

## General Recommendations on Immunization

### Recommendations of the Advisory Committee on Immunization Practices (ACIP)



Continuing Education Examination available at <http://www.cdc.gov/mmwr/cme/conted.html>



**U.S. Department of Health and Human Services**  
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1. The nonsimultaneous administration of yellow fever (YF) vaccine and inactivated vaccines.
2. Simultaneous administration of an inactivated and live vaccine (e.g., pneumococcal polysaccharide vaccine [PPSV] and zoster [Zos] vaccine).
3. Interchangeability of combination vaccines and single-component vaccines (e.g., using single-component *Haemophilus influenzae* type b [Hib], diphtheria and tetanus toxoids and acellular pertussis (DTaP), and inactivated poliovirus [IPV] for later doses in series, after a series has begun with DTaP-IPV/Hib).
4. Interchangeability of brands of combination vaccines and single-component vaccines (e.g., using DTaP-IPV/Hib and single-component hepatitis B [Hep B] vaccine for later doses in series that might have previously included DTaP-IPV-HepB and Hib).
5. Rotarix and RotaTeq need not be repeated if an infant spits up or regurgitates a dose.
6. Contact allergy to latex is neither a contraindication nor a precaution to the use of quadrivalent meningococcal conjugate vaccine (MCV4) in the absence of an anaphylactic allergy.
7. No need to repeat a dose of MCV4 vaccine given subcutaneously.
8. Revaccination with MCV4.
9. Appropriate storage and handling for the following vaccines at 35°F–46°F:
  - DTaP
  - Hib
  - Hepatitis A
  - Hepatitis B
  - Human papillomavirus (HPV)
  - PPSV
  - Measles, mumps, and rubella (MMR)
  - Pneumococcal conjugate vaccine (PCV)
  - Rotavirus (RV)
  - Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine
  - Trivalent inactivated influenza vaccine (TIV)
10. Initiation of live Zos vaccine in immunocompetent patients 3 months after remission from chemotherapy.
11. Avoiding conception for 1 month after vaccination with MMR or varicella (Var) vaccine.
12. A minimum age of 12 months for the fourth dose of DTaP.
13. Use of pneumococcal conjugate vaccine and *Haemophilus influenzae* b vaccine in persons receiving hematopoietic cell transplant or who are infected with human immunodeficiency virus, regardless of age.

There is no commercial support for this activity.

**Credit:** Constant Joseph Desbordes (1761–1827), *Baron Jean Louis Alibert (1768–1837) performing the vaccination against smallpox in the Château of Liancourt* (detail), c. 1820, French. Oil on canvas. Courtesy: Musée de l'Assistance Publique — Hôpitaux de Paris, Paris, France / Archives Charmet / The Bridgeman Art Library.

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# General Recommendations on Immunization

## Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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### Summary

*This report is a revision of the General Recommendations on Immunization and updates the 2006 statement by the Advisory Committee on Immunization Practices (ACIP) (CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2006;55[No. RR-15]). The report also includes revised content from previous ACIP recommendations on the following topics: adult vaccination (CDC. Update on adult immunization recommendations of the immunization practices Advisory Committee [ACIP]. MMWR 1991;40[No. RR-12]); the assessment and feedback strategy to increase vaccination rates (CDC. Recommendations of the Advisory Committee on Immunization Practices: programmatic strategies to increase vaccination rates—assessment and feedback of provider-based vaccination coverage information. MMWR 1996;45:219–20); linkage of vaccination services and those of the Supplemental Nutrition Program for Women, Infants, and Children (WIC program) (CDC. Recommendations of the Advisory Committee on Immunization Practices: programmatic strategies to increase vaccination coverage by age 2 years—linkage of vaccination and WIC services. MMWR 1996;45:217–8); adolescent immunization (CDC. Immunization of adolescents: recommendations of the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, the American Academy of Family Physicians, and the American Medical Association. MMWR 1996;45[No. RR-13]); and combination vaccines (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[No. RR-5]).*

*Notable revisions to the 2006 recommendations include 1) revisions to the tables of contraindications and precautions to vaccination, as well as a separate table of conditions that are commonly misperceived as contraindications and precautions; 2) reordering of the report content, with vaccine risk-benefit screening, managing adverse reactions, reporting of adverse events, and the vaccine injury compensation program presented immediately after the discussion of contraindications and precautions; 3) stricter criteria for selecting an appropriate storage unit for vaccines; 4) additional guidance for maintaining the cold chain in the event of unavoidable temperature deviations; and 5) updated revisions for vaccination of patients who have received a hematopoietic cell transplant. The most recent ACIP recommendations for each specific vaccine should be consulted for comprehensive details. This report, ACIP recommendations for each vaccine, and additional information about vaccinations are available from CDC at <http://www.cdc.gov/vaccines>.*

### Introduction

CDC recommends routine vaccination to prevent 17 vaccine-preventable diseases that occur in infants, children, adolescents, or adults. This report provides information for

clinicians and other health-care providers about concerns that commonly arise when vaccinating persons of various ages. Providers and patients encounter numerous issues, such as the timing of each dose, screening for contraindications and precautions, the number of vaccines to be administered, the educational needs of patients and parents, and interpreting and responding to adverse events. Vaccination providers help patients understand the substantial, occasionally conflicting, information about vaccination. These vaccination recommendations are intended for clinicians and other health-care providers who vaccinate patients.

The material in this report originated in the National Center for Immunization and Respiratory Diseases, Anne Schuchat, MD, Director.

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The guidance in this report will help vaccination providers to assess vaccine benefits and risks, use recommended administration and storage practices, understand the most effective strategies for ensuring that vaccination coverage in the population remains high, and communicate the importance of vaccination to reduce the effects of vaccine-preventable disease. These recommendations are intended for use in the United States; vaccine availability, use, and epidemiologic circumstances might differ in other countries and might warrant different recommendations.

## Methods

The Advisory Committee on Immunization Practices (ACIP) General Recommendations Work Group (GRWG) revises the *General Recommendations on Immunization* every 3 to 5 years. Relevant topics are those identified by ACIP as topics that relate to all vaccines, including timing and spacing of doses, vaccine administration, and vaccine storage and handling. New topics often are added when ACIP decides that previous ACIP statements on general issues such as combination vaccines, adolescent vaccination, or adult vaccination should be revised and combined with the *General Recommendations on Immunization*.

The recommendations in this report are based not only on available scientific evidence but also on expertise that comes directly from a diverse group of health-care providers and public health officials. GRWG includes professionals from academic medicine (pediatrics, family practice, and pharmacy); international (Canada), federal, and state public health professionals; and a member from the nongovernmental Immunization Action Coalition. GRWG, which met monthly beginning June 2007, formed subgroups on the basis of interest in topics such as timing and spacing, vaccine administration, and storage and handling. These subgroups also met monthly, conducted literature reviews, and contributed expert opinion on the need for revisions to specific language. In October 2008, GRWG consulted ACIP to determine the best mechanism for approving the resulting document. ACIP concluded that the document could be approved and finalized incrementally, with a final vote on the entire document.

Revisions to the following sections were approved through consensus vote in October 2008 (i.e., were approved as a part of the entire document and not through separate votes on each section): 1) Timing and Spacing of Immunobiologics; 2) Contraindications and Precautions; 3) Preventing and Managing Adverse Reactions; 4) Reporting Vaccine Adverse Events; 5) the National Vaccine Injury Compensation Program; and 6) Vaccine Administration. In February 2009, revisions were made to Storage and Handling of Immunobiologics, and ACIP approved the section. In June

2009, ACIP voted to incorporate the contents of a 1999 ACIP statement on combination vaccines. The statement was revised by GRWG and the ACIP Combination Vaccines Work Group. ACIP also approved minor changes to the section on Special Situations and the section on Vaccination Records. In October 2009, ACIP voted to revise the entire *General Recommendations on Immunization*, which incorporated ACIP recommendations on adolescent vaccination (1996) and adult vaccination (1991) into the section on Vaccination Programs. Three votes were taken to approve various sections of the document, and one vote was taken to approve the entire document. At this final meeting, ACIP also discussed concerns about the lack of evidence that supports use of antipyretics before or at the time of vaccination for the prevention of fever. Consequently, CDC added information highlighting the lack of evidence for the use of antipyretics to the section on Methods for Alleviating Discomfort and Pain Associated with Vaccination. The last meeting of GRWG was held on December 2, 2009. This meeting served solely to update the work group regarding the discussions and vote of the October 2009 meeting and CDC deliberations on changes to the recommendations on the use of antipyretics.

## Timing and Spacing of Immunobiologics

### General Principles for Vaccine Scheduling

Optimal response to a vaccine depends on multiple factors, including the type of vaccine, age of the recipient, and immune status of the recipient. Recommendations for the age at which vaccines are administered are influenced by age-specific risks for disease, age-specific risks for complications, age-specific responses to vaccination, and potential interference with the immune response by passively transferred maternal antibodies. Vaccines are recommended for members of the youngest age group at risk for experiencing the disease for which efficacy and safety have been demonstrated.

Certain products, including inactivated vaccines, toxoids, recombinant subunit vaccines, polysaccharide conjugate vaccines, and live vaccines, require  $\geq 2$  doses to elicit an adequate antibody response. Tetanus and diphtheria toxoids require booster doses to maintain protective antibody concentrations. Unconjugated polysaccharide vaccines do not induce T-cell memory, and additional doses (although they elicit the same or a lower antibody concentration) might increase the level of protection. Conjugation with a protein carrier improves the effectiveness of polysaccharide vaccines by inducing T-lymphocyte-dependent immunologic function. Many vaccines that stimulate both cell-mediated immunity and neutralizing antibodies (e.g., live, attenuated virus



vaccines) usually can induce prolonged immunity, even if antibody titers decline over time (1). Subsequent exposure to such viruses usually results in a rapid anamnestic antibody response without viremia.

Approximately 90%–95% of recipients of a single dose of certain live vaccines administered by injection at the recommended age (i.e., measles, rubella, and yellow fever vaccines) develop protective antibodies, generally within 14 days of the dose. For varicella and mumps vaccines, 80%–85% of vaccinees are protected after a single dose. However, because a limited proportion (5%–15%) of measles, mumps, and rubella (MMR) or varicella vaccinees fail to respond to 1 dose, a second dose is recommended to provide another opportunity to develop immunity (2). Of those who do not respond to the first dose of MMR or varicella vaccine, 97%–99% respond to a second dose (3,4).

The *Recommended Immunization Schedules for Persons Aged 0 Through 18 Years* and the *Recommended Adult Immunization Schedule* are revised annually. Physicians and other health-care providers should ensure that they are following the most up-to-date schedules, which are available from CDC at <http://www.cdc.gov/vaccines>.

## Spacing of Multiple Doses of the Same Antigen

Vaccination providers should adhere as closely as possible to recommended vaccination schedules (Table 1). Administration at recommended ages and in accordance with recommended intervals between doses of multidose antigens provide optimal protection.

Administration of doses of a multidose vaccine using intervals that are shorter than recommended might be necessary in certain circumstances, such as impending international travel or when a person is behind schedule on vaccinations but needs rapid protection. In these situations, an accelerated schedule can be implemented using intervals between doses that are shorter than intervals recommended for routine vaccination. The accelerated or minimum intervals and ages for scheduling catch-up vaccinations are available at <http://www.cdc.gov/vaccines>. Vaccine doses should not be administered at intervals less than these minimum intervals or at an age that is younger than the minimum age.\*

Before administering a vaccine dose, providers might need to verify that all previous doses were administered after the minimum age and in accordance with minimum intervals (Table 1). In clinical practice, vaccine doses occasionally are administered at intervals less than the minimum interval or at ages younger than the minimum age. Doses administered too close together or at too young an age can lead to a suboptimal immune response. However, administering a dose a few days earlier the minimum interval or age is unlikely to have a substantially negative effect on the immune response to that dose. Vaccine doses administered  $\leq 4$  days before the minimum interval or age are considered valid; however, local or state mandates might supersede this 4-day guideline.<sup>†</sup> (Day 1 is the day before the day that marks the minimum age or minimum interval for a vaccine.) Because of the unique schedule for rabies vaccine, the 4-day guideline does not apply to this vaccine (5). Doses of any vaccine administered  $\geq 5$  days earlier than the minimum interval or age should not be counted as valid doses and should be repeated as age appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval (Table 1). For example, if the first and second doses of *Haemophilus influenzae* type b (Hib) were administered only 14 days apart, the second dose would be invalid and need to be repeated because the minimum interval from dose 1 to dose 2 is 4 weeks. The repeat dose should be administered  $\geq 4$  weeks after the invalid dose (in this case, the second). The repeat dose is counted as the valid second dose.

If the first dose in a series is given  $\geq 5$  days before the recommended minimum age, the dose should be repeated on or after the date when the child reaches at least the minimum age. If the vaccine is a live vaccine, ensuring that a minimum interval of 28 days has elapsed from the invalid dose is recommended. For example, if the first dose of varicella vaccine were inadvertently administered at age 10 months, the repeat dose would be administered no earlier than the child's first birthday (the minimum age for the first dose). If the first dose of varicella vaccine were administered at age 11 months and 2 weeks, the repeat dose should be administered no earlier than 4 weeks thereafter, which would occur after the first birthday.

Certain vaccines (e.g., adult tetanus and diphtheria toxoids [Td], pediatric diphtheria and tetanus toxoids [DT]; and tetanus toxoid) produce increased rates of local or systemic reactions in certain recipients when administered more frequently than recommended (6,7). Careful record keeping, maintenance

\*During measles outbreaks, if cases are occurring among infants aged  $<12$  months, measles vaccination of infants as young as 6 months can be used as an outbreak control measure. However, doses administered at ages  $<12$  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[No. RR-8]).

<sup>†</sup>In certain situations, local or state requirements might mandate that doses of selected vaccines be administered on or after specific ages. For example, a school entry requirement might not accept a dose of MMR or varicella vaccine administered before the child's first birthday. ACIP recommends that physicians and other health-care providers comply with local or state vaccination requirements when scheduling and administering vaccines.

of patient histories, use of immunization information systems (IISs), and adherence to recommended schedules can decrease the incidence of such reactions without adversely affecting immunity.

