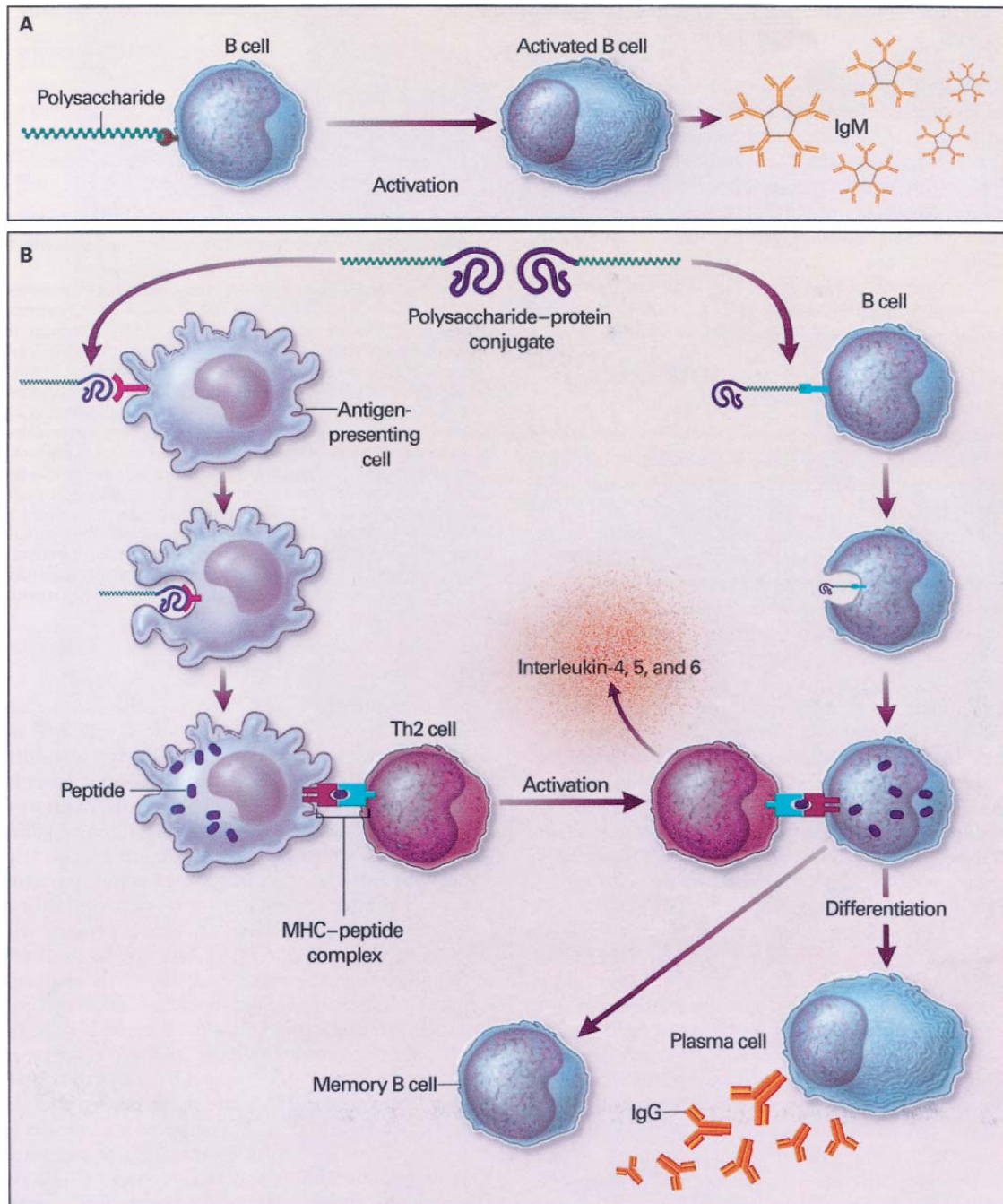


FIG 1. Antibody responses to polysaccharide antigens and polysaccharide-protein conjugates. **A**, Polysaccharide antigen binds to an IgM receptor on the surface of a B cell in lymphoid tissues. Once B cells are activated, they produce and then secrete IgM antibody molecules. The individual Fab segments of the IgM molecule have only a moderate affinity, but because there are 10 such segments, an IgM molecule has a high avidity. **B**, In contrast, some polysaccharide-protein conjugates will be taken up by dendritic cells (antigen-presenting cell), which present peptides from the protein portion of the conjugate to type 2 helper (T_H2) cells. Other conjugate molecules bind to B cells that have IgM receptors specific for the carbohydrate moiety and will undergo endocytosis and be processed by the B cell; the resulting peptides will be expressed with class II MHC molecules on the surface of the B cell. This complex is recognized by the activated T_H2 cell, which then secretes interleukin-4, interleukin-5, and interleukin-6. These cause the B cell to differentiate and express IgG molecules with polysaccharide specificity. These cells mature in the lymphoid follicles; only cells that express very high-affinity IgG molecules become plasma cells and secrete high-affinity IgG that binds strongly to the encapsulated bacteria and mediates opsonic activity and complement-mediated bactericidal activities. The formation of memory B cells is a critical component of protective immunity against certain encapsulated pathogens. Adapted with permission from the *New England Journal of Medicine*.⁸

viral vaccines remains unclear; however, as a booster MMR vaccine is currently recommended.

Live attenuated vaccines pose some risk for immunocompromised patients because they may behave as opportunistic pathogens. An example would include vaccine-associated paralytic poliomyelitis (VAPP), which may occur when the live attenuated poliovirus vaccine (OPV) is administered to an immunocompromised patient or to a contact of an immunocompromised patient.¹⁶ In this setting, vaccine virus strains replicate in the gut unchecked and may revert to wild-type with disastrous consequences. In addition, healthy infants may occasionally have paralysis as well as their susceptible contacts. Two types of poliovirus vaccine exist today, inactivated (IPV) or Salk and OPV or Sabin. Given that the only case of recent polio disease in the Americas was associated with the use of the OPV, and the fact that the risk for VAPP outweighs the benefit from the OPV administration, IPV is now recommended for all doses of the primary pediatric vaccine series.¹⁷ As affirmed by the Advisory Committee of Immunization Practices (ACIP), OPV remains the vaccine of choice for mass vaccination to control polio outbreaks.¹⁷ All live attenuated vaccines are associated with a risk for reversion to wild-type and ensuing dissemination.

FUTURE VACCINE TYPES

DNA vaccines

