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# Recent Developments in Pediatric Immunizations

## BACKGROUND

Since the development of the polio vaccine in the 1950s, the widespread use of childhood vaccines and broad implementation of immunization programs have become routine, resulting in significant reductions in morbidity and mortality of vaccine-preventable diseases. Moreover, continued advances in the research and development of vaccines and our understanding of diseases have resulted in a constantly changing landscape with regard to recommendations for pediatric immunizations. For example, as a result of a measles epidemic in 1989 to 1991, the National Vaccine Advisory Committee in 1995 developed and released recommendations to improve and sustain success in immunization programs.<sup>1</sup> As a result, standardization in immunization scheduling and documentation has improved. The majority of vaccine and immunobiologicals have demonstrated safety and cost-effectiveness.<sup>2-4</sup>

Despite this growing success, specialists in public health, pediatrics and infectious disease still face significant issues as there remains much to learn about major diseases, such as malaria and HIV infection. Furthermore, although many vaccine-preventable diseases have been minimized or eradicated, vaccine-related

adverse events (both real and perceived) have compromised immunization goals among some. A small, albeit active, anti-vaccine movement has risen and has been profiled by media attention and Internet reporting. To ensure continued success within immunization programs, all health care professionals must keep abreast of recent developments and take an active role in educating the public regarding adult and childhood immunization.

## DEFINITIONS AND PRINCIPLES OF IMMUNIZATION

Immunization is defined as the process of inducing or providing immunity artificially (active immunity) by administering an immunobiological agent or vaccine. The term immunization is considered more appropriate than the term vaccination, which refers to the process rather than the desired outcome. The intent is to produce immunity from infectious diseases similar to that which the body would have naturally produced had it been infected, without incurring the risks of infection.

Vaccines are classified as live-attenuated or inactivated. Live-attenuated vaccines are modified or weakened strains of a "wild" (disease-producing) virus or bacteria ca-

pable of producing immunity, but usually not illness. These vaccines must be able to replicate in the vaccinated host in order to produce an immune response. The immunity produced by live-attenuated vaccines is virtually identical to that produced by a natural infection. Live-attenuated vaccines should be used cautiously, if at all, in pregnant women and immunocompromised individuals, such as those with HIV infection or leukemia, or those on immunosuppressant drugs, as the immune response is suppressed in these individuals and the viral or bacterial replication can progress to infection. Live-attenuated vaccines should be used according to the suggested intervals provided by the Centers for Disease Control and Prevention (CDC) when circulating antibodies from any source (transplacental, transfusion) are present, as the antibodies can interfere with the growth of a live-attenuated vaccine and can lead to vaccine failure.<sup>5</sup> The measles vaccine seems to be the most sensitive in this regard. Live-attenuated vaccines also are very labile, are heat and light sensitive and warrant care in handling and storage to preserve vaccine integrity. Currently available live-attenuated vaccines include (live virus) measles-mumps-rubella (MMR), yellow fever, varicella, vaccinia (smallpox),

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Program Goal:  
To provide an objective review of childhood vaccine and immunization products, the recommended scheduling and administration, the clinical application of the vaccines and consensus

guidelines governing their use.

### Learning Objectives

At the completion of this program, the clinician should be able to:

1. Describe the various childhood vaccine products;
2. Counsel parents in regard to the advantages of immunization;
3. Explain to patients the vaccination schedule appropriate for their child;
4. Define and describe immunobiologic properties, including recent changes and recommendations regarding immunization products; and
5. Provide education to nurses, nurse practitioners, family practitioners and pediatricians with regard to vaccines and immunization projects.

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rotavirus, influenza and (live bacterial) BCG and oral typhoid.<sup>5</sup>

Inactivated vaccines are subdivided into 1) whole virus or bacteria, or 2) fractions of either. Fractional vaccines are further categorized as either protein-based, including inactivated bacterial toxins or toxoids, or polysaccharide-based. Polysaccharide vaccines may be composed of pure bacterial cellular wall polysaccharide or may be conjugated, in which case the polysaccharide chain is linked to a protein. The immune response to a pure polysaccharide vaccine is poor and inconsistent in children younger than 2 years of age. This is presumably due to the immaturity of the child's immune system.<sup>4,5</sup>

As a general rule, the more similar a vaccine is to the natural disease, the more optimal is the immune response to that vaccine. Repeat doses of a polysaccharide vaccine do not cause an antibody boost as with inactivated vaccines. Polysaccharide vaccines tend to stimulate IgM antibody rather than IgG (humoral) and, therefore, have less functional immune-producing activity than that produced by protein antigen. Conjugation has helped to overcome these problems by linking a protein antigen to the polysaccharide antigen that changes the immune response from T-cell independent to T-cell dependent, thus improving infant immunogenicity and antibody booster response.<sup>5</sup> *Haemophilus influenzae* type b (Hib), pneumococcal conjugate (Prevnar®), and meningococcal conjugate (MCV4 Menactra®) are conjugate polysaccharide vaccines.

Technology also has produced genetic re-engineering referred to as recombinant vaccines. Hepatitis-B vaccines represent pure hepatitis B surface antigen. Live typhoid vaccine has been modified genetically to not cause illness, and live attenuated influenza vaccine has been modified to only replicate effectively in the mucosa of the nasopharynx and not in the lungs.<sup>5</sup>

### VACCINE PRODUCTS

#### Diphtheria, tetanus and pertussis

The combination product of diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) is the vaccine of choice for children 6 weeks through 6 years of age. Acellular pertussis vaccine contains purified inactive components (subunits) of Bordetella pertussis cells and produces as efficacious

an immune response as whole-cell DPT with substantially less local reactions, fever and other adverse events. Whole-cell DPT is no longer available in the United States.<sup>6</sup> The usual schedule is a series of four doses at 2, 4, 6 and 15 months to 18 months of age (See Figure 1 at [http://www.4healtheducation.com/pdf/IZSchedule\\_2006.pdf](http://www.4healtheducation.com/pdf/IZSchedule_2006.pdf)). The first, second and third DTaP doses should be separated by a minimum of four weeks. At least six months should expire between the third and fourth doses. If the fourth dose of DTaP is administered before the fourth birthday, a fifth dose is needed at 4-6 years old. If a valid contraindication exists to the pertussis vaccine, pediatric DT (diphtheria and tetanus toxoids) should be used instead of DTaP in the vaccination series. Do not give DTaP/DT to children older than 6 years of age, as these children should receive the adult formulation.<sup>6</sup>

If the child has completed the recommended schedule of DTaP, and at least five years have passed since the last dose, the first booster may be given at 11-12 years of age. The CDC's Advisory Committee on Immunization Practices (ACIP) recommends a single dose of Tdap (tetanus, diphtheria toxoids and acellular pertussis) as the first booster for more protection against pertussis, because cases have been increasing leading to approximately 25,000 reported cases in 2004. Then, re-boost every 10 years with Td (tetanus and diphtheria toxoids) to achieve optimal antitoxin levels.<sup>6</sup>

An important counseling and educational point is that interrupting the recommended schedule or delaying the subsequent doses does not reduce the effectiveness of subsequent doses. The series should be continued, and there is no need to restart regardless of the elapsed time. If recommended dosing schedules are interrupted or delayed, CDC recommendations for a catch-up schedule should be referenced.

Adverse reactions are usually local, self-limiting and include erythema and tenderness. Increasing frequency and magnitude of reactions at the injection site with increasing dose can also occur.<sup>7</sup> A history of neurologic or severe allergic reaction following a previous dose would constitute a contraindication to receiving further DTaP and indicate the use of DT. Immunosuppression in and of itself is not

a contraindication to DTaP/Tdap vaccine.