## Simultaneous Administration

Simultaneous administration of vaccines is defined as administering more than one vaccine on the same clinic day, at different anatomic sites, and not combined in the same syringe. Experimental evidence and extensive clinical experience provide the scientific basis for administering vaccines simultaneously. Simultaneously administering all vaccines for which a person is eligible at the time of a visit increases the probability that a child, adolescent, or adult will be vaccinated fully by the appropriate age (8). A study conducted during a measles outbreak demonstrated that approximately one third of measles cases among unvaccinated but vaccine-eligible preschool children might have been prevented if MMR had been administered at the same visit when another vaccine was administered (9). Simultaneous administration also is critical when preparing for foreign travel and when a health-care provider is uncertain that a patient will return for additional doses of vaccine.

With some exceptions, simultaneously administering the most widely used live and inactivated vaccines has produced seroconversion rates and rates for adverse reactions similar to those observed when the vaccines are administered separately (10–13). Routine administration of all age-appropriate doses of vaccines simultaneously is recommended for children for whom no specific contraindications exist at the time of the visit. MMR and varicella vaccine can be administered simultaneously. Live, attenuated influenza vaccine (LAIV) does not interfere with the immune response to MMR or varicella vaccines administered at the same visit. No data exist about the immunogenicity of oral Ty21a typhoid vaccine when administered concurrently or within 30 days of live virus vaccines. In the absence of such data, if typhoid vaccination is warranted, administration should not be delayed because of recent administration of live, attenuated virus vaccines (14). Simultaneous administration of pneumococcal polysaccharide vaccine (PPSV) and inactivated influenza vaccine elicits a satisfactory antibody response without increasing the incidence or severity of adverse reactions (15). Simultaneous administration of PPSV and inactivated influenza vaccine is recommended for all persons for whom both vaccines are indicated. Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) and trivalent inactivated influenza vaccine (TIV) can be administered simultaneously (16). Hepatitis B vaccine administered with yellow fever vaccine is as safe and immunogenic as when

these vaccines are administered separately (17). Measles and yellow fever vaccines have been administered safely at the same visit and without reduction of immunogenicity of either of the components (18,19).

Depending on which vaccines are administered during the first year of life, a child might receive up to nine injections at the 12- through 15-month visit (MMR, varicella, Hib, pneumococcal conjugate vaccine [PCV], pediatric diphtheria and tetanus toxoids and acellular pertussis [DTaP], inactivated poliovirus [IPV], hepatitis A, hepatitis B, and influenza vaccines). Although there is no exact limit on the number of injections, with a little flexibility, a provider can ensure that the primary series doses are given without administering too many injections at each visit. To reduce the number of injections at the 12- through 15-month visit, the hepatitis B series and 3 doses of IPV (20) can be administered before the child's first birthday.

There are many other examples of ways the vaccination schedule provides flexibility. The majority of children aged 1 year who have received 2 Hib vaccine doses (polyribosylribitol phosphate-meningococcal outer membrane protein [PRP-OMP]) or 3 Hib vaccine doses (PRP-tetanus [PRP-T]) and 3 previous doses of DTaP and PCV have protection against Hib, diphtheria, pertussis, tetanus, and pneumococcus, which lasts throughout infancy (21,22). The third (PRP-OMP) or fourth (PRP-T) dose of the Hib series and the fourth doses of DTaP and PCV are critical in boosting antibody titer and ensuring continued protection (22–25). The fourth dose of DTaP is recommended at age 15–18 months but may be administered as early as age 12 months if 6 months have elapsed since the third dose and if there is concern that the child might not return by age 18 months (23). For infants at low risk for infection with hepatitis B virus (i.e., mother tested negative for hepatitis B surface antigen [HBsAg] at the time of delivery and is not in a high risk group), the hepatitis B series can be completed at any time for children aged 6–18 months (26). The minimum age for administration of combination vaccines is the oldest minimum age for any of the individual components; the minimum interval between doses is equal to the greatest minimum interval of any of the individual components. With use of the combination Hib-hepatitis B vaccine, the minimum age of administration of the final dose is 12 months because of the minimum age requirement for the last dose of the Hib series (26). Recommended spacing of doses should be maintained (Table 1).

## Combination Vaccines

Combination vaccines merge equivalent component vaccines into single products to prevent more than one disease

or to protect against multiple strains of infectious agents causing the same disease. Licensed combination vaccines can be used whenever any components of the combination are indicated and its other components are not contraindicated and if licensed by the Food and Drug Administration (FDA) for that dose in the series. Use of combination vaccines can reduce the number of injections patients receive and alleviate concern associated with the number of injections (20,27,28). Studies have demonstrated that parents and providers might be uncomfortable with multiple injections during single visits (29–31). Potential advantages of combination vaccines include 1) improved vaccine coverage rates (32), 2) timely vaccination coverage for children who are behind the schedule (33,34), 3) reduced shipping and stocking costs, 4) reduced costs for extra health-care visits necessitated by deferral of vaccination, and 5) facilitation of additional new vaccines into vaccination programs.

Potential disadvantages of combination vaccines include the following: 1) adverse events that might occur more frequently after administration of a combination vaccine compared with administration of separate antigens at the same visit, such as those that occur with the combination measles, mumps, rubella, and varicella (MMRV) vaccine and combination DTaP-hepatitis B-IPV vaccine (35,36); 2) confusion and uncertainty about selection of vaccine combinations and schedules for subsequent doses, especially when vaccinations are given by multiple providers who might be using different products; 3) reduced immunogenicity of one or more components (37); 4) extra doses of certain antigens in the fixed product (e.g., a provider who uses DTaP-hepatitis B-IPV vaccine will give an extra dose of hepatitis B component); and 5) a shorter shelf-life than the individual component vaccines. The economic impact of the use of combination vaccines is unclear because combination products have the potential for either increased or decreased costs compared with single-antigen component vaccines. The price of a combination vaccine might exceed the total price of separate vaccines containing the same antigens. However, combination vaccines might represent a better overall economic value if the direct and indirect costs of extra injections, delayed or missed vaccinations, and additional handling and storage are taken into consideration (38).

### Licensed Combination Vaccines

In this report, a combination vaccine is defined as a product containing components that can be divided equally into independently available routine vaccines. A dash ( - ) between vaccine products indicates that products are supplied in their final form by the manufacturer and do not require mixing or reconstitution by the user. A slash ( / ) indicates that the products must be mixed or reconstituted by the user. Seven

combination vaccines for which separate antigens or antigen combinations exist have been licensed by FDA since 1996 in the United States (Table 2) (39–45). In the future, combination vaccines might include increasing numbers of components in different arrays to protect against these and other diseases. (The status of licensure and recommendations for new vaccines is available at <http://aapredbook.aappublications.org/news/vaccstatus.shtml>.) The use of a combination vaccine generally is preferred over separate injections of the equivalent component vaccines. Considerations should include provider assessment,<sup>§</sup> patient preference, and the potential for adverse events. An exception is the first dose of MMRV. Unless the parent or caregiver expresses a preference for MMRV vaccine, MMR and varicella vaccine should be administered for the first dose for children aged 12–47 months (35).

Situations might arise in which one component of a combination vaccine is specifically preferred to another component in that same vaccine. Future research considerations for newly licensed combination vaccines should focus on safety of doses that are not needed because a patient is already vaccinated against the agents, whether the combination vaccine will improve the timeliness of vaccination, and potential reduced costs from disease prevention resulting from timely vaccination.

### Combination Vaccines and FDA Licensure

Only combination vaccines licensed by FDA should be used. Vaccination providers should not combine separate vaccines into the same syringe to administer together unless mixing is indicated for the patient's age and is explicitly specified on the FDA-approved product label inserts. Only two combination vaccines (DTaP-IPV/Hib vaccine, marketed as Pentacel, and DTaP/Hib, marketed as TriHibit) contain separate antigen components for which FDA approves mixing by the user. The safety, immunogenicity, and effectiveness of unlicensed combinations are unknown.

### Interchangeability of Formulations

FDA generally licenses a combination vaccine based on studies demonstrating that the product's immunogenicity (or efficacy) and safety are comparable or equivalent to monovalent or combination products licensed previously (46). FDA licensure also generally indicates that a combination vaccine may be used interchangeably with monovalent formulations and other combination products with similar component antigens produced by the same manufacturer to continue the vaccination series. For example, DTaP, DTaP/Hib, and future

<sup>§</sup> Provider assessment should include number of injections, vaccine availability, likelihood of improved coverage, likelihood of patient return, and storage and cost considerations.

DTaP vaccines that contain similar acellular pertussis antigens from the same manufacturer may be used interchangeably if licensed and indicated for the patient's age (45).

### Interchangeability of Combination Vaccines from Different Manufacturers

Licensure of a vaccine by FDA does not necessarily indicate that the vaccine is interchangeable with products from other manufacturers. Such data are ascertained and interpreted more readily for diseases with known correlates of protective immunity (e.g., specific serologic markers). For diseases without such surrogate laboratory markers, prelicensure field vaccine efficacy (phase III) trials or postlicensure surveillance generally are required to determine protection (47). ACIP prefers that doses of vaccine in a series come from the same manufacturer; however, if this is not possible or if the manufacturer of doses given previously is unknown, providers should administer the vaccine that they have available.

### Vaccine Supply

Although vaccination providers should stock sufficient quantities of combination and monovalent vaccines needed to vaccinate children, adolescents, and adults against all diseases for which vaccines are recommended (20,28), all available types or brand-name products need not be stocked. Potential advantages of stocking a limited number of vaccines include 1) reducing confusion and potential errors when staff members must handle redundant products and formulations, 2) minimizing waste when less commonly used products expire, 3) decreasing cold storage capacity requirements, and 4) minimizing administrative costs related to accounting, purchasing, and handling.

### Extra Doses of Vaccine Antigens

Administering extra antigens contained in a combination vaccine should be avoided in most situations. Using combination vaccines containing certain antigens not indicated at the time of administration to a patient might be justified when 1) the extra antigen is not contraindicated, 2) products that contain only the needed antigens are not readily available, and 3) potential benefits to the patient outweigh the potential risk for adverse events associated with the extra antigens. An extra dose of many live-virus vaccines and Hib or hepatitis B vaccine has not been found to be harmful (48). However, the risk for an adverse event might increase when extra doses are administered at an earlier time than the recommended interval for certain vaccines (e.g., tetanus toxoid vaccines and PPSV) (16,24,49).

A vaccination provider might not have vaccines available that contain only the antigens needed as indicated by a child's

vaccination history. Alternatively, although the indicated vaccines might be available, the provider might prefer to use a combination vaccine to reduce the required number of injections. In such cases, the benefits and risks of administering the combination vaccine with an unneeded antigen should be carefully considered and discussed with the patient or parent.

When inactivated (i.e., killed), or particularly subunit vaccines (which are often adsorbed to aluminum-salt adjuvants), are administered, the reactogenicity of the vaccine must be considered in balancing the benefits and risks of extra doses. Because clinical experience suggests low reactogenicity, an extra dose of Hib or hepatitis B vaccine may be administered as part of a combination vaccine to complete a vaccination series for another component of the combination. Administration of extra doses of tetanus toxoid vaccines earlier than the recommended intervals can increase the risk for hypersensitivity reactions (16,24,50). Examples of such vaccines include DTaP, DTaP/Hib, DT (for children), Td (for adolescents and adults), and Tdap. Extra doses of tetanus-toxoid-containing vaccines might be appropriate for certain patients, including for children who previously received DT or Td vaccine and need protection from pertussis (in DTaP or Tdap) or for immigrants with uncertain vaccination histories.

### Conjugate Vaccine Carrier Proteins

Certain carrier proteins in existing conjugated Hib vaccines also are used as components of other vaccines (e.g., pneumococcal and meningococcal vaccines) (51). Protein conjugates used in Hib conjugate vaccines produced in the United States include an outer membrane protein complex from *Neisseria meningitidis* (in PRP-OMP), and tetanus toxoid (in PRP-T). Simultaneous administration of quadrivalent meningococcal conjugate vaccine (MCV4), PCV, and Tdap, all of which contain diphtheria toxoid, is not associated with reduced immunogenicity or an increase in local adverse events (24,51).

### Nonsimultaneous Administration

There is no evidence that inactivated vaccines interfere with the immune response to other inactivated vaccines or to live vaccines. Any inactivated vaccine can be administered either simultaneously or at any time before or after a different inactivated vaccine or live vaccine (Table 3).

Limited data are available regarding interference between live vaccines used in the United States. The immune response to one live-virus vaccine might be impaired if administered within 28 days (i.e., 4 weeks) of another live-virus vaccine (52,53). In a study conducted in two U.S. health maintenance organizations, the risk for varicella vaccine failure (i.e., varicella disease in a vaccinated person) among persons who received varicella



vaccine within 28 days of MMR vaccination was threefold higher than among persons who received varicella vaccine >28 days after MMR vaccination (54). Another study determined that the response to yellow fever vaccine is not affected by monovalent measles vaccine administered 1–27 days earlier (18). The effect of nonsimultaneous administration of rubella, mumps, varicella, and yellow fever vaccines is unknown.

To minimize the potential risk for interference, injectable or nasally administered live vaccines not administered on the same day should be administered  $\geq 4$  weeks apart (Table 3). If injectable or nasally administered live vaccines are separated by <4 weeks, the second vaccine administered should not be counted as a valid dose and should be repeated. The repeat dose should be administered  $\geq 4$  weeks after the last invalid dose. Oral vaccines (Ty21a typhoid vaccine and rotavirus) can be administered simultaneously or at any interval before or after other live vaccines (injectable or intranasal) if indicated.