DNA-based vaccination is a novel technique to efficiently stimulate humoral and cellular immune responses to protein antigens. DNA that encodes foreign antigens may be incorporated into plasmids or vectors.¹⁸ In animal models, plasmid-coated beads have been blasted across the skin by means of a gene gun, then taken up by dendritic cells with a resultant T-helper cell response and subsequent antibody production. Attenuated viruses or bacteria may be used as vectors containing DNA encoding antigen from another infectious agent. The DNA contained in the vector codes for important T- and B-cell-specific viral or bacterial epitopes with resultant cellular and humoral immune responses. Leading candidate virus vectors include poxviruses (eg, vaccinia, fowlpox, and canarypox) that have the ability to replicate but not infect human cells. Alternatively, adenovirus or *Salmonella spp* may be adapted to induce mucosal immunity. DNA technology has also been applied to replace virulent genes contained within a viral or bacterial genome sequence while maintaining genes necessary to stimulate an immune response; the mutant genes are of sufficient size to minimize the risk of reversion to wild type.¹⁹ Genetic DNA vectors consist of closed-circle DNA containing a promoter, the foreign DNA insert, a terminator, and a marker gene. Possible adverse events subsequent to DNA vaccination include the formation of anti-DNA antibodies, unexpected consequences of persistent expression of foreign antigen, and the potential for a transformation event.

Peptide vaccines

Peptides representing part of an antigen may be used as a vaccine. The advantages include the fact that the product is chemically defined, stable, safe, and contains only important B-cell and T-cell-specific epitopes. Conversely, it is difficult to replicate exact immunogenic epitopes, and peptides are subject to proteolysis in addition to being poorly immunogenic for both humoral and cellular responses. In vivo processing through natural antigen-processing pathways may be achieved by conjugating peptides with protein carriers or viral vectors. Additionally adjuvants, such as lipid carriers, load peptides into the host cell cytoplasm, allowing MHC class I-restricted T-cell responses to occur. Peptide vaccines have revolutionized the field of tumor immunogenetics.²⁰

ADJUVANTS

A vaccine is only as successful as the quality of the immune response it stimulates. Certain antigens, namely peptides and polysaccharides, are poorly immunogenic. In addition, host factors, such as extremes of age and poor nutritional status, reduce the immunogenicity of a vaccine. An adjuvant is any substance that improves the immunogenicity of substances mixed with it. The use of adjuvants to enhance vaccine immunogenicity was introduced in the 1920s.²¹ Despite extensive research in the field to date, only aluminum-containing compounds, such as alum, aluminum hydroxide, and aluminum phosphate, are approved for use in human beings. Adjuvants alter the immune response to antigen in a variety of ways (Table IV).²²⁻²⁵ Of the proposed activities of adjuvants, two of the more important immune-modulating functions include conversion of soluble proteins into particulate matter that is more easily ingested by antigen-presenting cells and the use of microbial constituents that signal macrophages or dendritic cells to become more efficient at antigen presentation.