The vaccine should be stored continuously at 2°C to 8°C (35°F to 46°F), but can be out of refrigeration for up to four days. Freezing compromises the potency of the tetanus component.

DTaP vaccines that are licensed and available include: Infanrix® (GlaxoSmithKline), Tripedia® (Sanofi Pasteur) and Daptacel® (Sanofi Pasteur). For use among infants and young children, Infanrix® and Tripedia® are approved and recommended for all five doses. The ACIP recommendations are that, whenever feasible, the same brand of DTaP be used for all doses, though substituted vaccines can be used to complete the series if the provider cannot ascertain or procure the type used for previous doses.

Two brands of Tdap are available for use in the United States: Boostrix® (GlaxoSmithKline) for those 10-18 years of age and Adacel® (Sanofi Pasteur) for those 11-64 years of age.<sup>6</sup>

### Polio vaccine

Two types of trivalent poliovirus vaccines have been used in the United States: live oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV). In the past, OPV was the first choice for routine vaccination, but in 2000 regular use of OPV was discontinued in the United States.<sup>8</sup> It still remains the vaccine of choice for most countries in the world due to storage requirements, cost and ease of use.

IPV is an enhanced potency trivalent poliovirus vaccine that became available in 1988 and is used almost exclusively in the United States.<sup>8</sup> It is highly effective in producing immunity to poliovirus (99 percent immunity after three doses). The most important advantage of IPV is that it is inactive and, therefore, it cannot replicate and cause vaccine-associated paralytic poliomyelitis (VAPP). It also cannot be shed in the stool of a vaccinated person and can be used safely in immunodeficient people or in household contacts of immunodeficient people. It is more costly, does require a series of four injections and produces less local (GI) immunity. IPV probably provides protection for many years after a complete series, but actual duration of immunity is unknown.<sup>8</sup>

OPV produces excellent intestinal immunity, which helps prevent infection

from wild virus. This is important if one is exposed while visiting a polio-endemic country or region. Oral poliovirus vaccine viruses replicate in the gut and are shed in the stool, thus, they may spread from the recipient to contacts. This was thought to contribute to "herd immunity" to poliovirus in the United States. Immunity from OPV is probably life-long.

Administration of OPV is associated with a risk of paralysis among healthy recipients and their contacts, commonly referred to as vaccine-associated paralytic poliomyelitis (VAPP). These instances are rare (one in 2.4 million), but have resulted in 8 to 10 cases of VAPP each year in the United States.<sup>8</sup>

In 1997, to decrease the risk of VAPP but still maintain the benefits of OPV, ACIP recommended a sequential schedule of IPV (two doses) followed by OPV (two doses). Since 1997, global eradication of polio has progressed significantly and it has been observed that no declines in childhood vaccination coverage occurred despite the need for additional injections. Based on these data, in 1999, the ACIP further recommended an all-IPV schedule for routine childhood polio vaccination in the United States to eliminate the risk for VAPP.<sup>9</sup> At the present time in the United States, OPV is no longer routinely available. VAPP has been virtually eliminated, due to the exclusive use of IPV.<sup>8</sup>

All children should receive a primary three dose series of IPV at ages 2 months, 4 months and 6-18 months. If all three doses are given before the fourth birthday, the child should receive a fourth dose of IPV at 4-6 years old. OPV should be used only as outlined (See Table 1).<sup>8</sup>

While the risk of poliomyelitis remains very small in the United States, it is possible that an epidemic could occur if the high immunity level of the general population is not maintained by childhood immunization programs or if wild poliovirus is intro-

duced into susceptible populations in communities with low immunization levels.

### Haemophilus influenzae type b

More than 85 percent of invasive *Haemophilus influenzae* (otitis media, bronchitis, etc.) occurs among children younger than five years of age.<sup>11</sup> Therefore, vaccination against this agent is important. There are three immunologically distinct Hib vac-

symptomatic infections as infants, therefore are immune to Hib. Some older children and adults are at increased risk of acquiring invasive Hib. If they have not been vaccinated in childhood, they should be given at least one dose of any Hib conjugate vaccine.<sup>13</sup>

Data has suggested that giving the vaccine to infants younger than 6 weeks of age may induce immunologic tolerance to the later Hib doses and render the child incapable of immunogenic response. Therefore, Hib conjugate vaccine should not be administered to children younger than 6 weeks of age. All three conjugate vaccines can be interchanged or substituted for one another at any time, but this requires a three-dose series.<sup>13</sup>

Combination vaccines include DTaP/Hib (TRiHIBiT<sup>®</sup>), and hepatitis B-Hib (Comvax<sup>®</sup>). Combination vaccines that include Hib and whole cell pertussis are no longer available in the United States.<sup>13</sup> The DtaP/Hib (TRiHIBiT<sup>®</sup>) product has been approved for use by the FDA only as the fourth dose after single antigen Hib primary series.<sup>14</sup> Infants who receive TRiHIBiT<sup>®</sup>, for any of the first three doses of the Hib series may not have immunological protection.<sup>13</sup>

Hep B-Hib (Comvax<sup>®</sup>) combination can be used when both agents are indicated, but should not be used in infants younger than 6 weeks of age (can not be used for the birth dose of hepatitis B or the 1 month dose) Comvax<sup>®</sup> as a third dose must be given at 12 months of age and older and must be two months after the second dose. Recently, Comvax<sup>®</sup> has been approved by the ACIP for off-labeled use in children whose mothers' hepatitis B surface antigen status is positive or unknown.<sup>13</sup>

Adverse reactions are uncommon following Hib vaccine and usually involve self-limiting (spontaneously resolving within 12 hours to 24 hours) local reactions. The vaccine is contraindicated in those known to have experienced an anaphylactic reaction following a previous

**TABLE 1**  
**Circumstances for OPV use**

- Unvaccinated children traveling to polio-endemic areas in less than 4 weeks (only one dose of OPV can be given before travel)
- Third and fourth dose of poliovirus vaccine series for parents objecting to IPV injection (providers should discuss risk of VAPP with parents)
- Mass vaccination campaigns to control paralytic polio outbreaks
- People with life-threatening allergic reaction to a dose of IPV

cines available, and all are polysaccharide-conjugate vaccines. As previously discussed, the conjugate vaccines produce more immunogenicity among children younger than 2 years of age and among immunocompromised individuals.

All three Hib conjugate vaccines produce protective immunity in more than 95 percent of infants after a primary series of two or three doses. Clinical efficacy has been estimated at 95 to 100 percent in completely vaccinated infants.<sup>11,12</sup> Hib vaccine is immunogenic in patients who are immunosuppressed, including HIV infection, sickle-cell disease and splenectomized patients. The primary Hib series should begin at two months of age. The number of doses in the primary series depends on the type of vaccine used. Pedvax HIB<sup>®</sup>, is a two-dose (two month, four month) vaccine, while HibTITER<sup>®</sup> and ActHIB<sup>®</sup> are three-dose vaccines (two, four and six month). Regardless of which primary series vaccine is used, a booster is recommended at 12-15 months. Optimal spacing between doses is two months with a minimum of one month. Two months should separate the booster dose from the last dose.