## Spacing of Vaccines and Antibody-Containing Products

### Live Vaccines

Ty21a typhoid, yellow fever, LAIV, zoster, and rotavirus vaccines may be administered at any time before, concurrent with, or after administration of any immune globulin, hyperimmune globulin, or intravenous immune globulin (IGIV) (55). Blood (e.g., whole blood, packed red blood cells, and plasma) and other antibody-containing blood products (e.g., immune globulin, hyperimmune globulin, and IGIV) can inhibit the immune response to measles and rubella vaccines for  $\geq 3$  months. The effect of blood and immune globulin preparations on the response to mumps and varicella vaccines is unknown; however, commercial immune globulin preparations contain antibodies to these viruses. Blood products available in the United States are unlikely to contain a substantial amount of antibody to yellow fever vaccine virus. The length of time that interference with injectable live-virus vaccine (other than yellow fever) can persist after the antibody-containing product is a function of the amount of antigen-specific antibody contained in the product (56–58). Therefore, after an antibody-containing product is received, live vaccines (other than yellow fever, oral Ty21a typhoid, LAIV, zoster, and rotavirus) should be delayed until the passive antibody has degraded (Table 4). If a dose of injectable live-virus vaccine (other than yellow fever and zoster) is administered after an antibody-containing product but at an interval shorter than recommended in this report, the vaccine dose should be repeated unless serologic testing is feasible and indicates a response to the vaccine. The repeat dose or serologic testing should be performed after

the interval indicated for the antibody-containing product (Table 5).

Although passively acquired antibodies can interfere with the response to rubella vaccine, the low dose of anti-Rho(D) globulin administered to postpartum women has not been demonstrated to reduce the response to the RA27/3 strain rubella vaccine (59). Because of the importance of rubella and varicella immunity among women of child-bearing age (4,60), the postpartum vaccination of women without evidence of immunity to rubella or varicella with MMR, varicella, or MMRV vaccines should not be delayed because of receipt of anti-Rho(D) globulin or any other blood product during the last trimester of pregnancy or at delivery. These women should be vaccinated immediately after giving birth and, if possible, tested  $\geq 3$  months later to ensure immunity to rubella and, if appropriate, to measles (2).

Interference might occur if administration of an antibody-containing product becomes necessary after administration of MMR or varicella vaccines. Usually, vaccine virus replication and stimulation of immunity occurs 1–2 weeks after vaccination. If the interval between administration of any of these vaccines and subsequent administration of an antibody-containing product is <14 days, vaccination should be repeated after the recommended interval (Tables 4 and 5) unless serologic testing indicates a protective antibody response.

A humanized mouse monoclonal antibody product (palivizumab) is available as prophylaxis for serious lower respiratory tract disease from respiratory syncytial virus among infants and young children. This product contains only antibody to respiratory syncytial virus and does not interfere with the immune response to licensed live or inactivated vaccines.

### Inactivated Vaccines

Antibody-containing products interact less with inactivated vaccines, toxoids, recombinant subunit, and polysaccharide vaccines than with live vaccines (61). Therefore, administering inactivated vaccines and toxoids either simultaneously with or at any interval before or after receipt of an antibody-containing product should not substantially impair development of a protective antibody response (Table 4). The vaccine or toxoid and antibody preparation should be administered at different sites using the standard recommended dose. Increasing the vaccine dose volume or number of vaccinations is not indicated or recommended.

## Interchangeability of Single-Component Vaccines from Different Manufacturers

Certain vaccines that provide protection from the same diseases are available from different manufacturers, and these

vaccines usually are not identical in antigen content or in amount or method of formulation. Manufacturers use different production processes, and their products might contain different concentrations of antigen per dose or a different stabilizer or preservative.

Available data indicate that infants who receive sequential doses of different Hib conjugate, hepatitis B, and hepatitis A vaccines produce a satisfactory antibody response after a complete primary series (62–65). All brands of Hib conjugate, hepatitis B,<sup>‡</sup> hepatitis A, rotavirus,\*\* and quadrivalent meningococcal conjugate vaccines are interchangeable within their respective series. If different brands of a particular vaccine require a different number of doses for series completion (e.g., Hib and rotavirus vaccines) and a provider mixes brands, the higher number of doses is recommended for series completion (e.g., 3 doses of either rotavirus or Hib vaccines).

Limited data are available about the safety, immunogenicity, and efficacy of using acellular pertussis (e.g., DTaP) vaccines from different manufacturers for successive doses of the pertussis series. Data from one study indicate that for the first 3 doses of the DTaP series, 1–2 doses of Tripedia (Sanofi Pasteur) followed by Infanrix (GlaxoSmithKline) for the remaining dose (or doses) is comparable to 3 doses of Tripedia with regard to immunogenicity, as measured by antibodies to diphtheria, tetanus, and pertussis toxoids, and filamentous hemagglutinin (66). However, in the absence of a clear serologic correlate of protection for pertussis, the relevance of these immunogenicity data for protection against pertussis is unknown. When feasible, the same brand of DTaP vaccine should be used for all doses of the vaccination series. If vaccination providers do not know or have available the type of DTaP vaccine previously administered to a child, any DTaP vaccine may be used to continue or complete the series. For a child who needs 2 doses of influenza vaccine (TIV or LAIV), it is preferable to use the same type of vaccine for both doses. However, if the child is eligible for either TIV or LAIV, and the type of vaccine used for the first dose is not available, either vaccine can be used for the second dose. For vaccines in general, vaccination should not be deferred because the brand used for previous doses is not available or is unknown (23,67).

## Lapsed Vaccination Schedule

Vaccination providers should administer vaccines as close to the recommended intervals as possible. However, intervals between doses that are longer than recommended typically do

not reduce final antibody concentrations, although protection might not be attained until the recommended number of doses has been administered. With exception of oral typhoid vaccine, an interruption in the vaccination schedule does not require restarting the entire series of a vaccine or toxoid or addition of extra doses.

## Unknown or Uncertain Vaccination Status

Vaccination providers frequently encounter persons who do not have adequate documentation of vaccinations. With the exception of influenza vaccine and PPSV, providers should only accept written, dated records as evidence of vaccination; self-reported doses of influenza vaccine and PPSV are acceptable (49,68). Although vaccinations should not be postponed if records cannot be found, an attempt to locate missing records should be made by contacting previous health-care providers, reviewing state or local IISs, and searching for a personally held record. If records cannot be located within a reasonable time, these persons should be considered susceptible and started on the age-appropriate vaccination schedule. Serologic testing for immunity is an alternative to vaccination for certain antigens (e.g., measles, rubella, hepatitis A, and tetanus). However, commercial serologic testing might not always be sufficiently sensitive or standardized for detection of vaccine-induced immunity (with the exception of hepatitis B vaccination at 1–2 months after the final dose), and research laboratory testing might not be readily available.

## Contraindications and Precautions

Contraindications and precautions to vaccination are conditions under which vaccines should not or likely should not be administered. Because the majority of contraindications and precautions are temporary, vaccinations often can be administered later if one or more exist. A contraindication is a condition in a recipient that increases the risk for a serious adverse reaction. A vaccine should not be administered when a contraindication is present; for example, MMR vaccine should not be administered to severely immunocompromised persons. In contrast, certain conditions are commonly misperceived as contraindications (i.e., are not valid reasons to defer vaccination).

National standards for pediatric vaccination practices have been established and include descriptions of valid contraindications and precautions to vaccination. Persons who administer vaccines should screen patients for contraindications and precautions to the vaccine before each dose of vaccine is administered (Table 6). Screening is facilitated by consistent use of screening questionnaires, which are available from certain

<sup>‡</sup> The exception is the 2-dose hepatitis B vaccination series for adolescents aged 11–15 years. Only Recombivax HB (Merck Vaccine Division) should be used in this schedule. Engerix-B (GlaxoSmithKline) is not approved by FDA for this schedule.

\*\* Based on expert opinion.

state vaccination programs and other sources (e.g., the Immunization Action Coalition, <http://www.immunize.org>).

The only contraindication applicable to all vaccines is a history of a severe allergic reaction (i.e., anaphylaxis) after a previous dose of vaccine or to a vaccine component (unless the recipient has been desensitized; see Special Situations section). In addition, severely immunocompromised persons generally should not receive live vaccines. Children who experienced encephalopathy within 7 days after administration of a previous dose of diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP), DTaP, or Tdap not attributable to another identifiable cause should not receive additional doses of a vaccine that contains pertussis. Because of the theoretical risk to the fetus, women known to be pregnant generally should not receive live, attenuated virus vaccines (see Special Situations section).

A precaution is a condition in a recipient that might increase the risk for a serious adverse reaction or that might compromise the ability of the vaccine to produce immunity (e.g., administering measles vaccine to a person with passive immunity to measles from a blood transfusion or administering influenza vaccine to someone with a history of Guillain-Barré syndrome within 6 weeks of a previous influenza vaccination). A person might experience a more severe reaction to the vaccine than would have otherwise been expected; however, the risk for this happening is less than the risk expected with a contraindication. In general, vaccinations should be deferred when a precaution is present. However, a vaccination might be indicated in the presence of a precaution if the benefit of protection from the vaccine outweighs the risk for an adverse reaction. For example a dose of DTaP should be considered for a person in a community with a pertussis outbreak even if that person previously developed Guillain-Barré syndrome after a dose.

The presence of a moderate or severe acute illness with or without a fever is a precaution to administration of all vaccines (Table 6). A personal or family history of seizures is a precaution for MMRV vaccination. A recent study found an increased risk for febrile seizures in children who receive MMRV compared with MMR and varicella vaccine (35).

Clinicians or other health-care providers might misperceive certain conditions or circumstances as valid contraindications or precautions to vaccination when they actually do not preclude vaccination (Table 7). These misperceptions result in missed opportunities to administer recommended vaccines (69). Among the most common conditions mistakenly considered to be contraindications are diarrhea, minor upper respiratory tract illnesses (including otitis media) with or without fever, mild to moderate local reactions to a previous dose of vaccine, current antimicrobial therapy, and being in the convalescent phase of an acute illness.

The decision to administer or delay vaccination because of a current or recent acute illness depends on the severity of symptoms and etiology of the condition. The safety and efficacy of vaccinating persons who have mild illnesses have been documented (70–73). Vaccination should not be delayed because of the presence of mild respiratory tract illness or other acute illness with or without fever. Vaccination should be deferred for persons with a moderate or severe acute illness. This precaution avoids causing diagnostic confusion between manifestations of the underlying illness and possible adverse effects of vaccination or superimposing adverse effects of the vaccine on the underlying illness. After screening them for contraindications, persons with moderate or severe acute illness should be vaccinated as soon as the acute illness has improved. Studies indicate that failure to vaccinate children with minor illnesses can impede vaccination efforts (74–76). Among persons whose compliance with medical care cannot be ensured, use of every opportunity to administer appropriate vaccines is critical.

Routine physical examinations and procedures (e.g., measuring temperatures) are not prerequisites for vaccinating persons who appear to be healthy. The provider should ask the parent or guardian if the child is ill. If the child has a moderate or severe illness, the vaccination should be postponed.

## Preventing and Managing Adverse Reactions

### Benefit and Risk Communication

Parents, guardians, legal representatives, and adolescent and adult patients should be informed about the benefits of and risks from vaccines in language that is culturally sensitive and at an appropriate educational level. Opportunity for questions should be provided before each vaccination. Discussion of the benefits of and risks from vaccination is sound medical practice and is required by law.

The National Childhood Vaccine Injury Act of 1986<sup>††</sup> requires that vaccine information materials be developed for each vaccine covered by the act. These materials, known as vaccine information statements (VISs), must be provided by all public and private vaccination providers each time a vaccine is administered. Copies of VISs are available from state health authorities responsible for vaccination and from CDC (<http://www.cdc.gov/vaccines>). Translations of VISs into languages other than English are available from certain state vaccination programs and from the Immunization Action Coalition website

<sup>††</sup> National Childhood Vaccine Injury Act of 1986. 42 U.S.C. Sect. 300aa-26 (1986).



(<http://www.immunize.org>). The act does not require that a signature be obtained; however, documentation of consent might be recommended or required by certain state or local health authorities or school authorities.

Certain parents or patients question the need for or safety of vaccinations and want to discuss the risks from and benefits of certain vaccines. Some refuse certain vaccines or reject all vaccinations for personal or religious reasons. Having a basic understanding of how patients and parents of patients view vaccine risk and developing effective approaches to address vaccine safety concerns are imperative for vaccination providers.

Each person understands and reacts to vaccine information on the basis of different factors, including previous experience, education, personal values, method of data presentation, perceptions of the risk for disease and perceived ability to control these risks, and risk preference. Increasingly, decisions about vaccination are based on inaccurate information about risk provided by the media and certain websites. Websites and other sources of vaccine information might be inaccurate or incomplete. Health-care providers can be a pivotal source of science-based credible information by discussing with parents and patients the risks from and benefits of vaccines, which helps patients make informed decisions.

When a parent or patient initiates a discussion about a perceived vaccine adverse reaction, the health-care provider should discuss the specific concerns and provide factual information, using appropriate language. Effective, empathetic vaccine risk communication is essential in responding to misinformation and concerns, with health-care providers recognizing that risk assessment and decision-making can be difficult and confusing. Certain vaccines might be acceptable to a parent who is resistant to other vaccines. This partial acceptance can be used to facilitate additional communication. Their concerns can be addressed using the VIS and offering other resource materials (e.g., vaccination information from CDC: <http://www.cdc.gov/vaccines>).

The American Academy of Pediatrics (AAP) does not recommend that providers exclude from their practice patients whose parents or guardians question or refuse vaccination. A limited number of providers might exclude patients on this basis; however, an effective public health strategy is to identify common ground and discuss measures that need to be followed if the decision is to defer vaccination. Health-care providers should reinforce key points about each vaccine, including safety, and emphasize risks for disease among unvaccinated children. Parents should be advised of state laws regarding entry to schools or child-care facilities, which might require that unvaccinated children be excluded from the facility during outbreaks. These discussions should be documented in the patient's medical record, including the refusal to receive certain vaccines (i.e., informed refusal).