Nonmammalian DNA containing unmethylated CpG motifs (differ from mammalian CpG in frequency and extent of cytosine methylation) has been shown to induce strong T_H1-polarized immune responses.²³ This technology has been applied to vaccinology. First, aeroallergen immunotherapy in which CpG or immunostimulatory DNA sequences act as adjuvants and switch the immune response from T_H2 to a nonatopic T_H1 state. Additionally, CpG motifs are being explored as adjuvants for a variety of vaccines to augment immunogenicity.²⁶

SCHEDULES

Childhood

The childhood vaccination schedule is published annually, and recommendations are coordinated through (a) the ACIP, (b) the American Academy of Family Physicians, and (c) the American Academy of Pediatrics. The schedule includes delivery of first doses of a single antigen (Hepatitis B) at birth/2 months, 6 vaccine anti-

TABLE IV. Vaccine adjuvants

Adjuvant type	Activity	Example
Inorganic salt ²¹	Depot effect, delays release of antigen, enhanced macrophage uptake	Aluminum hydroxide, calcium phosphate, beryllium hydroxide
Delivery systems	Depot effect, delays release of antigen, enhanced macrophage uptake	Incomplete Freund's adjuvant (oil-in-water emulsion)
Bacterial products	Delayed release of antigen, enhanced uptake by macrophages, induction of co-stimulators in macrophages	Complete Freund's adjuvant (oil-in-water emulsion with dead mycobacteria), BCG, plasmid
DNA ²²	Potentiate clinical expansion of T cells responding to a specific peptide not coded for by the DNA	Unmethylated CpG motifs
Immune stimulatory complexes (ISCOMs) ²³	Delivers antigen to cytosol, allows induction of cytotoxic T cells	Matrix of Quil A containing viral proteins
Cytokines ²⁴	Stimulates cytotoxic T-cells or dendritic cells	GM-CSF, Interleukins -12, -1, and -2.

gens (diphtheria, tetanus, pertussis, *Haemophilus influenzae* type B, polio, and 7 serotypes of *Streptococcus pneumoniae*) at 2 months, and 4 vaccine antigens (measles, mumps, rubella and varicella) at 12 to 15 months of age. Initial vaccination for each of these antigens requires subsequent booster doses (Table II) to provide optimal production of neutralizing antibody in the recipient. Hepatitis A vaccine is recommended for children over 2 years living in endemic areas of the United States; influenza vaccine is currently recommended for children 6 months of age and older with chronic diseases, for example, chronic lung disease. In the future, recommendations for childhood delivery of influenza vaccine, like guidelines for adults, will be suggested for children 6 to 35 months of age who are reported in the literature to have the highest morbidity from influenza disease.^{27,28} Delivery of this complex childhood immunization schedule has provided significant challenges for both care givers and health care providers. Strategies to enhance delivery of all recommended dosing includes taking advantage of all missed opportunities and offering an accelerated schedule for infants and children who could not meet the outlined dosing schedules. Table II provides minimal dosing intervals for each vaccine. Some caveats to accelerated dosing are notable. Children 5 years of age or older should not routinely be offered *Haemophilus influenzae* type B vaccine because they have probably already seroconverted after natural infection. Minimal intervals are longer (6 months) for series delivery after DTaP3 and DTaP4; DTaP4 does not need to be repeated if already given at least 4 months after DTaP3.

Multiple manufacturers provide varying formulations (antigen quantity and processing/preparation methodology) of the commercially available vaccinations outlined in the United States childhood vaccination schedule. Interchangeability of vaccines has been documented for some but not all vaccine antigens. For example, Anderson et al²⁹ documented equivalent seroconversion with multiple formulations of *H influenzae* type B vaccines. Other data support interchangeability of commercially available Hepatitis A and Hepatitis B vaccines. In contrast, the literature does not completely support interchangeability of vaccines containing acellular pertussis antigen.