In general, it is not recommended to vaccinate children older than 59 months of age with Hib. Most likely, older children had as-

dose. Vaccination should be delayed with moderate or severe illness, but mild upper respiratory illnesses do not constitute contraindications. Storage of the vaccine is between 2°C to 8°C (35°F to 46°F), and it should be kept from freezing.<sup>13</sup>

### Hepatitis B vaccine

Recombinant hepatitis B vaccine was licensed in the United States in 1986 and was the first vaccine produced by recombinant DNA technology. The recombinant product is greater than 95 percent hepatitis B surface antigen (HbsAg), but it should be noted that vaccination cannot produce hepatitis B (HBV) disease. There are two currently licensed and available hepatitis B vaccines: Recombivax HB® (Merck) and Engerix-B® (GlaxoSmithKline). These are available in both pediatric and adult concentrations—therefore, attention must be given to the vaccine strength. Although the antigen content differs, the two vaccines are interchangeable, except only Recombivax HB® is approved for the two-dose schedule used for adolescents aged 11-15 years.

The hepatitis B vaccination series consists of three IM injections and produces good immunogenic response in more than 95 percent of infant recipients. The usual schedule is birth, 1-2 months and 6-18 months. Infants whose mothers are HBsAg positive or whose HBsAg status is unknown should receive the third dose by 6 months of age. Booster doses are not recommended, but the optimal titers of anti-hepatitis antibodies are produced when the last two doses of vaccine are spaced at least four months apart. Thus, immunization schedules that can accommodate this spacing are preferable. It is important in this regimen that the third dose be administered at least two months after the second dose and should follow the first dose by at least four months (See Table 2). It is not necessary to add doses or restart the series if the interval between doses is longer than recommended. However, only doses given at, or longer than, recommended time limits suffice as legitimate vaccination in the series.

Adverse drug reactions include pain at the injection site in about 6 percent of children receiving the vaccine, along

with some headache and fatigue. Serious allergic reactions to prior doses constitute contraindications and children with moderate to severe acute illness should not be vaccinated until their

illness resolves. Minor illnesses, such as upper respiratory infections and colds, are not reasons to withhold vaccination. Contraindications to the individual components of the vaccines apply to the combination products.

Data, to date, support estimates that the duration of vaccine protection is at least 15 years. For people with normal immune status, neither booster doses nor serologic testing are indicated. However, the possibility for booster doses after longer periods of time will continue to be assessed as further information becomes available. Post-vaccination immunity testing is not routinely suggested, but is advised for those whose subsequent management depends upon knowing their immune status.

Pregnancy should not be considered a contraindication to vaccinating women who are otherwise candidates for receiving hepatitis B vaccine. Hepatitis B vaccine contains only noninfectious HBsAg particles and should pose no risk to the fetus, albeit no safety trials have confirmed this.

Hepatitis B vaccine should be refrigerated at 2°C to 8°C (35°F to 46°F), but not frozen as freezing significantly compromises the vaccine potency.

As mentioned previously, a combination product of hepatitis B-Hib (Comvax®, Merck) currently is available. Hepatitis B-Hib is approved for use at 2, 4 and 12-15 months of age and can be used whenever both antigens are indicated. The vaccine is not to be used in infants younger than 6 weeks of age as the immune response is less than adequate and results in vaccine failure. Therefore, a child on a 0-, 1- and 6-month hepatitis B vaccine schedule must not use Comvax® for doses at birth or 1 month of age.

Pediarix™ (GlaxoSmithKline) is a combi-

**TABLE 2**  
**Routine HBV vaccine schedules<sup>15</sup>**

Dose	Usage Age	Minimal Interval
Primary 1	Birth	—
Primary 2	1-2 months	1 month
Primary 3	6-18 months	2 months

nation vaccine consisting of DTaP-hepatitis B-inactivated poliovirus. It is licensed for use starting at 6 weeks of age as a 3-dose series. Pediarix™ is not approved for infants younger than 6 weeks of age or individuals 7 years of age and older, therefore it cannot be given as the birth dose of hepatitis B. Pediarix™ is only approved for the first three doses (usually given at 2, 4 and 6 months of age) of the DTaP and IPV series. It is not approved for fourth or fifth (booster) doses of the series. Since Pediarix™ is approved through 6 years of age it can be used for children who are behind schedule.

Twinrix® (GlaxoSmithKline) is a combination product of hepatitis A and hepatitis B. It is only approved for people 18 years of age and older. The vaccine is administered on a three-dose schedule at 0, 1 and 6 months.

### Measles, mumps and rubella vaccine

As with other vaccine-preventable diseases, outbreaks of measles, mumps or rubella are characteristically due to low vaccination rates or vaccine failure. All three vaccine components of MMR are live-attenuated viruses and the vaccine is given as the combination in a two dose series. ACIP recommendations are that the MMR vaccine be administered when any individual component is indicated. A two-dose series is recommended as up to 2 percent to 5 percent of MMR vaccine recipients may not respond to the first MMR dose, but studies have shown that most of these non-responders will respond to the second dose.<sup>17</sup>

The first dose of MMR/MMRV should be given on or after the first birthday, as immunologic response is more favorable after 12 months of age. The second dose must follow the first dose by at least one month (28 days), and is recommended at 4-6 years of age to assure immunogenic response as

some do not respond to the first dose.<sup>19</sup>

If the recipient has or will receive antibody-containing blood products in close proximity to the MMR/MMRV vaccine, this may interfere with seroconversion to the vaccines and vaccination should be delayed (see Table 3).<sup>5</sup>

Because the vaccine contains live virus that must replicate in the host to produce immunity, adverse reactions following MMR may represent mild clinical disease. They usually occur 5-12 days post vaccination and occur only in recipients who are susceptible to infection. Therefore, the vaccine should not be administered to those who are severely immunocompromised (i.e., HIV infection or persons receiving large doses of corticosteroids). However, in otherwise healthy individuals, this illness is mild and al-

most always resolves spontaneously. Fever also can occur (5 percent to 15 percent of vaccinated individuals) and usually lasts one day to two days before spontaneously resolving. The measles and rubella components of the vaccine have been reported to cause a transient rash in approximately 5 percent of people who receive it.<sup>19</sup>

Parents of children with autism have raised the issue of a possible connection between the MMR vaccine and autism. Symptoms of autism usually are noticed by parents throughout the second year of life which can be weeks to months after the MMR vaccine. However, evidence that has been reviewed by two non-governmental independent groups does not support an association between autism and the MMR vaccine.<sup>20</sup>

The measles and mumps components are grown in chick embryo fibroblast culture, but this does not represent a contraindication to those allergic to eggs, as was thought previously.<sup>17</sup> MMR/MMRV does contain small amounts of human albumin, neomycin, sorbitol and gelatin which have been associated with hypersensitivity following the vaccine.<sup>19</sup> Similarly, a history of penicillin sensitivity is not a contraindica-

tion to MMR vaccine. Pregnant women should not receive this vaccine, and pregnancy should be avoided for four weeks after administration.<sup>19</sup>

The MMR vaccine should be kept and stored at a refrigerated temperature of 2°C to 8°C (35°F to 46°F) and can be frozen if needed. This vaccine is light sensitive and should be protected as such. After reconstitution, MMR can be refrigerated for up to eight hours.

As of June 2006, the ACIP has approved the use of MMRV (ProQuad® Merck) a combination vaccine consisting of measles,

prevalence also remains high and is estimated to be the causative agent in 28 percent to 55 percent of acute otitis media (AOM) cases.<sup>23</sup> AOM is also the leading reason for prescribing antibiotics during childhood, and use of antibiotics for treatment of AOM and sinusitis contributes substantially to increased antimicrobial resistance.<sup>24</sup> Pneumococcal otitis media may progress to more serious complications, such as mastoiditis and meningitis, thus underscoring the value of this vaccine.