## Preventing Adverse Reactions

Vaccines are intended to produce active immunity to specific antigens. An adverse reaction is an undesirable side effect that occurs after a vaccination. Vaccine adverse reactions are classified as 1) local, 2) systemic, or 3) allergic (additional information available at <http://www.fda.gov>). Local reactions (e.g., redness) are usually the least severe and most frequent. Systemic reactions (e.g., fever) occur less frequently than local reactions, and severe allergic reactions (e.g., anaphylaxis) are the least frequent reactions. Severe adverse reactions are rare.

Syncope (vasovagal or vasodepressor reaction) can occur after vaccination and is most common among adolescents and young adults. In 2005, the Vaccine Adverse Event Reporting System (VAERS) began detecting a trend of increasing syncope reports that coincided with the licensure of three vaccines for adolescents: human papillomavirus (HPV), MCV4, and Tdap (77). Of particular concern among adolescents has been the risk for serious secondary injuries, including skull fracture and cerebral hemorrhage. Of 463 VAERS reports of syncope during January 1, 2005, to July 31, 2007, a total of 41 listed syncope with secondary injury with information on the timing after vaccination, and the majority of these syncope reports (76%) occurred among adolescents. Among all age groups, 80% of reported syncope episodes occur within 15 minutes of vaccine administration (additional information available at <http://www.cdc.gov/vaccinesafety/concern/syncope.htm>). Providers should take appropriate measures to prevent injuries if a patient becomes weak or dizzy or loses consciousness. Adolescents and adults should be seated or lying down during vaccination. Vaccine providers, particularly when vaccinating adolescents, should consider observing patients (with patients seated or lying down) for 15 minutes after vaccination to decrease the risk for injury should they faint (77). If syncope develops, patients should be observed until the symptoms resolve.

## Managing Acute Vaccine Reactions

Although anaphylactic reactions are rare after vaccination, their immediate onset and life-threatening nature require that all personnel and facilities providing vaccinations have procedures in place for anaphylaxis management. All vaccination providers should be familiar with the office emergency plan and be currently certified in cardiopulmonary resuscitation. Epinephrine and equipment for maintaining an airway should be available for immediate use.

Anaphylaxis usually begins within minutes of vaccine administration (78–80). Rapid recognition and initiation of treatment are required to prevent possible progression to cardiovascular collapse. If flushing, facial edema, urticaria, itching, swelling of the mouth or throat, wheezing, dyspnea, or other



signs or symptoms of anaphylaxis occur, the patient should be placed in a recumbent position with the legs elevated if possible (81,82). Administration of epinephrine is the management of choice. Additional drugs also might be indicated (Table 8) (83). Maintenance of the airway and oxygen administration might be necessary. After the patient is stabilized, arrangements should be made for immediate transfer to an emergency facility for additional evaluation and treatment.

## Reporting Adverse Events After Vaccination

Modern vaccines are safe and effective; however, adverse events have been reported after administration of all vaccines (84). More complete information about adverse reactions to a specific vaccine is available in the package insert for each vaccine and from CDC at <http://www.cdc.gov/vaccines/vac-gen/side-effects.htm>. An adverse event is an untoward event that occurs after a vaccination that might be caused by the vaccine product or vaccination process. These events range from common, minor, local reactions to rare, severe, allergic reactions (e.g., anaphylaxis). Establishing evidence for cause and effect on the basis of case reports and case series alone is usually not possible because health problems that have a temporal association with vaccination do not necessarily indicate causality.

Many adverse events require more detailed epidemiologic studies to compare the incidence of the event among vaccinees to the incidence among unvaccinated persons. Reporting adverse events, including serious events, to VAERS is a key mechanism for identifying potential vaccine safety concerns. Potential causal associations between reported adverse events after vaccination can be assessed through epidemiologic or clinical studies.

The National Childhood Vaccine Injury Act requires health-care providers and vaccine manufacturers to report to VAERS specific adverse events that occur after vaccination. The reporting requirements are different for manufacturers and health-care providers. Manufacturers are required to report all adverse events that occur after vaccination to VAERS, whereas health-care providers are required to report events that appear in the reportable events table on the VAERS website at <http://vaers.hhs.gov/reportable.htm>.

In addition to the mandated reporting of events listed on the reportable events table, health-care providers should report to VAERS all events listed in product inserts as contraindications, as well as all clinically significant adverse events, even if they are uncertain that the adverse event is related causally to vaccination. Persons other than health-care providers also can report adverse events to VAERS.

There are three ways to report to VAERS:

1. Submit the report online via a secure website at <https://vaers.hhs.gov/esub/step1>,
2. Fax a completed VAERS form to 877-721-0366, or
3. Mail a completed VAERS form: VAERS, P.O. Box 1100, Rockville, MD 20849-1100.

A VAERS form can be downloaded from the VAERS website at [http://vaers.hhs.gov/resources/vaers\\_form.pdf](http://vaers.hhs.gov/resources/vaers_form.pdf). VAERS forms also can be requested by e-mail ([info@vaers.org](mailto:info@vaers.org)), telephone (800-822-7967), or fax (877-721-0366).

## National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, is a no-fault system in which persons thought to have experienced an injury or to have died as a result of administration of a covered vaccine can seek compensation. The program became operational on October 1, 1988, and is intended as an alternative to civil litigation under the traditional tort system in that negligence need not be proven. Claims arising from covered vaccines must first be adjudicated through the program before civil litigation can be pursued.

The program relies on the Vaccine Injury Table, which lists the vaccines covered by the program and the injuries (including death), disabilities, illnesses, and conditions for which compensation might be awarded. The table defines the time during which the first symptom or substantial aggravation of an injury must appear after vaccination to be eligible. Successful claimants receive a legal presumption of causation if a condition listed in the table is proven, thus avoiding the need to prove actual causation in an individual case. Claimants also can prevail for conditions not listed in the reportable events table if they prove causation for covered vaccines. Additional information is available from the Health Resources and Services Administration (HRSA) (<http://www.hrsa.gov/vaccinecompensation>, telephone: 800-338-2382). Persons who would like to file a claim for vaccine injury should contact the U.S. Court of Federal Claims (717 Madison Place, N.W., Washington, DC 20005; telephone: 202-357-6400).

## Vaccine Administration

### Infection Control and Sterile Technique

#### General Precautions

Persons administering vaccinations should follow appropriate precautions to minimize risk for spread of disease. Hands

should be cleansed with an alcohol-based waterless antiseptic hand rub or washed with soap and water before preparing the vaccine and between each patient contact (85). Occupational Safety and Health Administration (OSHA) regulations do not require gloves to be worn when administering vaccinations, unless persons administering vaccinations are likely to come into contact with potentially infectious body fluids or have open lesions on their hands. If gloves are worn, they should be changed between patients.

## Needles and Syringes

Needles and syringes used for vaccine injections must be sterile and disposable. A separate needle and syringe should be used for each injection. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated. Different vaccines should never be mixed in the same syringe unless specifically licensed for such use, and no attempt should be made to transfer between syringes. Single-dose vials and manufacturer-filled syringes are designed for single-dose administration and should be discarded if vaccine has been withdrawn or reconstituted and subsequently not used within the time frame specified by the manufacturer. This typically is no longer than the same clinic day (typically recommended as a maximum for inactivated vaccines).

Sometimes providers prefill syringes themselves. ACIP discourages the routine practice of prefilling syringes because of the potential for administration errors and vaccine wastage. Because the majority of vaccines have a similar appearance after being drawn into a syringe, prefilling might result in administration errors. In certain circumstances in which a single vaccine type is being used (e.g., in preparation for a community influenza vaccination campaign), filling a small number of syringes may be considered. Vaccine doses should not be drawn into a syringe until immediately before administration. When syringes are filled, the type of vaccine, lot number, and date of filling must be labeled on each syringe, and the doses should be administered as soon as possible after filling. Unused syringes filled by the end user (i.e., not filled by the manufacturer) should be discarded at the end of the vaccination session. In addition to administration errors, prefilling of syringes is a concern because FDA does not license administration syringes for vaccine storage. Unused syringes that are prefilled by the manufacturer and activated (i.e., syringe cap removed or needle attached) should be discarded at the end of the clinic day. When in doubt about the appropriate handling of a vaccine, vaccination providers should contact the manufacturer.

Bloodborne diseases (e.g., hepatitis B, hepatitis C, and human immunodeficiency virus [HIV]) are occupational hazards for clinicians and other health-care providers. The

Needlestick Safety and Prevention Act was enacted in 2000 to reduce the incidence of needle-stick injury and the consequent risk for bloodborne diseases acquired from patients. The act directed OSHA to strengthen its existing bloodborne pathogen standards. The revised standards became effective in 2001 (86). These federal regulations require that safety-engineered injection devices (e.g., needle-shielding syringes or needle-free injectors) be used for injectable vaccination in all clinical settings. The regulations also require maintenance of records documenting injuries caused by needles and other medical sharp objects and that nonmanagerial employees be involved in the evaluation and selection of safety-engineered devices before they are procured.

Safety-engineered needles and syringes or needle-free injection devices are preferred and should be encouraged to reduce risk for injury. To prevent inadvertent needle-stick injury or reuse, safety mechanisms should be deployed after use and needles and syringes should be discarded immediately in labeled, puncture-proof containers located in the same room where the vaccine is administered. Used needles should never be recapped.

Needle-shielding or needle-free devices that might satisfy the occupational safety regulations for administering injectable vaccines are available in the United States (87–89). Additional information about implementation and enforcement of these regulations is available from OSHA (<http://www.osha.gov>).

## Route of Administration

### Oral Route

Rotavirus and oral typhoid vaccines are the only vaccines administered orally in the United States. Oral typhoid capsules should be administered as directed by the manufacturer. The capsules should not be opened or mixed with any other substance. Rotavirus vaccines are licensed for infants. There are two brands of rotavirus vaccine, and they have different types of applicators. Providers should consult the package insert for details. A dose of rotavirus vaccine need not be repeated if the vaccine is spit up or vomited. The infant should receive the remaining recommended doses of rotavirus vaccine following the routine schedule.

### Intranasal Route

LAIV is licensed for healthy nonpregnant persons aged 2–49 years and is the only vaccine administered by the intranasal route. The administration device is a nasal sprayer with a dose-divider clip that allows introduction of one 0.1-mL spray into each naris. The tip should be inserted slightly into the naris before administration. Even if the person coughs or sneezes immediately after administration or the dose is expelled any other way, the vaccine

dose need not be repeated. Introduction of low levels of vaccine viruses into the environment likely is unavoidable when administering LAIV; however, no instances have been reported of illness or attenuated vaccine virus infections among inadvertently exposed health-care providers or immunocompromised patients. The risk for acquiring vaccine viruses from the environment is unknown but is likely low; in addition, vaccine viruses are cold-adapted and attenuated and unlikely to cause symptomatic influenza. Severely immunosuppressed persons should not administer LAIV. However, other persons at higher risk for influenza complications can administer LAIV. These include persons with underlying medical conditions placing them at higher risk or who are likely to be at risk, including pregnant women, persons with asthma, and persons aged  $\geq 50$  years (68).

### Injectable Route

With the exception of bacille Calmette-Guérin (BCG) vaccine and smallpox vaccine, injectable vaccines are administered by the intramuscular or subcutaneous route. The method of administration of injectable vaccines is determined, in part, by the presence of adjuvants in some vaccines. An adjuvant is a vaccine component distinct from the antigen that enhances the immune response to the antigen. Inactivated vaccines containing an adjuvant should be injected into a muscle because administration subcutaneously or intradermally can cause local irritation, induration, skin discoloration, inflammation, and granuloma formation. Routes of administration are recommended by the manufacturer for each immunobiologic (Table 9). Deviation from the recommended route of administration might reduce vaccine efficacy (90,91) or increase the risk for local adverse reactions (92–94).

### Intramuscular Injections

#### Needle Length

Injectable immunobiologics should be administered where local, neural, vascular, or tissue injury is unlikely. Use of longer needles has been associated with less redness or swelling than occurs with shorter needles because of injection into deeper muscle mass (92). Appropriate needle length depends on age and body mass. Injection technique is the most important parameter to ensure efficient intramuscular vaccine delivery.

For all intramuscular injections, the needle should be long enough to reach the muscle mass and prevent vaccine from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels, or bone (91,95–97). Vaccinators should be familiar with the anatomy of the area into which they are injecting vaccine. Intramuscular injections are administered at a 90-degree angle to the skin, preferably into the anterolateral aspect of the thigh or the deltoid

muscle of the upper arm, depending on the age of the patient (Table 10).

A decision on needle size and site of injection must be made for each person on the basis of the size of the muscle, the thickness of adipose tissue at the injection site, the volume of the material to be administered, injection technique, and the depth below the muscle surface into which the material is to be injected (Figure 1). Aspiration before injection of vaccines or toxoids (i.e., pulling back on the syringe plunger after needle insertion but before injection) is not necessary because no large blood vessels are present at the recommended injection sites, and a process that includes aspiration might be more painful for infants (98).

#### Infants (Aged <12 Months)

For the majority of infants, the anterolateral aspect of the thigh is the recommended site for injection because it provides a large muscle mass (Figure 2). In certain circumstances (e.g., physical obstruction to other sites and no reasonable indication to defer doses), the gluteal muscle can be used. If the gluteal muscle must be used, care should be taken to define the anatomic landmarks.<sup>§§</sup> Injection technique is the most important parameter to ensure efficient intramuscular vaccine delivery. If the subcutaneous and muscle tissue are bunched to minimize the chance of striking bone (95), a 1-inch needle is required to ensure intramuscular administration in infants aged  $\geq 1$  month. For the majority of infants, a 1-inch, 22- to 25-gauge needle is sufficient to penetrate the thigh muscle. For neonates (first 28 days of life) and preterm infants, a  $\frac{5}{8}$ -inch needle usually is adequate if the skin is stretched flat between the thumb and forefinger and the needle is inserted at a 90-degree angle to the skin (97).

#### Toddlers (Aged 12 Months–2 Years)

For toddlers, the anterolateral thigh muscle is preferred, and if used, the needle should be at least 1 inch long. The deltoid muscle can be used if the muscle mass is adequate. A  $\frac{5}{8}$ -inch needle is adequate only for the deltoid muscle and only if the skin is stretched flat between thumb and forefinger and the needle is inserted at a 90-degree angle to the skin.