Implementation of the current childhood vaccine schedule can result in 4 to 5 injections for any single child at early visits (2, 4, or 6 months). Combination vaccines are licensed in the United States but represent only a minority of commercially available products. To enhance vaccine delivery and minimize the number of infections needed, manufacturers are actively pursuing licensure for vaccines containing five or greater antigens. Development of combination vaccines is currently limited by a number of factors including availability of compatible and appropriate antigen stabilizing agents.

Adult

Certain vaccines should be kept updated in the adult population. Persons ≥ 65 years of age and all adults with underlying medical conditions that place them at increased risk for pneumococcal infection should receive ≥ 1 dose of the 23-valent pneumococcal vaccine. Similarly, all persons ≥ 50 years of age should receive an annual influenza immunization, in addition to all adults with underlying medical conditions that place them at an increased risk for severe influenza infection.³⁰ Booster immunizations with tetanus and diphtheria toxoids (Td) should be administered every 10 years after completion of the primary series. All adults born after 1956 should have received at least one dose of the MMR or have other evidence of immunity. All other adults born after 1956 at increased risk for measles transmission (eg, health care employees), college students, and those traveling to endemic areas should have documentation of receipt of two doses of MMR on or after their first birthday or other evidence of immunity. Immunization against Hepatitis A and B is recommended for those adults at increased risk for disease transmission/acquisition.

IMMUNOCOMPROMISED

Live attenuated vaccines (viral and bacterial) are generally not administered to immunocompromised individuals. However, as with every rule in medicine, caveats exist.

Primary inherited immunodeficiency syndromes generally result in a combination of humoral and cellular defects (eg, severe combined immunodeficiency syn-

drome, ataxia telangiectasia, Wiskott-Aldrich syndrome); however, certain conditions, such as Bruton's agammaglobulinemia, affect a single arm of the immune system. Secondary immunodeficiency can result from a number of conditions such as severe malnutrition, hematologic malignancy, chemotherapy, prolonged high-dose corticosteroids, or after HIV infection. Immunocompromised patients are at increased risk for development of disseminated disease after live attenuated vaccine administration.^{31,32} Therefore, all live viral vaccines are contraindicated for patients with severe impaired cellular immunity. However, individuals with hypogammaglobulinemia or dysgammaglobulinemia may receive varicella vaccine³³ and measles vaccine; however, OPV should not be administered to any patient with impaired humoral immunity.¹⁶ Additionally, OPV should not be administered to the household contacts of individuals with severely impaired immunity, given the risk for prolonged fecal shedding. Inactivated vaccines may be administered without adverse effects to patients with impaired immunity, although response may be suboptimal.

Certain caveats have arisen concerning HIV-infected individuals and administration of live attenuated vaccines. Given the increased risk for development of severe disease among HIV-infected patients after natural measles or varicella infection, the latter vaccines are recommended for HIV-infected patients without evidence of immunocompromise (CDC class N1 or A1, age-specific CD4+ lymphocyte percentages ≥ 25).^{34,35} OPV should not be administered to HIV-infected individuals.

Despite recent advances in immune reconstitution of patients with severe inherited immune defects, at this time insufficient data exist regarding general recommendations for administration of live attenuated vaccines to patients with restored immunity. No vaccine contraindications exist regarding immunizing patients with complement deficiencies; additionally, patients with phagocyte defects should not receive live bacterial vaccines.³⁶

The immunosuppressive effects of steroid treatment are unclear. The majority of clinicians consider a dose equivalent to either >2 mg/kg of body weight or a total of 20 mg/d of prednisone or equivalent for children who weigh >10 kg, when administered for >2 weeks as sufficiently immunosuppressive to raise concern regarding the safety of vaccination with live-virus vaccines.³⁷ In general, live-virus vaccines may be administered in the following circumstances: persons receiving short-term therapy (<2 weeks); low to moderate dose therapy; long-term, alternate-day therapy with short-acting preparations; maintenance physiologic dose of steroids or topically administered steroid therapy. A period of 2 to 4 weeks should elapse before administering live viral vaccines to patients after discontinuation of high-dose steroid therapy.

PREGNANCY

Although certain vaccines should not be administered during pregnancy, other vaccines are of direct benefit to both the fetus and mother. In general, live attenuated vac-

cines should not be administered to the mother during pregnancy because of a theoretical risk to the fetus. In a recent report following up on inadvertent administration of varicella virus vaccine to 58 women during their first or second trimester of pregnancy, there were no reports of congenital varicella in 56 live births.³⁸ Although limited by number, this report may serve to alleviate some anxiety after accidental immunization of pregnant women. Inadvertent administration of MMR or varicella virus vaccines to a pregnant patient is not an indication for termination. In relation to yellow fever vaccine, also a live attenuated vaccine, pregnant patients traveling to an endemic area should be immunized because risk to the fetus after infection outweighs possible adverse effects on the fetus after immunization.