Two types of pneumococcal vaccines exist. One is a 23-valent polysaccharide vaccine (PPV23), which has been licensed and approved since 1983. PPV23 contains immunogenic antigen from 23 subtypes of pneumococcal bacteria that are responsible for almost 90 percent of pneumococcal disease. Pneumovax® (Merck) may be administered either intramuscularly or subcutaneously.

In 2000, a seven-serotype pneumococcal conjugate vaccine (PCV7) was introduced and contains polysaccharide antigen from seven serotypes of *S. pneumoniae* conjugated to a nontoxic variant of diphtheria toxin (CRM197). These seven pneumococcal serotypes account for more than 80 percent of bacteremia and meningitis cases and 65 percent of acute otitis media cases in children younger than 6 years old in the United States. The necessity for a conjugated vaccine stems from a lack of immunogenic efficacy of the PPV23 vaccine in children younger than 2 years old. Prevnar® (PCV7 Wyeth) vaccine is administered intramuscularly as a series of four doses. Approximately 90 percent of healthy infants will develop antibodies to the seven serotypes contained in the conjugate vaccine. Immunogenicity from the PCV7 vaccine also has been shown in children with sickle-cell and HIV infection.<sup>24</sup>

All children younger than 24 months of age should be vaccinated routinely with PCV7. For newborns, the primary vaccination series consists of a total of four in-

**TABLE 3**  
**Immune serum antibody (IG) and live vaccines<sup>5</sup>**

Product given first	Usage age
Live vaccine	Wait two weeks before vaccine is given
AB (IG)	Wait up to 12 months before vaccination (depending on vaccine)

mumps, rubella and varicella.<sup>18</sup> It can be used in children 12 months to 12 years of age, when a dose of MMR or varicella vaccine is indicated (first or second dose). MMRV should not be administered to people 13 years old and older.<sup>18</sup> It must be stored at a temperature of -15°C (5°F) or less at all times. It must be administered 30 minutes following reconstitution.<sup>19</sup>

#### **Pneumococcal polysaccharide and conjugate vaccines**

Throughout the United States, invasive disease by *Streptococcus pneumoniae* remains a major cause of morbidity and mortality in adults and children with clinical syndromes progressing to bacteremia, pneumonia and meningitis. Pneumococcal bacteremia without a known site of infection is the most common invasive clinical presentation among children younger than 2 years of age and accounts for almost 70 percent of invasive disease in this group.<sup>21,22</sup> Because of the Hib vaccine and effective immunization programs, *S. pneumoniae* now represents the leading cause of bacterial meningitis among children younger than 5 years of age.<sup>14,15,16</sup> *S. pneumoniae* otitis media

jections given at two, four and six months, with a booster dose at 12-15 months. PCV7 should be administered concurrently with other routine childhood immunizations using a separate syringe and injection site. Spacing between doses is at least four weeks if the child is younger than 12 months of age, or eight weeks apart if older than 12 months.<sup>24</sup>

On the catch-up schedule, the number of doses a child needs to complete the series depends upon the child's current age. Unvaccinated children aged 7-11 months should receive two doses of vaccine at least four weeks apart, followed by a booster dose at 12-15 months.<sup>21</sup> Unvaccinated children aged 12-23 months should receive two doses of vaccine at least eight weeks apart.<sup>14</sup> Any previously unvaccinated healthy child aged 24-59 months should receive a single dose of vaccine. High-risk, previously unvaccinated children aged 24-59 months should receive two doses of PCV7 eight weeks apart, then a single dose of PPV23 two months after the second dose of PCV7. PCV7 is not routinely used in people older than 59 months.<sup>24</sup>

The ACIP recommends PPV23 for children 2-18 years of age who have asplenia, immunocompromising medications or illness, received a bone marrow transplant, chronic illness and those who are Native Alaskan or American Indian.<sup>25</sup> These groups are at increased risk for pneumococcal infection or its complications. PPV23 should follow the PCV7 series by at least two months. It is not recommended to administer PPV23 to healthy children. PPV23 also is routinely administered to adults 65 years old and older.<sup>25</sup>

Data are scarce regarding the use of PCV7 in children previously vaccinated with PPV23. ACIP recommends that children 24-59 months of age who have only received PPV23 and who are at high risk of invasive pneumococcal disease (sickle cell, asplenic and HIV infection, etc.) receive two doses of PCV7 separated by at least eight weeks, with the first dose no sooner than two months after PPV23.<sup>24</sup>

Because of the lack of evidence of improved protection with multiple doses of pneumococcal vaccine, routine revaccination (booster) of immunocompetent people previously vaccinated with PPV23 is not recommended. Revaccination with PPV23 is recommended, however, for people older than 2 years of age at high risk for serious pneumococcal

doses represent contraindications, however, these are rare. Minor illnesses, such as colds or respiratory tract infections, are not contraindications to vaccination. The CDC recommends that PPV23 should not be given to healthy pregnant women, but women at high risk of pneumococcal disease should be vaccinated before pregnancy if possible. The CDC

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infection. Only one PPV23 booster dose is recommended for these high-risk individuals. If the child is 10 years of age and older, this second PPV23 dose should be given 3-5 years after the first dose. If older than 10, 5 or more years should elapse between doses of PPV23. Revaccination also is recommended for persons 65 and older if they were younger than 65 at the time of the first dose and more than 5 years have elapsed. Revaccination with PCV7 after appropriate-age immunization is not currently recommended.<sup>25</sup>

Adverse reactions to pneumococcal vaccines are similar to other vaccines and include local reactions in up to 30-50 percent of doses for PPV23 and 10-20 percent for PCV7. These local reactions are more commonly associated with the fourth dose of PCV7 than with the first three doses.<sup>24</sup> Revaccination with PPV23 was reported to cause more local effects than the first dose. Fever and myalgias were reported as well.

Serious allergic reactions to previous

also recommends storage of these vaccines at refrigeration temperatures of 2°C to 8°C (35°F to 46°F) and freezing should be avoided.

### **Varicella Zoster Virus (VZV) vaccine**

The Varicella Zoster Virus, a member of the herpes virus group, can cause acute contagious disease (chicken pox) and also is responsible for recurrent infection (herpes zoster or shingles). Primary infection can progress to illness, such as pneumonia, or can be further complicated with secondary bacterial infections or CNS involvement, including aseptic meningitis and encephalitis. Secondary bacterial pneumonia is more common in children younger than one year of age.

VZV virus vaccine (Varivax® Merck) is a live attenuated viral vaccine approved for use in the United States in 1995. Recent policy changes have been made to the ACIP's recommendation schedule for the varicella vaccine. The recommended schedule for varicella vaccine

now includes two subcutaneous doses. A primary dose administered at 12-15 months of age, and a booster dose at 4-6 years of age is recommended for all children without a reliable history of immunity and no contraindications.<sup>19</sup> Children with a reliable history of chicken pox can be assumed to be immune to varicella. In 2005, the ACIP approved a revised definition for evidence of immunity to varicella, which is available in its entirety from the CDC.<sup>19</sup> The ACIP also suggests a second catch-up dose for people who had received only one dose. This dose is to improve protection against VZV, and for more rapid impact on school outbreaks. The catch-up dose can be administered up to three months after the first dose. The new ACIP recommendations also include a two-dose schedule for all people 13 years of age and older, with doses separated by 4-8 weeks.

The effectiveness of the vaccine recently has been studied, concluding that the vaccine as used in clinical practice is 95 percent effective against moderately severe and severe disease.<sup>19</sup> Immunity appears to be long-lasting and is probably permanent in the majority of those vaccinated.