#### Children (Aged 3–18 Years)

The deltoid muscle is preferred for children aged 3–18 years (Figure 3); the needle size for deltoid site injections can range from 22 to 25 gauge and from  $\frac{5}{8}$  to 1 inch on the basis of technique. Knowledge of body mass can be useful for estimating

<sup>§§</sup> If the gluteal muscle is chosen, injection should be administered lateral and superior to a line between the posterior superior iliac spine and the greater trochanter or in the ventrogluteal site, the center of a triangle bounded by the anterior superior iliac spine, the tubercle of the iliac crest, and the upper border of the greater trochanter.

the appropriate needle length (99); however, neither a physical examination nor measurement of body mass is necessary to administer vaccines. Most children in this age range require a 5/8- or 1-inch needle (or intermediate size, if available).

### Adults (Aged $\geq 19$ Years)

For adults, the deltoid muscle is recommended for routine intramuscular vaccinations. The anterolateral thigh also can be used. For men and women who weigh  $<130$  lbs ( $<60$  kg), a 5/8-inch needle is sufficient to ensure intramuscular injection in the deltoid muscle if the injection is made at a 90-degree angle and the tissue is not bunched. For men and women who weigh 130–152 lbs (60–70 kg), a 1-inch needle is sufficient. For women who weigh 152–200 lbs (70–90 kg) and men who weigh 152–260 lbs (70–118 kg), a 1- to 1½ -inch needle is recommended. For women who weigh  $>200$  lbs ( $>90$  kg) or men who weigh  $>260$  lbs ( $>118$  kg), a 1½ -inch needle is recommended (Table 10) (96).

### Subcutaneous Injections

Subcutaneous injections are administered at a 45-degree angle, usually into the thigh for infants aged  $<12$  months and in the upper-outer triceps area of persons aged  $\geq 12$  months. Subcutaneous injections may be administered into the upper-outer triceps area of an infant if necessary. A 5/8-inch, 23- to 25-gauge needle should be inserted into the subcutaneous tissue (Figures 4 and 5).

### Multiple Injections

If multiple vaccines are administered at a single visit, administer each preparation at a different anatomic site. For infants and younger children, if more than two vaccines are injected in a single limb, the thigh is the preferred site because of the greater muscle mass; the injections should be sufficiently separated (i.e.,  $\geq 1$  inch if possible) so that any local reactions can be differentiated (92,100). For older children and adults, the deltoid muscle can be used for more than one intramuscular injection. If a vaccine and an immune globulin preparation are administered simultaneously (e.g., Td/Tdap and tetanus immune globulin [TIG], hepatitis B and hepatitis B immunoglobulin [HBIG]), separate anatomic sites (i.e., different limbs) should be used for each injection. The location of all injection sites should be documented in the patient's medical record. Health-care practices should consider using a vaccination site map so that all persons administering vaccines routinely use a particular anatomic site for each different vaccine.

### Jet Injections

Jet injectors are needle-free devices that pressurize liquid medication, forcing it through a nozzle orifice into a narrow

stream capable of penetrating skin to deliver a drug or vaccine into intradermal, subcutaneous, or intramuscular tissues (101,102). Jet injectors prevent needle-stick injuries to health-care providers (86) and can overcome improper, unsterile reuse and other drawbacks of needles and syringes in developing countries (87,103–104). Immune responses generated by jet injectors against both attenuated and inactivated viral and bacterial antigens are usually equivalent to, and occasionally greater than, immune responses induced by needle injection. However, local reactions or injuries are sometimes more frequent on delivery of vaccine by jet injectors compared with needle injection, depending on the inherent irritability of the vaccine and operator technique (102). Jet injectors that use the same nozzle for consecutive injections without intervening sterilization were used in mass vaccination campaigns from the 1950s through the 1990s (102); however, these were found to be unsafe because of the possibility of bloodborne pathogen transmission (105–108) and should not be used. A new generation of jet injectors with disposable cartridges and syringes has been developed since the 1990s. With a new, sterile dose chamber and nozzle for each patient and correct use, these devices do not have the same safety concerns as multiple-use nozzle jet injectors. Several of the newer devices have been approved by FDA for sale in the United States (102).

## Methods for Alleviating Discomfort and Pain Associated with Vaccination

Comfort measures, such as distraction (e.g., playing music or pretending to blow away the pain), ingestion of sweet liquids, breastfeeding, cooling of the injection site, and topical analgesia, can help infants or children cope with the discomfort associated with vaccination (109,110). Pretreatment (30–60 minutes before injection) with a 5% topical lidocaine-prilocaine emulsion might decrease the pain of vaccination by causing superficial anesthesia (111,112). Evidence indicates that this cream does not interfere with the immune response to MMR (113). Topical lidocaine-prilocaine emulsion should not be used on infants aged  $<12$  months who are receiving treatment with methemoglobin-inducing agents because of the possible development of methemoglobinemia (114). Use of a topical refrigerant (vapocoolant) spray immediately before vaccination can reduce the short-term pain associated with injections and can be as effective as lidocaine-prilocaine cream (115). Evidence does not support use of antipyretics before or at the time of vaccination; however, they can be used for the treatment of fever and local discomfort that might occur following vaccination. Studies of children with previous febrile seizures have not demonstrated antipyretics to be effective in the prevention of febrile seizures (116).



## Nonstandard Vaccination Practices

Recommendations for route, site, and dosage of immunobiologics are derived from data from clinical trials, practical experience, normal periodicity of health-care visits, and theoretical considerations. ACIP discourages variations from the recommended route, site, volume, or number of doses of any vaccine.

Variation from the recommended route and site can result in inadequate protection. In adults (but not in infants) (117), the immunogenicity of hepatitis B is substantially lower when the gluteal rather than the deltoid site is used for administration (90). Hepatitis B administered intradermally might result in a lower seroconversion rate and final titer of hepatitis B surface antibody than when administered by the deltoid intramuscular route (118,119). Hepatitis B administered by any route other than intramuscular, or in adults at any site other than the deltoid or anterolateral thigh, should not be counted as valid and should be repeated. Similarly, doses of rabies vaccine administered in the gluteal site should not be counted as valid doses and should be repeated (120). MCV4 should be administered intramuscularly; however, revaccination is not necessary if a vaccine dose is administered subcutaneously (121). Inactivated influenza vaccine is immunogenic when administered in a lower than standard dose by the intradermal route to healthy adult volunteers (122). However, the immunogenicity for persons aged  $\geq 60$  years is inadequate, and varying the recommended route and dose is not recommended.

Live, attenuated injectable vaccines (e.g., MMR, varicella, and yellow fever) and certain inactivated vaccines (e.g., meningococcal polysaccharide) are recommended by the manufacturers to be administered by subcutaneous injection. PPSV and IPV are recommended by the manufacturer to be administered by the subcutaneous or intramuscular route. Response to vaccines recommended by the subcutaneous route are unlikely to be affected if the vaccines are administered by the intramuscular rather than subcutaneous route. Repeating doses of vaccine administered by the intramuscular route when recommended to be by the subcutaneous route is not necessary.

Administering volumes smaller than recommended (e.g., inappropriately divided doses) might result in inadequate protection. Using reduced doses administered at multiple vaccination visits that equal a full dose or using smaller divided doses is not recommended. Any vaccination using less than the standard dose should not be counted, and the person should be revaccinated according to age unless serologic testing indicates that an adequate response has developed. If less than a full recommended dose of a parenteral vaccine is administered because of syringe or needle leakage, the dose should be repeated. Using larger than recommended dosages can be hazardous because of excessive local or systemic concentrations of antigens or other vaccine constituents.

## Storage and Handling of Immunobiologics

Failure to adhere to recommended specifications for storage and handling of immunobiologics can reduce or destroy their potency, resulting in inadequate or no immune response in the recipient. Recommendations in the product package inserts, including methods for reconstitution of the vaccine, should be followed carefully. Maintenance of vaccine quality is the shared responsibility of all handlers of vaccines from the time a vaccine is manufactured until administration. All vaccines should be inspected on delivery and monitored during storage to ensure that the recommended storage temperatures are maintained. Vaccines should continue to be stored at recommended temperatures immediately on receipt until use. Inadequate vaccine storage also can result in the loss of thousands of dollars worth of vaccine inventory and the cost of inventory replacement.

### Storage Temperature

Vaccines licensed for refrigerator storage should be stored at 35°F–46°F (2°C–8°C). Liquid vaccines containing an aluminum adjuvant permanently lose potency when exposed to freezing temperatures. Live, attenuated virus vaccines that should be frozen lose potency when exposed to higher temperatures because the viruses degrade more quickly at storage temperatures that are warmer than recommended (Table 11).

### Storage Units

Refrigerators and freezers used for vaccine storage must maintain the required temperature range year-round, be large enough to hold the year's largest inventory, and be dedicated to storage of vaccines. Vaccine storage units must be carefully selected, used properly, and consistently monitored to ensure that recommended temperatures are maintained. Refrigerators without freezers and stand-alone freezers (either manual defrost or automatic defrost) are usually the most effective at maintaining the precise temperatures required for vaccine storage. Such single-purpose units sold for home use are less expensive alternatives to medical specialty equipment (123) and are preferable to combination units. A combination refrigerator-freezer unit sold for home use might be adequate for storing limited quantities of vaccines if the refrigerator and freezer compartments have separate external doors. Before using the refrigerator for vaccine storage, the temperature should be allowed to stabilize and then be measured in various locations within the refrigerator compartment to document that a consistent temperature can be maintained within the compartment (Table 11) (124). New units might need  $\geq 2$  days of operation to establish a stable operating temperature; vaccine should not be stored in the unit

until the unit maintains an appropriate and stable storage temperature. Refrigerator temperatures are most reflective of the actual compartment temperature after the door has remained closed and undisturbed for several hours (e.g., overnight). The refrigerator temperature should be set at the midpoint of the recommended range (i.e., 40°F [5°C]) (125,126). A storage unit should be sufficiently sized so that vaccines can be placed away from the walls in the part of the unit best able to maintain the constant, required temperature. Combination units, with separate compartments of smaller size, can only be used to store limited quantities of vaccines. Frequent opening and closing of doors can cause fluctuations in compartment temperature; food, beverages, and clinical specimens should not be stored in vaccine storage units. If it becomes necessary to store clinical specimens in the same unit as vaccines, the clinical specimens should be on a shelf below the vaccine to prevent contamination should the specimen leak.

### Temperature Monitoring

Temperature monitoring is a critical component of temperature management. All office and clinical staff members should be aware of vaccine vulnerabilities and storage requirements. Assigning one person in the office the primary responsibility for maintaining and reviewing temperature logs (Figure 6) generally is most effective, with a second person assigned as backup. Temperatures for both the refrigerator and freezer should be documented twice a day and recorded. The backup person should review the log at least once each week. Temperature logs should be maintained for 3 years unless state or local authorities require a longer time. An automated monitoring system that alerts staff when a temperature deviation occurs is optimal. However, even if an automated monitoring system is used, temperatures still should be manually checked and recorded twice each day.

Thermometers should be placed in each compartment near the vaccines. Different types of thermometers can be used, including standard fluid-filled, minimum-maximum, and continuous chart recorder thermometers (Table 12). Standard fluid-filled thermometers are the simplest and least expensive products. Product temperature thermometers are encased in biosafe liquids and generally reflect refrigerator temperature more accurately than standard fluid-filled thermometers. Minimum-maximum thermometers monitor the temperature range. Continuous chart recorder thermometers monitor temperature range and duration. All thermometers used for monitoring vaccine storage temperatures should be calibrated and certified by an appropriate agency (e.g., National Institute of Standards and Technology or the American Society for Testing and Materials). Because all thermometers are calibrated as part

of the manufacturing process, this recommendation refers to a second calibration process that occurs after manufacturing but before marketing and is documented with a certificate that comes with the product. Some products (e.g., continuous chart recorder thermometers) usually include a manufacturer-defined schedule for additional recalibration. For many types of thermometers, replacement might be less expensive than recalibration. Thermometers that require batteries need to have the batteries changed; review the documentation that comes with the product for guidance.

### Response to Out-of-Range Temperature Reading

An out-of-range temperature reading should prompt immediate action. A plan should be developed ahead of time to address various types of emergencies that might require removal of vaccine from the original storage unit. Transfer of vaccines to a predesignated alternative emergency storage site might be necessary if a temperature problem cannot be resolved immediately (e.g., plugging in an unplugged unit or closing a door that has been left open). Vaccine should be marked “do not use” and moved to the alternate site after verifying that the alternate unit is at the proper temperature. After the vaccine has been moved, determine whether the vaccine is still useable by contacting the state or local health department or manufacturer. Damage to the immunogenicity of a vaccine exposed to temperatures outside of the recommended range might not be apparent visually. As a general rule, vaccines that have been stored at inappropriate temperatures should not be administered. If such vaccines already have been administered, guidance is available from the state health department or CDC. Vaccine exposed to inappropriate temperatures that is inadvertently administered should generally be repeated. Clinicians should consult with state or local health departments in these situations.

### Expiration Dates and Windows

All vaccines have an expiration date determined by the manufacturer that must be observed. Providers should record the vaccine expiration dates and lot numbers on a stock or inventory record for each vaccine vial when a shipment is received. When vaccines are removed from storage, clinicians and other health-care providers should note whether an expiration window exists for vaccine stored at room temperature or at an intermediate temperature. For example, single-component varicella vaccine that is stored frozen must be discarded after 72 hours of storage at refrigerator temperature. Vaccine transport between the storage site and the administration clinic is

discouraged unless the cold chain is maintained, and vaccine transport by the patient (e.g., transporting zoster vaccine from a pharmacy to a clinic) is particularly discouraged. An expiration window also applies to vaccines that have been reconstituted. For example, after reconstitution, MMR vaccine should be kept at refrigerator temperature and must be administered within 8 hours. Doses of expired vaccines that are administered inadvertently generally should not be counted as valid and should be repeated. Inactivated vaccines should be repeated as soon as possible. Live vaccines should be repeated after a 28-day interval from the invalid dose to reduce the risk for interference from interferon on the subsequent doses. Additional information about expiration dates is available at <http://www.cdc.gov/vaccines/recs/storage>.