No evidence exists to support risk to the fetus or mother after immunization with inactivated viral, bacterial vaccines, or toxoids. Td (reduced diphtheria content) toxoid is routinely indicated for pregnant women; partially immunized or nonimmune patients should complete the primary series. Pregnant patients in their second and third trimester are at an increased risk for severe influenza infection and should therefore receive the inactive vaccine if they are at ≥ 14 weeks' gestation at the onset of the influenza season. Maternal immunization during the influenza season may provide some added benefit to the newborn infant secondary to transplacental transfer of maternal antibodies. This method of indirect immunization of the newborn infant is under investigation for a variety of other pathogens, most notably group B streptococcus and RSV.³⁹

TRAVEL

A variety of resources are available to the international traveler, as well as the primary care provider, concerning immunizations that are recommended for travel to certain parts of the globe (Centers for Disease Control and Prevention Traveler's Health Hotline: 1-404-332-4559).⁴⁰ In relation to travel, there are three categories of immunizations: routine childhood immunizations, vaccines that are required for entry into certain member countries of the World Health Organization (WHO), and vaccines that may be of additional benefit to the traveler, depending on the travel destination.

Many countries require proof of vaccination with yellow fever vaccine by a WHO-approved site before entry. The vaccine is a live attenuated viral vaccine that is derived from chick embryo cultures. Immunity is conferred for up to 10 years. The vaccine should not be administered to patients allergic to eggs, immunocompromised patients, infants <4 months of age, or pregnant or lactating women. A relative contraindication exists for infants <9 months of age, in whom risks of disease acquisition need to be weighed against the risk, albeit remote, associated with vaccine administration. Despite recent reports of possible vaccine-related disease,⁴¹ the vaccine remains mandatory for travel to endemic areas.⁴²

Additional vaccines currently recommended for travel to certain destinations include hepatitis A vaccine,

typhoid fever vaccine, cholera vaccine, meningococcal vaccine, rabies virus vaccine, Japanese encephalitis virus vaccine, and the more recently licensed Lyme disease vaccine.⁴³ At the present time, the manufacture and sale of the only licensed cholera vaccine in the United States (Wyeth Ayerst) has been discontinued. It has not been recommended for travelers because of the brief and incomplete immunity provided. No cholera vaccination requirements exist for entry or exit in any country. Outside the United States, 2 additional vaccines are commercially available: an oral killed whole cell–cholera toxin recombinant B subunit vaccine (WC-rBS) and an oral live attenuated *Vibrio cholerae* vaccine (CVD 103-HgR). Both vaccines are safe and efficacious, and FDA approval is currently pending in the United States.⁴⁴

HEALTH CARE WORKERS

Health care workers are at risk for acquisition, as well as transmission, of infectious agents. Certain occupations within the health care system are associated with an increased risk; for example, anesthesia, general surgery, and dentistry are associated with a greater risk for transmission of blood-borne pathogens. Vaccine-preventable infections of special concern to those involved in health care delivery and especially pediatric practice include measles, mumps, rubella, hepatitis B, and varicella. Immunity to the latter infections should be documented before initiating employment in the health care setting. Additionally, annual influenza immunization should be offered to all employees to minimize the risk for influenza outbreaks. Health care workers may be a source for *Mycobacterium tuberculosis* and should therefore be tested annually to minimize exposure and spread of disease.

EFFECTS OF BIOTERRORISM EFFORTS ON IMMUNIZATION

The events of September 11, 2001, have affected all aspects of life in the 21st century. Successful global eradication of smallpox disease has come under serious threat. More alarmingly is the fact that concerns about smallpox as a differential diagnosis for a childhood vesicular rash are not as remote as before September 11. Additional infectious agents with potential for mass destruction include *Bacillus anthracis*, *Yersinia pestis*, *Francisella tularensis*, botulinum toxin, hemorrhagic fever viruses, and multi-drug resistant *Mycobacterium tuberculosis*. Vaccines are available in the United States against variola virus (smallpox), *B anthracis* (anthrax), and *Y pestis* (bubonic plaque), but immunization recommendations are confined to specific situations. Guidelines from the CDC address the release of smallpox vaccine in the event of bioterrorism⁴⁵; updated recommendations are available at the Infectious Disease Society of America (IDSA) website (www.idsociety.org). As per current CDC/IDSA recommendations, in the absence of naturally occurring smallpox, the general public should not be vaccinated before an attack. Preex-

posure immunization with anthrax vaccine is licensed for individuals 18 to 65 years of age who have a high likelihood of coming into contact with *B anthracis* (eg, laboratory personnel and abattoir workers), complete immunization guidelines are available from the CDC⁴⁶ and these recommendations are under current update.