There have been case reports of breakthrough infections, including development of varicella disease despite responding to the vaccine. Studies have found that children have a 2.5-fold increased risk of breakthrough varicella if they received the VZV vaccine less than 30 days after MMR. This risk is compared to those who received varicella before, at the same time, or more than 30 days after MMR. Therefore, the ACIP recommends that MMR and varicella vaccine be administered at the same visit, or separated by at least 28 days.<sup>19</sup>

Limited data exist on the post-exposure efficacy of the varicella vaccine in previously unvaccinated individuals. The ACIP recommends the use of the vaccine following exposure to varicella in persons who do not have evidence of immunity.<sup>19</sup> Use of the vaccine within three days of exposure may prevent infection in 70-100 percent of children.

The vaccine is not effective longer than 5 days after exposure, but it will produce some immunity if not infected.<sup>19</sup>

Precautions and contraindications parallel those of the other live-attenuated vaccines, including severe allergic reactions to a vaccine component or following a previous dose. The varicella vaccine does not contain egg protein or preservative, but it does contain small amounts of gelatin and neomycin.<sup>19</sup> Immunosuppressed children should not be vaccinated. Women known to be or attempting to become pregnant should not receive varicella vaccine. The effects of the vaccine on the developing fetus are unknown. If the vaccine has been administered, pregnancy should be avoided for at least one month following vaccination. Women who do not have evidence of varicella immunity upon completion of pregnancy, should receive the first dose of varicella vaccine before being discharged from the health care facility and receive the second dose 4-8 weeks later.<sup>19</sup>

Because of the unknown effect of antibody-containing blood products (e.g. immune globulin, varicella zoster immune globulin and transfusions) the ACIP recommends applying the same intervals used with the MMR vaccine. The VZV vaccine should not be given for 3-11 months after the administration of such products. Conversely, IG or varicella zoster IG should not be given for at least 3 weeks following vaccination unless the benefits outweigh those of the vaccine. Revaccination or immune testing should occur with the later scenario.

Transmission of vaccine virus has shown to be a rare event by available data. It appears that transmission mainly occurs when the vaccinee develops a rash. If a child develops a rash, it is recommended that people without evidence of immunity and immunocompromised people should avoid the child until the rash has resolved.<sup>19</sup>

No adverse events following varicella vaccination related to the use of salicylates, such as aspirin, have been reported to date. The manufacturer recommends

that vaccine recipients avoid aspirin and other salicylates for six weeks following varicella vaccination secondary to an associated risk of Reye's Syndrome with aspirin use following chicken pox.<sup>19</sup>

VZV vaccine is one of the more fragile vaccines and must be handled with appropriate care. Lyophilized vaccine must be frozen at an average temperature of -15°C (5°F) to maintain potency. Providers need to ensure this temperature can be reached and maintained with existing refrigeration. The vaccine diluent is stored separately at room temperature or under refrigeration. Once reconstituted, the vaccine must be used within 30 minutes to minimize potency loss.

The changes to the VZV vaccination schedule have made it very similar to the MMR vaccination schedule. In September 2005, a new vaccine was licensed (ProQuad® Merck) containing measles, mumps, rubella and varicella (MMRV) and is preferred over separate injections for children 12 months to 12 years old, who have indications for all components and no contraindications. The MMRV must be shipped at a temperature of -20°C (-4°F) or colder. It must be stored at -15°C (5°F) or colder at all times. After reconstitution, the MMRV must be administered within 30 minutes.

### Hepatitis A vaccine

Until 2004, hepatitis A was the most common type of hepatitis reported in the United States. In the past, prophylaxis with hygienic measures and passive immunization with immune globulin have been the primary methods of combating this disease and providing short-term protection. Hepatitis A vaccines now are available for use and can provide long-term protection against the hepatitis A virus (HAV). In 2005, the ACIP added hepatitis A vaccine to the routine childhood vaccination schedule based on successful implementation of hepatitis A vaccination programs that significantly reduced the incidence of hepatitis A. Originally, these vaccines were licensed for children 2 years of age and older, but

in 2005 the U.S. Food and Drug Administration approved the vaccines for use down to 12 months of age. Now all children aged 12-23 months should receive the hepatitis A vaccine.<sup>29</sup>

Two inactivated whole-HAV vaccines are available: Havrix<sup>®</sup> (GlaxoSmithKline) and VAQTA<sup>®</sup> (Merck). Both vaccines are cultured and propagated in human fibroblasts, inactivated with formalin and then adsorbed to aluminum hydroxide adjuvants.<sup>19</sup> Havrix<sup>®</sup> is prepared with 2-phenoxyethanol (a preservative); VAQTA<sup>®</sup> does not contain any kind of preservative. Both products are available as adult and pediatric formulations.<sup>29</sup>

The immunogenic effectiveness of both vaccines is high. More than 97 percent of pediatric patients will develop protective antibody within a month of the first dose of vaccine. The length of immune memory remains a question at this point because of the relative newness of the vaccine. The need for booster doses will be determined by post-marketing surveillance studies.

The vaccination schedule for both vaccines is a two-dose series. The Havrix<sup>®</sup> is measured in ELISA units (EL.U.). The pediatric formulation for children 12 months to 18 years of age contains 720 EL.U. The primary dose should be followed by a booster dose 6-12 months later. A 1,440 EL.U. adult formulation also is available for people 19 years of age and older and requires one primary dose followed by a booster dose in 6-12 months. In contrast, VAQTA<sup>®</sup> is quantified in units (U.) of antigen, and its manufacturer recommends the pediatric formulation for patients aged 12 months to 18 years. One injection of 25 units followed by a booster dose in 6-18 months suffices for immunoprotection. For vaccination of adults 19 and older, a dose of the adult formulation (50 units) is recommended with a booster 6-18 months following the

primary dose. Both vaccines should be administered intramuscularly.<sup>29</sup>

Data on the interchangeability of the vaccines is lacking, thus, staying with the same product to complete the immunization course is preferable. However, in the event of unknown information with regard to the first dose, either vaccine is acceptable. The minimum interval between the first and second dose of the HAV vaccine is six months. It is not necessary to repeat the first dose if the interval extends beyond 18 months.<sup>30</sup>

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### *Until 2004, hepatitis A was the most common type of hepatitis reported in the United States*

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HAV vaccine adverse reactions include pain at the injection site and occasional systemic complaints, such as malaise or low-grade fever. These are usually low in intensity and self-limiting. Contraindications include a history of a serious allergic reaction to a prior dose of HAV vaccine, a hypersensitivity to alum or a hypersensitivity to the preservative used in Havrix<sup>®</sup>. HAV vaccine should be refrigerated at 2°C to 8°C (35°F to 46°F) and should not be frozen.