### Multidose Vials

Certain vaccines (i.e., quadrivalent meningococcal polysaccharide vaccine [MPSV4], PPSV, TIV, IPV, and yellow fever) are available in multidose vials. Because several doses are withdrawn from the same vial, proper technique must be followed to prevent contamination. For multidose vials that do not require reconstitution, doses that remain after withdrawal of a dose can be administered until the expiration date printed on the vial or vaccine packaging if the vial has been stored correctly and the vaccine is not visibly contaminated, unless otherwise specified by the manufacturer. Multidose vials that require reconstitution must be used within the interval specified by the manufacturer. After reconstitution, the new expiration date should be written on the vial.

## Altered Immunocompetence

### General Principles

Altered immunocompetence, a term often used synonymously with immunosuppression and immunocompromise, can be classified as primary or secondary. Primary immunodeficiencies generally are inherited and include conditions defined by an absence or quantitative deficiency of cellular or humoral components or both that provide immunity. Examples include congenital immunodeficiency diseases such as X-linked agammaglobulinemia, severe combined immunodeficiency disease, and chronic granulomatous disease. Secondary immunodeficiency generally is acquired and is defined by loss or qualitative deficiency in cellular or humoral immune components that occurs as a result of a disease process or its therapy. Examples of secondary immunodeficiency include HIV infection, hematopoietic malignancies, treatment with radiation, and treatment with immunosuppressive drugs including alkylating

agents and antimetabolites. The degree to which immunosuppressive drugs cause clinically significant immunodeficiency generally is dose related and varies by drug. Primary and secondary immunodeficiencies might include a combination of deficits in both cellular and humoral immunity. In this report, the general term altered immunocompetence also is used to include conditions such as asplenia and chronic renal disease, and treatments with therapeutic monoclonal antibodies (specifically, the tumor necrosis factor inhibitors) (127–132) and prolonged administration of high-dose corticosteroids.

Determination of altered immunocompetence is important to the vaccine provider because incidence or severity of some vaccine-preventable diseases is higher in persons with altered immunocompetence; therefore, certain vaccines (e.g., inactivated influenza vaccine and pneumococcal vaccines) are recommended specifically for persons with these diseases (28,68). Vaccines might be less effective during the period of altered immunocompetence. Live vaccines might need to be deferred until immune function has improved. Inactivated vaccines administered during the period of altered immunocompetence might need to be repeated after immune function has improved. In addition, persons with altered immunocompetence might be at increased risk for an adverse reaction after administration of live, attenuated vaccines because of uninhibited replication.

The degree of altered immunocompetence in a patient should be determined by a physician. The challenge for clinicians and other health-care providers is assessing the safety and effectiveness of vaccines for conditions associated with primary or secondary immunodeficiency, especially when new therapeutic modalities are being used and information about the safety and effectiveness of vaccines has not been characterized fully in persons receiving these drugs (Table 13). Laboratory studies can be useful for assessing the effects of a disease or drug on the immune system. Tests useful to assess humoral immunity include immunoglobulin (and immunoglobulin subset) levels and specific antibody levels (e.g., tetanus and diphtheria). Tests that demonstrate the status of cellular immunity include lymphocyte numbers (i.e., a complete blood count with differential), a test that delineates concentrations and proportions of lymphocyte subsets (i.e., B and T lymphocytes, CD4<sup>+</sup> T versus CD8<sup>+</sup> T lymphocytes), and tests that measure T-cell proliferation in response to specific or nonspecific stimuli (e.g., lymphocyte proliferation assays) (133,134). The ability to characterize a drug or disease condition as affecting cellular or humoral immunity is only the first step; using this information to draw inferences about whether particular vaccines are indicated or whether caution is advised with use of live or inactivated vaccines is more complicated and might require consultation with an infectious disease or immunology specialist.

## Altered Immunocompetence as an Indication to Receive a Vaccine

Persons with altered immunocompetence generally are advised to receive TIV and age-appropriate polysaccharide-based vaccines (PCV, PPSV, MCV4, MPSV4, and Hib) on the basis of demonstrated effectiveness or an increased risk for disease if the vaccine is withheld.

### Pneumococcal Vaccines

Two types of vaccine against invasive pneumococcal disease are available in the United States: PCV and PPSV. PCV is recommended routinely for all children beginning at age 2 months. PCV is recommended routinely up to age 59 months for healthy children and up to 71 months for children with conditions that place them at high risk for invasive disease from *Streptococcus pneumoniae*. PPSV is licensed for persons aged  $\geq 2$  years and recommended for persons with certain underlying medical conditions (including altered immunocompetence) and for all persons aged  $\geq 65$  years. Complete recommendations on use of PCV and PPSV are available in the *Recommended Immunization Schedules for Persons Aged 0 Through 18 Years* and the *Recommended Adult Immunization Schedule* (25,49).

### Influenza Vaccines

Two types of influenza vaccine are used in the United States: TIV and LAIV. Vaccination with TIV is recommended specifically for persons with altered immunocompetence, including HIV infection. LAIV usually is contraindicated for persons with altered immunocompetence, although healthy persons with anatomic or functional asplenia and household and other close contacts of persons with altered immunocompetence can receive this vaccine (68).

### Meningococcal Vaccines

Two types of meningococcal vaccine are licensed in the United States: MCV4 and MPSV4. Persons with asplenia, C3 complement deficiency (51), or persistent complement component deficiency are at increased risk for meningococcal disease and should receive MCV4 or MPSV4. Quadrivalent MCV4 is licensed for persons aged 2–55 years; persons aged  $\geq 56$  years should receive MPSV4.

### Hib Vaccines

Hib conjugate vaccines are available in single or combined antigen preparations. Hib vaccine is recommended routinely for all children through age 59 months. However, a single dose of Hib vaccine also may be considered for asplenic older

children, adolescents, and adults who did not receive the vaccine series in childhood. Clinicians and other health-care providers might consider use of Hib vaccine for persons with HIV infection who did not receive the vaccine during infancy or childhood.

## Vaccination of Contacts of Persons with Altered Immunocompetence

Household contacts and other close contacts of persons with altered immunocompetence may receive all age-appropriate vaccines, with the exception of smallpox vaccine. MMR, varicella, and rotavirus vaccines should be administered to susceptible household contacts and other close contacts of immunocompromised patients when indicated. MMR vaccine viruses are not transmitted to contacts, and transmission of varicella vaccine is rare (2,4,135). No specific precautions are needed unless the varicella vaccine recipient has a rash after vaccination, in which case direct contact with susceptible household contacts should be avoided until the rash resolves (4,135). All members of the household should wash their hands after changing the diaper of an infant. This minimizes rotavirus transmission, for an undetermined number of weeks after vaccination, from an infant who received rotavirus vaccine (136). Household and other close contacts of persons with altered immunocompetence should receive annual influenza vaccination. LAIV may be administered to healthy household and other close contacts of persons with altered immunocompetence (68).

## Vaccination with Inactivated Vaccines

All inactivated vaccines can be administered safely to persons with altered immunocompetence whether the vaccine is a killed whole-organism or a recombinant, subunit, toxoid, polysaccharide, or polysaccharide protein-conjugate vaccine. If inactivated vaccines are indicated for persons with altered immunocompetence, the usual doses and schedules are recommended. However, the effectiveness of such vaccinations might be suboptimal.

Except for inactivated influenza vaccine, vaccination during chemotherapy or radiation therapy should be avoided if possible because antibody response might be suboptimal. Patients vaccinated within 14 days before starting immunosuppressive therapy or while receiving immunosuppressive therapy should be considered unimmunized and should be revaccinated at least 3 months after therapy is discontinued if immune competence has been restored.



## Vaccination with Live, Attenuated Viral and Bacterial Vaccines

Severe complications have followed vaccination with live, attenuated viral and live, attenuated bacterial vaccines among persons with altered immunocompetence (137–145). Persons with most forms of altered immunocompetence should not receive live vaccines (MMR, varicella, MMRV, LAIV, zoster, yellow fever, Ty21a oral typhoid, BCG, and rotavirus).

Children with defects in phagocyte function (e.g., chronic granulomatous disease or myeloperoxidase deficiency) can receive live, attenuated viral vaccines in addition to inactivated vaccines but should not receive live, attenuated bacterial vaccines (e.g., BCG or Ty21a oral typhoid vaccines). Children with deficiencies in complement or with asplenia can receive live, attenuated viral and live, attenuated bacterial vaccines.

Persons with severe cell-mediated immunodeficiency should not receive live, attenuated viral or bacterial vaccines. However, two factors support vaccination of HIV-exposed or HIV-infected infants: 1) the HIV diagnosis might not be established in infants born to HIV-infected mothers before the age of the first rotavirus vaccine dose (only 1.5% to 3% of HIV-exposed infants in the United States will be determined to be HIV-infected), and 2) vaccine strains of rotavirus are considerably attenuated (136,146).

Children with HIV infection are at increased risk for complications from varicella and herpes zoster compared with immunocompetent children (145,147). Limited data among HIV-infected children (specifically CDC class N, A, or B with age-specific CD4<sup>+</sup> T-lymphocyte percentages of  $\geq 15\%$ ) indicate that varicella vaccine is immunogenic, effective, and safe (4,147). Varicella vaccine should be considered for children who meet these criteria. Eligible children should receive 2 doses of varicella vaccine with a 3-month interval between doses (4,147). Doses separated by  $< 3$  months are invalid for persons with altered immunocompetence.

Persons with HIV infection are at increased risk for severe complications if infected with measles. No severe or unusual adverse events have been reported after measles vaccination among HIV-infected persons who did not have evidence of severe immunosuppression (148–151). Therefore, MMR vaccination is recommended for all asymptomatic HIV-infected persons who do not have evidence of severe immunosuppression (age-specific CD4<sup>+</sup> T-lymphocyte percentages of  $\geq 15\%$ ) and for whom measles vaccination would otherwise be indicated. Similarly, MMR vaccination should be considered for mildly symptomatic HIV-infected persons (pediatric category A1 or A2 or adolescent/adult category A) who do not have

evidence of severe immunosuppression (age-specific CD4<sup>+</sup> T-lymphocyte percentages  $\geq 15\%$ ) for whom measles vaccination would otherwise be indicated (2,146). MMRV (licensed only through age 12 years) should not be administered to children or adolescents with HIV infection (35).

HIV-infected persons who are receiving regular doses of IGIV might not respond to varicella vaccine or MMR vaccine because of the continued presence of passively acquired antibody. However, because of the potential benefit, MMR and varicella vaccines should be considered approximately 14 days before the next scheduled dose of IGIV (if not otherwise contraindicated), although an optimal immune response might not occur depending on the dose and interval since the previous dose of IGIV. Unless serologic testing indicates that specific antibodies have been produced, vaccination should be repeated (if not otherwise contraindicated) after the recommended interval (Table 5). In most cases, this is after the therapy has been discontinued. An additional dose of IGIV should be considered for persons receiving maintenance IGIV therapy who are exposed to measles or varicella  $\geq 3$  weeks after administering a standard dose (100–400 mg/kg body weight) of IGIV. Patients with leukemia, lymphoma, or other malignancies whose disease is in remission, who have restored immunocompetence, and whose chemotherapy has been discontinued for at least 3 months can receive live-virus vaccines. Persons with impaired humoral immunity (e.g., hypogammaglobulinemia or dysgammaglobulinemia) may be vaccinated with varicella vaccine (4). However, most persons with these disorders also receive periodic doses of IGIV. Appropriate spacing should be maintained between administration of IGIV and varicella vaccine to prevent an inadequate response to vaccination caused by the presence of neutralizing antibodies from the IGIV. Household members should not receive smallpox vaccine.

Zoster incidence is higher in persons with altered immunocompetence (55). Adults with most types of altered immunocompetence are expected to maintain residual immunity to varicella-zoster virus because of previous infection that protects against primary varicella but provides incomplete protection against zoster. Zoster vaccine is contraindicated in persons with primary or acquired immunodeficiency (e.g., lymphoma, leukemia, tumors involving bone marrow, and patients receiving chemotherapy) and some patients with AIDS (55). ACIP has no recommendation for or against vaccination of persons with HIV infection with CD4<sup>+</sup> T-lymphocyte counts  $> 200$  cells/ $\mu$ L. Zoster vaccine may be administered to certain persons with altered immunocompetence, such as persons with HIV infection who have CD4<sup>+</sup> T-lymphocyte counts  $> 200$  cells/ $\mu$ L.

## Recipients of Hematopoietic Cell Transplants

A hematopoietic cell transplant (HCT) results in immunosuppression because of the hematopoietic ablative therapy administered before the transplant, drugs used to prevent or treat graft-versus-host disease, and, in some cases, from the underlying disease process necessitating transplantation (152–154). HCT involves ablation of the bone marrow followed by reimplantation of the person's own stem cells or stem cells from a donor. Antibody titers to vaccine-preventable diseases (e.g., tetanus, poliovirus, measles, mumps, rubella, and encapsulated bacteria) decrease 1–4 years after autologous or allogeneic HCT if the recipient is not revaccinated. HCT recipients of all ages are at increased risk for certain vaccine-preventable diseases, including diseases caused by encapsulated bacteria (i.e., pneumococcal, meningococcal, and Hib infections). As a result, HCT recipients should be revaccinated routinely after HCT, regardless of the source of the transplanted stem cells (152–154). Most inactivated vaccines should be initiated 6 months after the HCT (154). Inactivated influenza vaccine should be administered beginning at least 6 months after HCT and annually thereafter for the life of the patient. A dose of inactivated influenza vaccine can be given as early as 4 months after HCT, but a second dose should be considered in this situation (154). A second dose is recommended routinely for all children receiving influenza vaccine for the first time. Sequential administration of 3 doses of pneumococcal conjugate vaccine is recommended, beginning 3–6 months after the transplant, followed by a dose of PPSV (152). A 3-dose regimen of Hib vaccine should be administered beginning 6 months after transplant; at least 1 month should separate the doses (154). MMR vaccine should be administered 24 months after transplant if the HCT recipient is immunocompetent. Because of insufficient experience using varicella vaccine among HCT recipients, physicians should assess the immune status of each recipient on a case-by-case basis and determine the risk for infection before using the vaccine. If a decision is made to vaccinate with varicella vaccine, the vaccine should be administered a minimum of 24 months after transplantation if the HCT recipient is presumed to be immunocompetent (152,153).