ADVERSE EVENTS

Administration of any vaccine is associated with a risk, albeit rare, for an adverse event. Table III highlights specific, recognized adverse events that have been causally linked to specific immunizations. Not included in this table are adverse events with speculated association with certain vaccines, which at this time have not been confirmed.

In 1998, Wakefield et al⁴⁷ reported on a possible causal association between measles immunization, inflammatory bowel disease, and a pervasive developmental disorder. Combined with isolated parental reports, Wakefield's publication triggered several epidemiologic studies, culminating in a review by the Institute of Medicine. At this time, available epidemiologic data in addition to scientific data refute a correlation between MMR immunization, inflammatory bowel disease, and autism.^{48,49} Additionally, the worldwide increase in the prevalence of autism has not been mirrored by an increase in MMR immunization uptake. As a result of the concern surrounding the MMR vaccine, there was a documented decrease in immunization rates in the United Kingdom and Ireland, with an upsurge in the annual rates of measles infection.⁵⁰ Similar adverse publicity affected Hepatitis B immunization in France when isolated case reports suggested receipt of the vaccine as a cause of multiple sclerosis in previously healthy subjects. Since these initial reports, thorough epidemiologic studies have ruled out any relation between the onset or relapse of multiple sclerosis.⁵¹

In August 1998, the United States FDA licensed the first rhesus rotavirus vaccine against rotavirus infection, the most important cause of severe childhood diarrhea. Fourteen months later, the vaccine was withdrawn after an association was found with intussusception.⁵² Vaccine technology has moved from the use of monovalent attenuated animal rotavirus strains to the development of multivalent human-animal reassortment vaccines. Retrospective studies have failed to highlight a link between natural rotavirus infection and a risk for intussusception,⁵³ implicating the possibility of animal components as a cause for the complications. Until the safety of the rotavirus vaccine can be ensured, this highly effective and useful vaccine will remain shelved.

Thimerosal is a mercury-containing preservative that has been used as an additive in biologic agents and vaccines since the 1930s because it prevents bacterial and fungal contamination, particularly in multidose containers. Thimerosal was used as a preservative in the Hib, DTaP, and hepatitis B childhood vaccines. Anxiety among parents and care givers concerning the risk (strictly theoretical, with no evidence of harm after exposure to

date) of administering multiple mercury-containing vaccines, prompted the development of thimerosal-free vaccines.⁵⁴ However, the demonstrated risks for not vaccinating children far outweigh the theoretical risk for exposure to thimerosal-containing vaccines during the first 6 months of life.

ADVERSE EVENT REPORTING

Health effects reported as being associated with vaccines may be true adverse reactions or associated with vaccination by coincidence. Vaccines undergo stringent prelicensure studies to ensure safety before administration to the general public. Detection of rare reactions, delayed reactions, or reactions within subpopulations not detected before licensure are included in postlicensure studies. The latter is largely the result of passive surveillance. The Vaccine Adverse Event Reporting System (VAERS) is an example of a spontaneous reporting system that addresses postlicensure vaccine safety. Jointly administered by the CDC and FDA, VAERS was created in 1990 to provide a unified national effort for the collection of all reports of clinically significant adverse events. The National Childhood Vaccine Injury Act of 1996 mandates that health care workers who administer vaccines and manufacturers of vaccines report certain adverse health effects that are linked to receipt of a vaccine (1-800-822-7967). Vaccine safety is also assessed in defined populations (West Coast HMOs) that allow calculation of rates of reactions with controls.

FUTURE DIRECTIONS FOR VACCINES

The promise of novel vaccine approaches (DNA and peptide vaccines) makes it possible to envision a global impact on both infectious disease morbidity and potential infectious sequelae, for example, altering autoimmune responses and/or carcinogenesis that has been reported in association with infection. A clear developmental direction for vaccinology is (1) to improve vaccine immunogenicity thus limiting the necessity for booster doses and (2) to markedly improve safety. This century offers real opportunities for collaboration between bench scientists, private and public health providers, and political scientists to develop new vaccines (RSV, human papilloma virus, human immunodeficiency virus) and then meet the challenge of adequately delivering these products to populations at need and highest risk.