Twinrix<sup>®</sup> (GlaxoSmithKline) is a combination hepatitis A and hepatitis B vaccine that is approved by the FDA for people 18 years of age and older. Each dose of Twinrix<sup>®</sup> contains the pediatric dose of hepatitis A vaccine and an adult dose of hepatitis B vaccine (20 mcg). Recommended administration of this vaccine is a three dose series. For people 18

years of age and older, the first and second doses should be separated by four weeks, and the third dose should come five months after the second dose (0, 1 and 6 months).<sup>29,30</sup>

#### **Rotavirus vaccine**

In infants and young children in the U.S. and worldwide, rotavirus continues to be the leading cause of gastroenteritis. Despite available therapies in the U.S., rotavirus continues to cause a high level of morbidity. Natural rotavirus infection studies have shown that original infection with the virus actually protects against later severe gastroenteritis. Mild or asymptomatic infections might still occur, but this presents reason to initiate vaccination in children. According to this data, vaccination early in a child's life could imitate the first natural infection, which could prevent most severe rotavirus infections and their complications.<sup>31</sup> Studies indicate that a vaccine could prevent 74 percent of all and about 98 percent of the most severe rotavirus cases.<sup>31</sup>

In 1998, the tetravalent rhesus-human reassortant rotavirus vaccine (RRT-TV; Rotashield<sup>®</sup>, Wyeth Lederle Vaccines) was shown effective in preventing severe rotavirus gastroenteritis in infants. However, concern regarding the association between vaccine and intussusception (a form of intestinal obstruction in which a segment of the bowel prolapses into a more distal segment) among otherwise healthy infants prompted a 1999 ACIP recommendation that this vaccine be withdrawn. This resulted in the removal of the vaccine from the market.<sup>32</sup>

In 2006, a new rotavirus vaccine was licensed. RotaTeq<sup>®</sup> (Merck) is a live, oral vaccine that is developed from human and bovine rotavirus strands. The risk of intussusception for RotaTeq<sup>®</sup> was assessed in a large study, which found no association of increased risk, but it will continue to be monitored post-licensure. The ACIP recommends rou-

tine vaccination at 2-, 4- and 6-months of age. The first dose should be administered by 12 weeks of age, and all doses should be received by 32 weeks of age.<sup>31</sup> Safety and efficacy cannot be guaranteed outside these age ranges. If an infant experiences rotavirus gastroenteritis before receiving all three doses of vaccine, they should still complete the schedule to obtain full immunity.<sup>31</sup>

Adverse effects most commonly reported with RotaTeq<sup>®</sup> are diarrhea and vomiting. According to the CDC, rotavirus vaccine is contraindicated in infants who experienced a severe allergic reaction to previous doses of the vaccine, and those who have experienced a previous episode of intussusception.<sup>31</sup> Caution should be used when administering the vaccine to immunocompromised infants, children with moderate to severe illness including gastroenteritis, and chronic gastrointestinal disease.<sup>31</sup>

RotaTeq<sup>®</sup> is designed to allow the vaccine to be administered directly into the infant's mouth. It is distributed in a plastic dosing tube with a twist-off cap that contains a single 2-mL dose of the pale, yellow-colored liquid. The vaccine is stable at refrigerator temperatures 2°C to 8°C (36°F to 46°F) for 24 months, but should be administered as soon as possible after being removed from refrigeration.<sup>31</sup>

If the infant does not ingest the whole dose, or vomits during or after ingestion, do not re-administer the dose of vaccine. The infant should receive proper immunity from the previous or remaining recommended doses.

### Meningococcal polysaccharide and conjugate vaccines

The bacteria *Neisseria meningitidis* is the cause of an acute and possibly severe illness called meningococcal disease. In the U.S., it is a leading cause of bacterial meningitis and sepsis, and also causes diseases such as arthritis and pneumonia.<sup>33</sup> Up to 10 percent of adolescents and adults are asymptomatic transient nasopharyngeal carriers of non-disease causing strains of *N. meningitidis*.<sup>34</sup> There

are two meningococcal vaccinations available in the U.S. at this time.

The meningococcal polysaccharide (MPSV4) is a tetravalent vaccine containing 50 mcg of all four purified *N. meningitidis* capsular polysaccharides (A, C, Y, W-135) and was licensed for use in 1978 (Menomune<sup>®</sup>, Sanofi Pasteur).<sup>34</sup> The response to this vaccine is age-dependent, which in this case means poor immune response in children 2 years of age and younger. MPSV4 is a subcutaneous injection and is available in a single-dose vial with sterile water as the diluent. It is also available as a 10-dose vial with a diluent that contains the preservative thimerosal.<sup>34</sup>

In 2005, the U.S. licensed the first meningococcal conjugate vaccine MCV4 (Menactra<sup>®</sup>, Sanofi Pasteur). This vaccine contains the same bacterial capsular polysaccharide serogroups (A, C, Y, and W-135), conjugated to diphtheria toxoid protein. The vaccine is administered IM and only is available as single-dose vials.<sup>34</sup>

Bacterial polysaccharides are T-cell independent antigens, therefore they do not induce a memory response. MPSV4 does not produce long-lasting immunity nor does it cause a lasting reduction in nasopharyngeal carriage of the bacteria. Conjugating the polysaccharides to a diphtheria toxoid protein changes the immune response to a T-cell dependent which allows for an improved and longer-lasting protection. The conjugate vaccine (MCV4) also is predicted to decrease the amount of nasopharyngeal carriage and produce "herd" immunity (like pneumococcal and Hib conjugate vaccines).<sup>33</sup>

The ACIP recommendations include use of both vaccines. MCV4 is recommended for administration to all children 11-12 years of age, unvaccinated adolescents upon entry into high school (15 years old) and all college freshman living in dormitories. The conjugate vaccine is also the suggested vaccine for people who are at increased risk of meningococcal disease and are 11-55 years of age.<sup>34</sup>

The meningococcal polysaccharide

vaccine (MPSV4) is not recommended by the ACIP for routine vaccination because of the lack of response in children younger than 2 years old and short duration of immunity. It should only be used in people 2-10 years old, and those older than 55 years of age who are at increased risk for *N. meningitidis* infection. MPSV4 also can be used when MCV4 is not available.<sup>34</sup> People at increased risk for infection include microbiologists who are routinely exposed to *N. meningitidis*, military recruits, people with complement deficiencies or asplenia, and people who travel or reside in countries where *N. meningitidis* is prevalent.<sup>33</sup> Both vaccines can be used during a meningococcal outbreak.

People who have been vaccinated with MPSV4 who continue to be at high risk for meningococcal infection may require revaccination. For a child who was less than 4 years of age when first vaccinated, revaccination should be considered after 2-3 years. For older children and adults who continue to be at risk, revaccination should be considered within 3-5 years of the first vaccination.<sup>33</sup> ACIP recommends revaccination of people 11-55 years of age with MCV4 if available.<sup>34</sup> Studies are expected to confirm the assumption that immunity with MCV4 lasts longer than that of MPSV4. Data that becomes available in the future should guide recommendations on revaccination for people vaccinated with MCV4 previously.

Adverse reactions following vaccination are similar with both vaccines. Local reactions, such as pain and redness at the injection site, are most common. Fever, malaise and fatigue also were reported, but few (3 percent) of these systemic reactions were classified as severe. Both MCV4 and MPSV4 are contraindicated in people who have experienced a severe allergic reaction following a prior dose and people with moderate or severe acute illness.<sup>34</sup>

Storage of both vaccines should be at refrigerator temperature of 2°C to 8°C (35°F to 46°F) and not frozen. After being reconstituted, single-dose vials of MPSV4 must

be used within 30 minutes, and multidose vials must be used within 10 days.<sup>34</sup>

### Influenza vaccines

Influenza is a highly infectious viral illness that occurs usually in the winter-time among all age groups. In the U.S., from 1990-1999, an average of 36,000 deaths per year were associated with influenza epidemics.<sup>35</sup> Infection occurs among children the most, but serious illness and death is more common in children younger than 2 years of age, adults older than 65 years of age and anyone who is high risk for complications from influenza. Table 4 summarizes patient populations at high risk.