## Conditions or Drugs that Might Cause Immunodeficiencies

Asplenia and use of corticosteroids or certain drugs have the potential to be immunosuppressive and are presumed to cause some degree of altered immunocompetence.

## Anatomic or Functional Asplenia

Persons with anatomic asplenia (e.g., surgical removal or congenital absence of the spleen) or functional asplenia (as occurs in persons with sickle cell disease) are at increased risk for infection by encapsulated bacteria, especially by *S. pneumoniae* (pneumococcus), *N. meningitidis* (meningococcus), and Hib (22,49,51). Children aged <5 years with anatomic or functional asplenia should receive an age-appropriate series of PCV. Persons aged ≥2 years should receive 2 doses of PPSV separated by 5 years (20,25,28,49).

Meningococcal vaccine is recommended for persons with anatomic or functional asplenia. A specific MCV4 (Menactra), is approved for persons aged 2–55 years and is the recommended vaccine for this age group unless a contraindication exists. Another MCV4 (Menveo) is approved only for ages 11–55 years. Persons aged ≥56 years should receive MPSV4. The duration of immunity after meningococcal vaccination is not certain; however, on the basis of serologic testing with recently licensed assays, revaccination is recommended for persons at continued high risk. A 3-year interval to the next dose is recommended for children at high risk who receive their first dose at ages 2–6 years. A 5-year interval is recommended for persons at high risk who receive their first dose at age ≥7 years.

No efficacy data are available on which to base a recommendation for use of Hib vaccine for older children and adults with the chronic conditions that are associated with an increased risk for Hib disease. Administering 1 dose of Hib vaccine to these patients who have not previously received Hib vaccine is not contraindicated.

Pneumococcal, meningococcal, and Hib vaccinations should be administered at least 14 days before elective splenectomy, if possible. If the vaccinations are not administered before surgery, they should be administered after the procedure as soon as the patient's condition is stable.

## Corticosteroids

The amount of systemically absorbed corticosteroids and the duration of administration needed to suppress the immune system of an otherwise immunocompetent person are not well defined. Corticosteroid therapy usually is not a contraindication to administering live-virus vaccine when administration is 1) short term (i.e., <14 days); 2) a low to moderate dose (<20 mg of prednisone or equivalent per day); 3) long-term, alternate-day treatment with short-acting preparations; 4) maintenance physiologic doses (replacement therapy); or 5) topical (skin or eyes), inhaled, or by intraarticular, bursal, or tendon injection (154). No evidence of more severe reactions to live, attenuated viral vaccines has been reported among persons receiving corticosteroid therapy by aerosol, and such

therapy is not a reason to delay vaccination. Although the immunosuppressive effects of steroid treatment vary, the majority of clinicians consider a dose equivalent to either  $\geq 2$  mg/kg of body weight or  $\geq 20$  mg/day of prednisone or equivalent for persons who weigh  $>10$  kg when administered for  $\geq 14$  days as sufficiently immunosuppressive to raise concern about the safety of vaccination with live-virus vaccines (154). Corticosteroids used in greater than physiologic doses also can reduce the immune response to vaccines. Vaccination providers should defer live-virus vaccination for at least 1 month after discontinuation of high-dose systemically absorbed corticosteroid therapy administered for  $>14$  days.

### Other Immunosuppressive Drugs

When feasible, clinicians should administer all indicated vaccines to all persons before initiation of chemotherapy, before treatment with other immunosuppressive drugs, and before radiation or splenectomy. Persons receiving chemotherapy or radiation for leukemia and other hematopoietic malignancies, for solid tumors, or after solid organ transplant should be assumed to have altered immunocompetence. Live, attenuated vaccines should not be administered for at least 3 months after such immunosuppressive therapy. Inactivated vaccines administered during chemotherapy should be readministered after immune competence is regained. Children receiving chemotherapy for leukemia, lymphoma, other malignancies, or radiation generally are thought to retain immune memory after treatment, although revaccination with the common childhood vaccines after chemotherapy for acute lymphoblastic leukemia might be indicated (155). In general, revaccination of a person after chemotherapy or radiation therapy is considered unnecessary if the previous vaccination occurred before therapy and not during therapy, with the exception of recipients of HCT, who should be revaccinated as recommended previously. Determination of the level of immune memory and the need for revaccination should be made by the treating physician.

Inactivated vaccines may be administered during low-dose intermittent or maintenance therapy with immunosuppressive drugs. The safety and efficacy of live, attenuated vaccines during such therapy is unknown. Physicians should carefully weigh the risks for and benefits of providing injectable live vaccines to adult patients receiving low-dose therapies for chronic autoimmune disease. The safety and efficacy of live, attenuated vaccines administered concurrently with recombinant human immune mediators and immune modulators are unknown. Evidence that use of therapeutic monoclonal antibody preparations, especially the antitumor necrosis factor agents adalimumab, infliximab, and etanercept, causes reactivation of latent tuberculosis infection and tuberculosis disease and predisposes persons to other opportunistic infections suggests

caution in the use of live vaccines in patients receiving these drugs (127–132). Until additional information becomes available, avoidance of live, attenuated vaccines during intermittent or low-dose chemotherapy or other immunosuppressive therapy is prudent, unless the benefit of vaccination outweighs the hypothetical increased risk for an adverse reaction after vaccination.

## Special Situations

### Concurrent Administration of Antimicrobial Agents and Vaccines

With a few exceptions, use of an antimicrobial agent is not a contraindication to vaccination. Antibacterial agents have no effect on the response to live, attenuated vaccines, except live oral Ty21a typhoid vaccine, and have no effect on inactivated, recombinant subunit, or polysaccharide vaccines or toxoids. Ty21a typhoid vaccine should not be administered to persons receiving antimicrobial agents until 24 hours after the last dose of antimicrobial (14). If feasible, to avoid a possible reduction in vaccine effectiveness, antibacterial drugs should not be started or resumed until 1 week after the last dose of Ty21a.

Antiviral drugs used for treatment or prophylaxis of influenza virus infections have no effect on the response to inactivated influenza vaccine (68). However, live, attenuated influenza vaccine should not be administered until 48 hours after cessation of therapy with antiviral influenza drugs. If feasible, to avoid possible reduction in vaccine effectiveness, antiviral medication should not be administered for 14 days after LAIV administration (68). Antiviral drugs active against herpesviruses (e.g., acyclovir or valacyclovir) might reduce the efficacy of live, attenuated varicella and zoster vaccines (4,55). These drugs should be discontinued at least 24 hours before administration of vaccines containing varicella zoster virus, including zoster vaccine, if possible. Delay use or resumption of antiviral therapy for 14 days after vaccination. No data exist to suggest that commonly used antiviral drugs have an effect on rotavirus vaccine or MMR.

### Tuberculosis Screening and Skin Test Reactivity

Measles illness, severe acute or chronic infections, HIV infection, and malnutrition can create a relatively anergic state during which the tuberculin skin test (TST) might have a false-negative reaction (156–158). Although any live, attenuated measles vaccine theoretically can suppress TST reactivity, the degree of suppression is likely less than that occurring from acute infection from wild-type measles virus. Although routine



TST screening of all children is no longer recommended, TST screening is sometimes needed (e.g., for well child care, school entrance, or employee health reasons) at the same time as administration of a measles-containing vaccine.

The TST and measles-containing vaccine can be administered at the same visit (preferred option). Simultaneously administering the TST and measles-containing vaccine does not interfere with reading the TST result at 48–72 hours and ensures that the person has received measles vaccine.

If the measles-containing vaccine has been administered recently, TST screening should be delayed for at least 4 weeks after vaccination. A delay in performing the TST removes the concern of any theoretical but transient suppression of TST reactivity from the vaccine.

TST screening can be performed and read before administration of the measles-containing vaccine. This option is the least favored because it delays receipt of the measles-containing vaccine. If a person is suspected to have tuberculosis, not only should the MMR vaccine be withheld before the TST, it should be withheld until after treatment has been initiated because a person with active tuberculosis who is moderately or severely ill should not receive MMR vaccine. In a general screening situation in which tuberculosis is not suspected, a TST may be administered simultaneously with live vaccines or should be deferred for 28 days after vaccination.

No data exist regarding the potential degree of TST suppression that might be associated with other live, attenuated virus vaccines (e.g., varicella or yellow fever). However, in the absence of data, following guidelines for measles-containing vaccine when scheduling TST screening and administering other live, attenuated virus vaccines is prudent. If the opportunity to vaccinate might be missed, vaccination should not be delayed only because of these theoretical considerations. Because of similar concerns about smallpox vaccine and TST suppression, a TST should not be performed until 4 weeks after smallpox vaccination (159).

A more specific test for diagnosis of tuberculosis or latent tuberculosis infection was licensed in 2005. The interferon-gamma release assay (IGRA) requires only one visit to complete and is less sensitive to the effects of previous BCG vaccination (160). The same timing guidelines that apply to the interval between a live vaccine and TST apply to IGRA (i.e., 28 days between live vaccine and IGRA if they do not occur on the same day), because IGRA (like TST) might be suppressed through immunologic mechanisms.

The potential for TST to cause boosting of results should be considered in adults who might have latent tuberculosis and have a negative initial TST (160). The two-step tuberculin test is recommended for certain situations (160). Because this test consists of two TSTs (or a TST followed by IGRA) separated

by an interval of 1–3 weeks, there is a greater window of time during which live vaccine replication could suppress reactivity. If a live vaccine is administered, the first dose of a two-step TST should be delayed for 4 weeks, and if additional doses of live vaccines are indicated thereafter, they should be delayed until the second TST (or the IGRA after an initial TST).

TST or IGRA reactivity in the absence of tuberculosis disease is not a contraindication to administration of any vaccine, including live, attenuated virus vaccines. Tuberculosis disease is not a contraindication to vaccination, unless the person is moderately or severely ill. Although no studies have reported on the effects of MMR vaccine on persons with untreated tuberculosis, a theoretical basis exists for concern that measles vaccine might exacerbate tuberculosis disease (2). As a result, before administering MMR to persons with untreated active tuberculosis, initiating antituberculosis therapy is advisable (2). Considering whether concurrent immunosuppression (e.g., immunosuppression caused by HIV infection) is a concern before administering live, attenuated vaccines also is prudent.

## Severe Allergy to Vaccine Components

Vaccine components can cause allergic reactions among certain recipients. These reactions can be local or systemic and can include anaphylaxis or anaphylactic-like responses (e.g., generalized urticaria or hives, wheezing, swelling of the mouth and throat, dyspnea, hypotension, and shock). Allergic reactions might be caused by the vaccine antigen, residual animal protein, antimicrobial agents, preservatives, stabilizers, or other vaccine components (161). Children who have had an apparent severe allergic reaction to a vaccine should be evaluated by an allergist to determine the responsible allergen and to make recommendations regarding future vaccination. Components of each vaccine are listed in the respective package insert. An extensive list of vaccine components and their use, as well as the vaccines that contain each component, has been published (162) and also is available from CDC (<http://www.cdc.gov/vaccines>).

The most common animal protein allergen is egg protein, which is found in influenza and yellow fever vaccines because they are prepared using embryonated chicken eggs. Ordinarily, persons who are able to eat eggs or egg products safely can receive these vaccines; persons who have had an anaphylactic or anaphylactic-like allergy to eggs or egg proteins generally should not receive these vaccines. Asking persons if they can eat eggs without adverse effects is a reasonable way to determine which persons might be at risk for allergic reactions from yellow fever and influenza vaccines. A regimen for administering influenza vaccine to children with egg hypersensitivity and severe asthma has been developed (163,164)



Measles and mumps vaccine viruses are grown in chick embryo fibroblast tissue culture. However, persons with a severe egg allergy can receive measles- or mumps-containing vaccines without skin testing or desensitization to egg protein (2). Rubella and varicella vaccines are grown in human diploid cell cultures and can safely be administered to persons with a severe allergy to eggs or egg proteins. The rare severe allergic reactions after measles or mumps vaccination or MMR are not thought to be caused by egg antigens but to other components of the vaccine (e.g., gelatin) (165–168). MMR, MMRV, and other vaccines contain hydrolyzed gelatin as a stabilizer. Extreme caution should be used when administering vaccines that contain gelatin to persons who have had an anaphylactic reaction to gelatin or gelatin-containing products.

Certain vaccines contain trace amounts of antimicrobial agents or other preservatives (e.g., neomycin or thimerosal) to which patients might be allergic, although such allergies are rare. The information provided in vaccine package inserts should be reviewed carefully before deciding whether a patient with such allergies should receive the vaccine. No licensed vaccine contains penicillin or penicillin derivatives.

Persons who have had anaphylactic reactions to neomycin should not receive vaccines containing neomycin. Most often, a neomycin allergy is a contact dermatitis, a manifestation of a delayed-type (cell-mediated) immune response rather than anaphylaxis (169,170). A history of delayed-type reactions to neomycin is not a contraindication for administration of these vaccines.

Thimerosal, an organic mercurial compound in use since the 1930s, is added to certain immunobiologics as a preservative. Since mid-2001, vaccines routinely recommended for young infants have been manufactured without thimerosal as a preservative. Live, attenuated vaccines have never contained thimerosal. Thimerosal-free formulations of inactivated influenza vaccine are available. Inactivated influenza vaccine also is available in formulations with trace thimerosal, in which thimerosal remains as a manufacturing residual but does not function as a preservative, and in formulations that contain thimerosal as a preservative. Thimerosal at a preservative concentration is present in certain other vaccines that can be administered to children (e.g., Td and DT). Information about the thimerosal content of vaccines is available from FDA (<http://www.fda.gov/cber/vaccine/thimerosal.htm>).