REFERENCES

- Salk J, Salk D. Control of influenza and poliomyelitis with killed virus vaccines. *Science* 1977;195:834-47.
- Sabin AB. Oral poliovirus vaccine. History of its development and prospects for eradication of poliomyelitis. *JAMA* 1965;194:872-6.
- Kim HW, Canchola JG, Brandt CD, Pyles G, Chanock RM, Jensen K, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. *Am J Epidemiol* 1969;89:422-34.
- From the Centers for Disease Control and Prevention. Intussusception among recipients of rotavirus vaccine: United States, 1998-1999. *JAMA* 1999;282:520-1.
- World Health Organization. Declaration of global eradication of smallpox. *Wkly Epidemiol Rec* 1980;55:145-52.
- Atkinson WL, Pickering LK, Schwartz B, Weniger BG, Iskander JK, Watson JC. Centers for Disease Control and Prevention. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR CDC Surveill Summ* 2002;51:1-35.
- Christie JM, Healey CJ, Watson J, Wong VS, Duddridge M, Snowden N, et al. Clinical outcome of hypogammaglobulinemia patients following outbreak of acute hepatitis C: 2 yr follow-up. *Clin Exp Immunol* 1997;110:4-8.
- Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants: the Impact-RSV Study Group. *Pediatrics* 1998;102:531-7.
- Ada G. Vaccines and vaccination. *N Engl J Med* 2001;345:1042-53.
- Adams WG, Deaver KA, Cochi SL, Plikaytis BD, Zell ER, Broome CV, et al. Decline of childhood *Haemophilus influenzae* type b (Hib) disease in the Hib vaccine era. *JAMA* 1993;269:221-6.
- Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, et al. Finnish Otitis Media Study Group: efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med* 2001;344:403-9.
- Wampler DE, Lehman ED, Boger J, et al. Multiple chemical forms of hepatitis B surface antigen produced in yeast. *Proc Natl Acad Sci U S A* 1985;82:6830-4.
- Sikand VK, Halsey N, Krause PJ, Sood SK, Geller R, Van Hoesche C, et al. Pediatric Lyme Vaccine Study Group: safety and immunogenicity of a recombinant *Borrelia burgdorferi* outer surface protein A vaccine against Lyme disease in healthy children and adolescents: a randomized controlled trial. *Pediatrics* 2001;108:123-8.
- Herlocher ML, Maassab HF, Webster RG. Molecular and biological changes in the cold-adapted "master strain" A/AA/6/60 (H2N2) influenza virus. *Proc Natl Acad Sci U S A* 1993;90:6032-6.
- Belshe RB, Mendelman PM, Treanor J, King J, Gruber WC, Piedra P. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine in children. *N Engl J Med* 1998;338:1405-12.
- Centers for Disease Control and Prevention. Prolonged poliovirus excretion in an immunodeficient person with vaccine-associated paralytic poliomyelitis. *MMWR Morb Mortal Wkly Rep* 1997;46:641-3.
- Centers for Disease Control and Prevention. Recommendations of the Advisory Committee on Immunization Practices: revised recommendations for routine poliomyelitis vaccination. *MMWR* 1999;48:590.
- Gregersen JP. DNA vaccines. *Naturwissenschaften* 2001;88:504-13.
- Watanabe T, Watanabe S, Neumann G, Kida H, Kawaoka Y. Immunogenicity and protective efficacy of replication-incompetent influenza virus-like particles. *J Virol* 2002;76:767-73.
- Weber J. Peptide vaccines for cancer. *Naturwissenschaften* 2001;88:504-13.
- Glenny AT, Pope CG, Waddington H, et al. Immunological notes. *J Pathol Bacteriol* 1926;29:31.
- Hem SL, White JL. Structure and properties of aluminum-containing adjuvants. *Pharm Biotechnol* 1995;6:249-79.
- Sun S, Kishimoto H, Sprent J. DNA as an adjuvant: capacity of insect DNA and synthetic oligodeoxynucleotides to augment T cell responses to specific antigen. *J Exp Med* 1998;187:1145-50.
- Bengtsson KL, Sjolander A. Adjuvant activity of ISCOMs: effect of ratio and co-incorporation of antigen and adjuvant. *Vaccine* 1996;14:753-60.
- Disis ML, Bernhard H, Shiota FM, Hand SL, Gralow JR, Huseby ES, et al. Granulocyte-macrophage colony-stimulating factor: an effective adjuvant for protein and peptide-based vaccines. *Blood* 1996;88:202-10.
- Krieg AM, Kline JN. Immune effects and therapeutic applications of CpG motifs in bacterial DNA. *Immunopharmacology* 2000;48:303-5.
- Izurieta HS, Thompson WW, Dramarz P, Shay DK, Davis RL, DeStefano F, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med* 2000;342:232-9.
- Neuzil KM, Zhu Y, Griffin MR, Edwards KM, Thompson JM, Tollefson SJ, et al. Burden of inter pandemic influenza in children younger than 4 years: a 25-year prospective study. *J Infect Dis* 2002;185:147-52.
- Anderson EL, Decker MD, Englund JA, Edwards KM, Anderson P, McInnes P, et al. Interchangeability of conjugated *haemophilus influenzae* type B vaccines in infants. *JAMA* 1995;273:849-53.
- Bridges CB, Fukuda K, Uyeki TM, et al. Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2002;51:1-31.