Trivalent inactivated influenza vaccine (TIV) and live attenuated influenza vaccine (LAIV) are the two types of vaccines available in the United States. TIV is an IM injection that has been available in the U.S. since the 1940s and is provided by three different manufacturers for the 2006-07 influenza season.<sup>36</sup> Certain inactivated influenza vaccines are approved for use as young as 6 months of age, including people who are healthy as well as those with chronic conditions. Both the TIV and LAIV contain three viruses (type A [H1N1], type A [H3N2] and type B) that are grown in eggs and may contain some egg protein. The virus strains can be changed yearly if new strains emerge. Table 5 summarizes the available products.<sup>35</sup>

The LAIV was approved in 2003 for use in the United States in healthy people 5-49 years of age. It is administered intranasally and provided in a single-dose sprayer with half the dose given in each nostril. Because LAIV contains live virus that must replicate to cause immunity, people can experience mild signs or symptoms related to the influenza infection. Studies have shown that children 8-36 months who

were vaccinated shed the vaccine virus for up to three weeks in their nasal secretions. More data is needed to establish the frequency of shedding among people 5-49 years old.

Effectiveness of the TIV depends largely on the age and health of the vaccinee, and how similar the viruses being transmitted are to the viruses administered in the vaccine. In healthy vacci-

nated starting in November. Children 6 months to 9 years old who are being vaccinated for the first time should receive two doses administered at least 30 days apart. TIV also is recommended for all people 50 years of age and older. Only TIV should be used to vaccinate pregnant women and can be administered during any trimester.<sup>35</sup>

The live attenuated influenza vaccine is given annually and approved only for use in healthy people 5-49 years of age. Children 5-8 years old receiving the vaccine for the first time should be administered two intranasal doses 6-10 weeks apart. People 9-49 years old should be administered one intranasal dose.<sup>35</sup>

Adverse effects of TIV include local reactions and allergic reactions (possibly caused by egg protein). Therefore, people should not receive the vaccine if they have had previous allergic reaction to the vaccine or eggs, and if they have moderate to severe illness.

Adverse effects associated with LAIV include an increased risk of asthma or reactive airway disease in children aged 12-59 months. Therefore, LAIV should not be used in children younger than 60 months of age or anyone who has asthma, reactive airway disease or other chronic pulmonary diseases. Adults who received LAIV reported increased cough, runny nose, sore throat, congestion and chills. People at high risk of complications of influenza should not receive LAIV until more data is available. Many contraindications exist for the live attenuated influenza vaccine. For a complete list, refer to the CDC.<sup>34</sup>

The CDC recommends that TIV be stored at refrigerator temperatures of 2°C to 8°C (35°F to 46°F), and must not be frozen. Expiration dates are printed on multidose vials. LAIV must be stored at -15°C (5°F) or colder, but it must be

**TABLE 4**  
**Patients at high risk for influenza complications**

Children 6-59 months of age
Children on chronic salicylate therapy
Women who will be pregnant during influenza season
Patients with chronic pulmonary or cardiovascular disorder (other than hypertension)
Patients with diabetes
Patients with renal dysfunction
Patients who are immunocompromised
Patients in nursing home or chronic-care facility residents
Patients with hemoglobinopathies
Patients with conditions that compromise handling of respiratory secretions
People 65 years of age and older

nated persons younger than 65 years of age, up to 90 percent are protected if the viruses are similar. In people 65 years old and older, the vaccine is only 30-40 percent effective in preventing illness, but 80 percent effective in preventing death. TIV is most effective when given 2-4 months before exposure. Data available also shows the efficacy of LAIV in healthy children (5-7 years old) and adults (18-49 years old).<sup>35</sup>

The ACIP recommends that the TIV be given annually to children 6-59 months of age and siblings or contacts of children 0-59 months old. Vaccinate people 5 years and older with risk factors (see Table 4), or living in a long-term care facility. Vaccination should start in October for health care workers, people at increased risk and children younger than 9 years old receiving their first influenza vaccination. All remaining groups should be vacci-

**TABLE 5**  
**Influenza vaccine products**

Vaccine	Manufacturer	Age indication
Fluzone® Inactivated TIV	Sanofi Pasteur, Inc.	6 months and older
FluMist™ LAIV	MedImmune Vaccines, Inc.	Healthy persons 5-49 years old
Fluvirin™ Inactivated TIV	Novartis Vaccine	4 years and older
Fluarix™ Inactivated TIV	GlaxoSmithKline, Inc.	18 years and older

thawed before intranasal administration. It can be thawed in a refrigerator and stored for up to 60 hours before use, or it can be held in the palm of the hand until thawed and administered immediately.<sup>35</sup>

#### Human Papillomavirus Vaccine

Human Papillomavirus (HPV) is a sexually transmitted infection that is the primary cause of anogenital warts and cervical cancer in women. Up to 70 percent of sexually active women will become infected with HPV. Persistent infection may lead to cervical cancer, the most common cause of cancer death in women. In 2006, labeling for a Human papilloma virus quadrivalent recombinant vaccine (Gardasil®, Merck) was approved by the FDA.

The HPV vaccine contains virus-like particles of HPV types 6, 11, 16 and 18. It is administered IM in a three-dose series. The initial injection is followed by subsequent doses at 2 and 6 months. At the time of this publication, HPV vaccine had not been added to the immunization schedule, however, it will be added during the next revision. It can be given to children as young as 9 years of age and currently is recommended for administration with other vaccines at 11-12 years of age by ACIP. At this time, it only is recommended for females and is most effective if given before exposure to HPV. ACIP recommends catch-up immunization for females 13-26 years of age.

In pre-marketing clinical trials, the most common adverse effects were injection site reactions and fever. Head-

ache, gastroenteritis and pelvic inflammatory disease also were reported. The only contraindications are immediate hypersensitivity to yeast or the HPV vaccine. Although no problems have been reported if administered during pregnancy, it is not recommended until further information is available. ACIP's recommendations on the HPV vaccine are expected to be published in the CDC Morbidity and Mortality Weekly Report in November 2006.<sup>37</sup>

#### Combination vaccine recommendations

The ACIP, the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) recommend that combination vaccines may be used whenever any components of the combination are indicated and its other components are not contraindicated.<sup>38</sup> To complete the CDC-recommended childhood vaccination schedule using single licensed vaccines, a minimum of 18 injections are needed from birth to 6 years of age. Up to 4 injections at any one office visit can be required. Using licensed combination vaccines indicated for the patient's age resolves the issue of multiple injections during single clinic visits and also can bring a child up-to-date quickly if they are behind schedule. Other advantages of combination products include a reduction in cost of stocking and inventory of the separate vaccines, reducing extra clinic visits and the facilitation of adding new vaccines into immunization programs.<sup>4,38</sup>

The drawbacks to combination vac-

cines are potential chemical incompatibility or immunologic interference when combining different antigens into one vaccine. Therefore, only FDA-approved and -licensed combination products should be used. In addition, vaccine combinations that require different schedules might cause confusion and uncertainty when children are treated by multiple vaccine providers who use different products.