31. Pohl KR, Farley JD, Jan JE, et al. Ataxia-telangiectasia in a child with vaccine-associated paralytic poliomyelitis. *J Pediatr* 1992;121:405-7.
32. Inaba H, Hori H, Ito M, Kuze M, Ishiko H, Asmar BI, et al. Polio vaccine virus-associated meningoencephalitis in an infant with transient hypogammaglobulinemia. *Scand J Infect Dis* 2001;33:630-1.
33. Prevention of Varicella. Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP) MMWR 1999;48:1-5.
34. American Academy of Pediatrics. Committee on Infectious Diseases. Varicella vaccine update. *Pediatrics* 2000;105:136-41.
35. Levin MJ, Gershon AA, Weinberg A, Blanchard S, Nowak B, Palumbo P, et al. AIDS Clinical Trials Group 265 Team. Immunization of HIV-infected children with varicella vaccine. *J Pediatr* 2001;139:305-10.
36. Gonzalez B, Moreno S, Burdach R, Valenzuela MT, Henriquez A, Ramos MI, et al. Clinical presentation of Bacillus Calmette-Guerin infections in patients with immunodeficiency syndromes. *Pediatr Infect Dis J* 1989;8:201-6.
37. Recommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immune globulins in persons with altered immunocompetence. MMWR 1993;42:1-18.
38. Shields KE, Galil K, Seward J, Sharrar RG, Cordero JF, Slater E. Varicella vaccine exposure during pregnancy: data from the first 5 years of the pregnancy registry. *Obstet Gynecol* 2001;98:14-9.
39. Glezen WP. Maternal vaccines. *Prim Care* 2001;28:791-806.
40. Wilson ME. Travel-related vaccines. *Infect Dis Clin North Am* 2001;15:231-51.
41. Vasconcelos PFC, Luna EJ, Galler R, Silva LJ, Coimbra TL, et al. Serious adverse events associated with yellow fever 17D vaccine in Brazil: a report of two cases. *Lancet* 2001;358:91-7.
42. Mortimer PP. Yellow fever vaccine. *BMJ* 2002;324:439.
43. Recommendations for the use of Lyme disease vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 1999;48:1-17, 21-5.
44. Ryan ET, Calderwood SB. Cholera vaccines. *Clin Infect Dis* 2000;31:561-5.
45. Vaccinia (Smallpox) Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2001. MMWR 2001;50:1-25.
46. Use of anthrax vaccine in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR 2000;40:1-20.
47. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998;351:637-41.
48. Farrington CP, Miller E, Taylor B. MMR and autism: further evidence against a causal association. *Vaccine* 2001;19:3632-5.
49. Marwick C. US report finds no link between MMR and autism. *BMJ* 2001;322:1083.
50. Coughlan S, Connell J, Cohen B, Jin L, Hall WW. Suboptimal measles-mumps-rubella vaccination coverage facilitates an imported measles outbreak in Ireland. *Clin Infect Dis* 2002;35:84-6.
51. Ascherio A, Zhang SM, Hernan MA, Olek MJ, Coplan PM, Brodovitz K, et al. Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med* 2001;344:327-32.
52. Withdrawal of Rotavirus Vaccine Recommendation. MMWR 1999;48:1007.
53. Chang EJ, Zangwill KM, Lee H, Ward JI. Lack of association between rotavirus infection and intussusception: implications for use of attenuated rotavirus vaccines. *Pediatr Infect Dis J* 2002;21:97-102.
54. Recommendations Regarding the Use of Vaccines That Contain Thimerosal as a Preservative. MMWR 1999;48:996-8.