As the terminology suggests, combination vaccines merge antigens that prevent different diseases or that protect against multiple strains of infectious agents causing the same disease into a single product. Older combination products include DTaP vaccine, MMR vaccine and the trivalent IPV vaccine. Recent combination products include MMRV vaccine, DTaP-Hib vaccines, Hib-HBV vaccine, HBV-HAV vaccine and DTaP-HBV-IPV vaccine.<sup>38</sup>

It is ill-advised for immunization providers to combine separate vaccines into the same syringe to administer together unless such mixing is indicated for the patient's age on the respective product label inserts approved by the FDA as the immunogenicity and efficacy of this type of unlicensed product are unknown.<sup>38</sup>

The licensure of a vaccine does not necessarily indicate that interchangeability with products of other manufacturers has been demonstrated, but generally vaccines produced by different manufacturers for the same disease are interchangeable in the sequential dosing of immunization series for an individual patient (e.g., HAV, HBV, Hib).<sup>38</sup>

Using combination vaccines containing some antigens not indicated at the time of administration to a pediatric patient might be justified when products that contain only the needed antigens are not readily available or would result in extra injections and potential benefits to the child outweighing the risk of adverse events associated with the extra antigens(s).<sup>38</sup> An extra dose of many live-virus vaccines and Hib or HepB vaccines has not been found to be harmful and, generally, in practice many patients receive extra doses of vaccines or vaccine

antigens without ill effects for diseases to which they are immune.<sup>4,38</sup>

Consideration of reactogenicity must be balanced with the beneficial vaccine effects when inactivated vaccines are administered. However, most clinical experience suggests these reactions to be very low.<sup>38</sup>

### THIMEROSAL PRESERVATIVES

Thimerosal is a mercury-containing compound that has been used as a preservative in biologicals and vaccines since the 1930s. Given the widely acknowledged value of reducing exposure to mercury, a possible link between thimerosal and autism and the precautionary recommendations of ACIP and AAP, vaccine manufacturers, the FDA and other Public Health Service agencies are collaborating to reduce the thimerosal content of vaccines or to replace them with formulations that do not contain thimerosal as a preservative as quickly as possible without causing unnecessary disruptions in the vaccine supply system.<sup>39,40</sup> Past evidence has suggested that the risk, if any, to infants from thimerosal exposure is slight and the risks for not vaccinating children far outweigh the theoretical risk for exposure to thimerosal-containing vaccines during the first six months of life. A 2004 report from the Institute of Medicine (IOM) concluded that there is no association between autism and vaccines that contain thimerosal as a preservative.<sup>20</sup> Even so, much progress has been made, to date, in removing or reducing thimerosal in vaccines. Presently, all vaccines (except inactivated influenza) routinely recommended for infants in the United States are available only as thimerosal-free formulations or containing only trace amounts. Inactivated influenza vaccine still is available in a formulation that contains thimerosal, but also is available as thimerosal-free and containing trace amounts.<sup>20</sup>

### TIMING AND SPACING OF VACCINES

Issues often encountered in clinical practice include timing of antibody-containing blood products (e.g. immune globulin), live vaccines (most important-

ly, measles vaccine) and simultaneous and nonsimultaneous administration of different vaccines and intervals between subsequent doses of the same vaccine.<sup>5</sup>

Antibody-vaccine interactions: Inactivated vaccines generally are not affected by circulating antibody to the antigen, therefore simultaneous administration of antibody (e.g. immune globulin) is recommended for post-exposure prophylaxis of certain diseases, such as HBV infection, rabies and tetanus.<sup>5</sup> However, as live attenu-

ated vaccines require viral replication to elicit the immune response, the presence of circulating antibody may ameliorate the immunogenic process. Therefore, if a live injected vaccine, such as MMR or varicella, must be given around the time that antibody is given, enough separation time must be allowed such that antibody interference with viral replication is minimized.<sup>5</sup> If the vaccine is given first, separation of at least two weeks is needed before giving antibody. If the time interval is less than two weeks, the recipient should be tested for immunity or the vaccine dose should be repeated (see Table 6). If the antibody is given first, it is necessary to wait until the antibody has decayed sufficiently (could be up to 11 months [refer to the ACIP for a complete list]) before giving the live vaccine.<sup>5</sup> Oral typhoid and yellow fever vaccines are not affected by blood products or immune globulin, and can be given simultaneously. Most Americans do not have immunity to these diseases, so donated blood products do not have much antibody. More information is needed before a recommendation can be made about the effect of circulating antibody on live attenuated influenza vaccine.<sup>5</sup>

**Simultaneous vaccine administration:** As a general rule, there are no contraindications to simultaneous administration of most vaccines and this

does not result in decreased antibody responses or increased rates of adverse reactions. Simultaneous administration of live attenuated vaccines is preferred when possible. Live vaccines not administered simultaneously should be given at least one month apart to prevent or reduce interference in response from the vaccine given first or the vaccine given

**TABLE 6**  
**Guidelines for spacing of live and inactivated vaccines<sup>3</sup>**

Combination	Minimum dosing interval
Two live antigens	Four week minimum
Inactivated + live	Give simultaneously or at any interval
Two inactivated	Give simultaneously or at any interval

later. Killed and live vaccines may be administered simultaneously. Inactivated vaccines can be simultaneously administered at separate sites.<sup>5</sup>

**Intervals between subsequent doses of the same vaccine:** Recommended spacing between doses should be maintained. Increasing the interval between doses of a multi-dose vaccine does not diminish the effectiveness of the vaccine; however, decreasing the interval may attenuate the immune response.<sup>5</sup> The ACIP recommends that vaccines can be counted as valid if they are given up to four days before minimum interval or age. If the dose is given five days before minimum age or interval, that dose must be repeated. It is not necessary to restart the series of any vaccine due to extended intervals between doses.<sup>5</sup>

### CONCLUSION

The art, science and biologicals of immunization continue to evolve. Vaccines for vaccine-preventable infectious diseases continue to be developed and post-marketing surveillance trials continue to uncover areas of suboptimal vaccination. Pharmacists are in positions of critical importance in sustaining successful programs, embarking on new programs and enhancing suboptimal programs both as immunization providers and as educators.

# Recent Developments in Pediatric Immunization

## Learning Assessment

- The recommended immunization schedule for children includes administration of the primary series at which of the following ages?
  - 1, 3 and 6 months
  - 1, 2, 6 and 12 months
  - 2, 4, 6 and 12 months
  - 2, 6 and 24 months
- Each of the following patients can safely receive live vaccines EXCEPT:
  - A child with a mild upper respiratory tract infection
  - A child receiving chemotherapy for leukemia
  - A child on a daily inhaled corticosteroid
  - A child with autism
- Which of the following is a contraindication to the DTaP vaccine?
  - Immunosuppression due to systemic corticosteroids
  - Egg allergy manifested as a rash
  - Mild gastroenteritis
  - Previous neurologic reaction to the vaccine
- Which of the following products should be used once as a diphtheria, tetanus, and pertussis booster after a patient has received their primary series?
  - Adacel®
  - Tripedia®
  - Daptacel®
  - Infanrix®
- Which of the following statements about poliovirus vaccination is TRUE?
  - It is given as a 4-dose series
  - Oral polio vaccine should be given to unvaccinated children planning travel to a polio-endemic area
  - Inactivated poliovirus vaccine produces excellent intestinal immunity
  - Inactivated poliovirus vaccine has been associated with vaccine-induced poliomyelitis
- At what age is immunization against haemophilus influenza type B no longer necessary?
  - 12 months and older
  - 24 months and older
  - 36 months and older
  - 60 months and older
- What is the minimum age at which a child can receive their first doses of MMR and varicella vaccines?
  - 6 months
  - 12 months
  - 24 months
  - 36 months
- How many doses are required to complete the varicella virus vaccination series?
  - 1
  - 2
  - 3
  - 4
- Which influenza virus vaccine product should be used to vaccinate a 12-month-old child?
  - Trivalent inactivated vaccine (Fluzone®)
  - Live attenuated vaccine (FluMist™)
  - None, influenza vaccine should not be administered to a 12-month-old
- If not administered on the same day, 2 live vaccines should be separated by at least how much time?
  - 3 days
  - 1 week
  - 2 weeks
  - 4 weeks

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