On the basis of limited scientific data, some investigators have asserted that receiving thimerosal-containing vaccines might induce an allergy. Allergies to thimerosal usually have been described as local delayed-type hypersensitivity reactions (171–173). Thimerosal elicits positive delayed-type hypersensitivity patch tests in 1%–18% of persons tested; however, these tests have limited or no clinical relevance (174,175). The

majority of persons do not experience reactions to thimerosal administered as a component of vaccines even when patch or intradermal tests for thimerosal indicate hypersensitivity (175). A local or delayed-type hypersensitivity reaction to thimerosal is not a contraindication to receipt of a vaccine that contains thimerosal.

## Latex Allergy

Latex is sap from the commercial rubber tree. Latex contains naturally occurring impurities (e.g., plant proteins and peptides) that might be responsible for allergic reactions. Latex is processed to form natural rubber latex and dry, natural rubber. Natural rubber latex and dry, natural rubber might contain the same plant impurities as latex but in lesser amounts. Natural rubber latex is used to produce medical gloves, catheters, and other products. Dry, natural rubber is used in the tip of syringe plungers, the tip on prefilled syringes, vial stoppers, and injection ports on intravascular tubing. Synthetic rubber and synthetic latex also are used in medical gloves, syringe plungers, and vial stoppers. Synthetic rubber and synthetic latex do not contain natural rubber or natural latex and do not contain impurities linked to allergic reactions. Latex or dry, natural rubber used in vaccine packaging generally is noted in the manufacturers' package inserts.

The most common type of latex sensitivity is a contact-type (type 4) allergy, usually as a result of prolonged contact with latex-containing gloves (176). However, latex allergies associated with injection procedures have been described among patients with diabetes mellitus (177–179). Allergic reactions (including anaphylaxis) after vaccinations are rare. A review of reports to VAERS identified only 28 cases of possible immediate-type anaphylactic reactions among more than 160,000 vaccine adverse event reports (180).

If a person reports a severe (anaphylactic) allergy to latex, vaccines supplied in vials or syringes that contain natural rubber latex should not be administered unless the benefit of vaccination clearly outweighs the risk for a potential allergic reaction. In these cases, providers should be prepared to treat patients who are having an allergic reaction. For latex allergies other than anaphylactic allergies (e.g., a history of contact allergy to latex gloves), vaccines supplied in vials or syringes that contain dry, natural rubber or natural rubber latex may be administered.

## Vaccination of Preterm Infants

In the majority of cases, preterm infants (infants born before 37 weeks' gestation), regardless of birth weight, should be vaccinated at the same chronological age and according to the same schedule and using the same precautions as for full-term

infants and children. Birth weight and size are not factors in deciding whether to vaccinate a clinically stable preterm infant (181–185), except for hepatitis B vaccination. The full recommended dose of each vaccine should be used. Divided or reduced doses are not recommended.

Decreased seroconversion rates might occur among certain preterm infants (i.e., with low birth weights [ $<2,000$  g]) after administration of hepatitis B vaccine at birth (186). However, by the chronological age of 1 month, all preterm infants, regardless of initial birth weight, are likely to respond as adequately as larger infants (187–189). Preterm infants born to HBsAg-positive mothers and mothers with unknown HBsAg status must receive immunoprophylaxis with hepatitis B vaccine within 12 hours after birth. The initial vaccine dose should not be counted toward completion of the hepatitis B series, and 3 additional doses of hepatitis B vaccine should be administered, beginning when the infant is aged 1 month. For mothers with unknown HBsAg status, attempts should be made to determine HBsAg status. The infant must be given HBIG within 12 hours of birth unless the mother is found to be HBsAg negative (26). Infants weighing  $<2,000$  g born to HBsAg-negative mothers should receive the first dose of the hepatitis B series at chronological age 1 month or at hospital discharge.

If a child aged at least 6 weeks has been in the hospital since birth, deferral of rotavirus vaccine is recommended until the time of discharge (136). The rotavirus vaccine series should not be initiated for infants aged  $\geq 15$  weeks, 0 days.

## Breastfeeding and Vaccination

Neither inactivated nor live-virus vaccines administered to a lactating woman affect the safety of breastfeeding for women or their infants. Although live viruses in vaccines can replicate in vaccine recipients (i.e., the mother), the majority of live viruses in vaccines have been demonstrated not to be excreted in human milk. Varicella vaccine virus has not been found in human milk (190). Although rubella vaccine virus might be excreted in human milk, the virus usually does not infect the infant. If infection does occur, it is well tolerated because the virus is attenuated (191). Inactivated, recombinant, subunit, polysaccharide, and conjugate vaccines, as well as toxoids, pose no risk for mothers who are breastfeeding or for their infants. Breastfeeding is a contraindication for smallpox vaccination of the mother because of the theoretical risk for contact transmission from mother to infant. Yellow fever vaccine should be avoided in breastfeeding women (19). However, when nursing mothers cannot avoid or postpone travel to areas endemic for yellow fever in which risk for acquisition is high, these women should be vaccinated.

Limited data indicate that breastfeeding can enhance the response to certain vaccine antigens (192). There are no data to suggest that passive transfer of antibodies in human milk can affect the efficacy of live-virus vaccines. Breastfed infants should be vaccinated according to the recommended schedule (193–195).

## Vaccination During Pregnancy

Risk to a developing fetus from vaccination of the mother during pregnancy is theoretical. No evidence exists of risk to the fetus from vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids (196,197). Live vaccines administered to a pregnant woman pose a theoretical risk to the fetus; therefore, live, attenuated virus and live bacterial vaccines generally are contraindicated during pregnancy. Benefits of vaccinating pregnant women usually outweigh potential risks when the likelihood of disease exposure is high, when infection would pose a risk to the mother or fetus, and when the vaccine is unlikely to cause harm. Recommendations for vaccination during pregnancy are developed using ACIP's *Guiding Principles for Development of ACIP Recommendations for Vaccination During Pregnancy and Breastfeeding* (198).

Pregnant women who received the last dose of tetanus-toxoid-containing vaccine  $>10$  years previously should generally receive Td rather than Tdap while they are pregnant (16), although Tdap is not contraindicated during pregnancy. A dose of Td during pregnancy ensures adequate tetanus immunity in the mother and prevents disease in both mother and infant. In specific situations, the dose of Td can be withheld if the provider is confident the pregnant woman is immune to tetanus (199). Regardless of a recent Td vaccination, pregnant women who have not already received Tdap should receive a dose of Tdap as soon as possible after delivery to ensure pertussis immunity and reduce the risk for transmission to the newborn. Pregnant women who are not vaccinated or are only partially vaccinated against tetanus should complete the primary series (16). Women for whom Td is indicated but who did not complete the recommended 3-dose series during pregnancy should receive follow-up after delivery to ensure the series is completed. Because Tdap is recommended as a one-time dose, pregnant women who previously have received Tdap should receive Td if indicated.

Women in the second and third trimesters of pregnancy are at increased risk for hospitalization from influenza (68,200). Because vaccinating against influenza before the season begins is critical, and because predicting exactly when the season will begin is impossible, routine influenza vaccination is recommended for all women who are or will be pregnant (in any

trimester) during influenza season, which in the United States is usually early October through late March (68).

IPV can be administered to pregnant women who are at risk for exposure to wild-type poliovirus infection (201). Hepatitis A, pneumococcal polysaccharide, meningococcal conjugate, and meningococcal polysaccharide vaccines should be considered for women at increased risk for those infections (49,51,202). Pregnant women who must travel to areas where the risk for yellow fever is high should receive yellow fever vaccine because the limited theoretical risk from vaccination is outweighed substantially by the risk for yellow fever infection (19,203). Hepatitis B vaccine is not contraindicated in pregnancy and should be given to a pregnant woman who has an indication for hepatitis B vaccine (26,204).

Pregnancy is a contraindication for smallpox (vaccinia) vaccine and measles-, mumps-, rubella-, and varicella-containing vaccines. Smallpox vaccine is the only vaccine known to harm a fetus when administered to a pregnant woman. In addition, smallpox vaccine should not be administered to a household contact of a pregnant woman (159). Data from studies of children born to mothers vaccinated with rubella vaccine during pregnancy demonstrate rubella antibody levels in unvaccinated infants. This could represent passive transfer of maternal antibody or a fetal antibody response to vaccine virus infection in the fetus. No cases of congenital rubella or varicella syndrome or abnormalities attributable to fetal infection have been observed among infants born to susceptible women who received rubella or varicella vaccines during pregnancy (205–207). Because of the importance of protecting women of childbearing age against rubella and varicella, reasonable practices in any vaccination program include asking women if they are pregnant or might become pregnant in the next 4 weeks; not vaccinating women who state that they are or plan to become pregnant; explaining the theoretical risk for the fetus if MMR, varicella, or MMRV vaccine were administered to a woman who is pregnant; and counseling women who are vaccinated not to become pregnant during the 4 weeks after MMR, varicella, or MMRV vaccination (2,59,205–207). MMRV is an unlikely option for a pregnant woman because the vaccine is only licensed through 12 years of age. Routine pregnancy testing of women of childbearing age before administering a live-virus vaccine is not recommended (2,4). If a pregnant woman is inadvertently vaccinated or becomes pregnant within 4 weeks after MMR or varicella vaccination, she should be counseled about the theoretical basis of concern for the fetus; however, MMR or varicella vaccination during pregnancy should not be considered a reason to terminate pregnancy (2,4,207).

Persons who receive MMR vaccine do not transmit the vaccine viruses to contacts (2). Transmission of varicella vaccine

virus to contacts is rare (4). MMR and varicella vaccines should be administered when indicated to children and other household contacts of pregnant women (2,4). Infants living in households with pregnant women should be vaccinated with rotavirus vaccine according to the same schedule as infants in households without pregnant women.

Pregnant women should be evaluated for immunity to rubella and varicella and be tested for the presence of HBsAg during every pregnancy (2,26,60). Women susceptible to rubella and varicella should be vaccinated immediately after delivery. A woman found to be HBsAg positive should be monitored carefully to ensure that the infant receives HBIG and begins the hepatitis B vaccine series no later than 12 hours after birth and that the infant completes the recommended hepatitis B vaccine series on schedule (26). No known risk exists for the fetus from passive immunization of pregnant women with immune globulin preparations.

## Persons Vaccinated Outside the United States

Clinicians have a limited ability to determine whether persons are protected on the basis of their country of origin and their records alone. Vaccines administered outside the United States generally can be accepted as valid if the schedule (i.e., minimum ages and intervals) is similar to that recommended in the United States. With the exception of the influenza vaccine and PPSV, only written documentation should be accepted as evidence of previous vaccination. Written records are more likely to predict protection if the vaccines, dates of administration, intervals between doses, and age at the time of vaccination are comparable to U.S. recommendations. Although vaccines with inadequate potency have been produced in other countries (208,209), the majority of vaccines used worldwide are produced with adequate quality control standards and are potent.

The number of U.S. families adopting children from outside the United States has increased substantially in the last decade (209). Adopted children's birth countries often have vaccination schedules that differ from the recommended childhood vaccination schedule in the United States. Differences in the U.S. schedule and those used in other countries include the vaccines administered, the recommended ages of administration, and the number and timing of doses.

Data are inconclusive regarding the extent to which an internationally adopted child's vaccination record reflects the child's protection. A child's record might indicate administration of MMR vaccine when only single-antigen measles vaccine was administered. A study of children adopted from orphanages in the People's Republic of China, Russia, and countries in Eastern

Europe determined that 67% of children with documentation of >3 doses of DTP before adoption had nonprotective titers to these antigens (209). In contrast, children adopted from these countries who received vaccination in the community (not only from orphanages) and had documentation of  $\geq 1$  doses of DTP exhibited protective titers 67% of the time (209). However, antibody testing was performed by using a hemagglutination assay, which tends to underestimate protection and cannot directly be compared with antibody concentration (210). Data are likely to remain limited for areas other than the People's Republic of China, Russia, and Eastern Europe. Health-care providers should ensure that household contacts of international adoptees are vaccinated adequately, particularly for measles, hepatitis A, and hepatitis B (211).

Health-care providers may use one of multiple approaches if the immunogenicity of vaccines administered to persons outside the United States is in question. Repeating the vaccinations is an acceptable option that usually is safe and prevents the need to obtain and interpret serologic tests. If avoiding unnecessary injections is desired, judicious use of serologic testing might help determine which vaccinations are needed. For some vaccines, the most readily available serologic tests cannot document protection against infection. These recommendations provide guidance on possible approaches to evaluation and revaccination for each vaccine recommended in the United States (Table 14).

### DTaP Vaccine

Vaccination providers can revaccinate children with DTaP vaccine without regard to recorded doses; however, data indicate increased rates of local adverse reactions after the fourth and fifth doses of DTaP (67). If a revaccination approach is adopted and a severe local reaction occurs, serologic testing for specific IgG antibody to tetanus and diphtheria toxins can be measured before administering additional doses. Protective concentration<sup>¶¶</sup> indicates that additional doses are unnecessary and subsequent vaccination should occur as age-appropriate. No established serologic correlates exist for protection against pertussis.

For a child whose record indicates receipt of  $\geq 3$  doses of DTP or DTaP, serologic testing for specific IgG antibody to both diphtheria and tetanus toxin before additional doses is a reasonable approach. If a protective concentration is present, recorded doses are considered valid, and the vaccination series should be completed as age appropriate. An indeterminate antibody concentration might indicate immunologic memory

but waning antibody; serologic testing can be repeated after a booster dose if the vaccination provider wants to avoid revaccination with a complete series.

Alternately, for a child whose records indicate receipt of  $\geq 3$  doses, a single booster dose can be administered followed by serologic testing after 1 month for specific IgG antibody to both diphtheria and tetanus toxins. If the child has a protective concentration, the recorded doses are considered valid, and the vaccination series should be completed as age appropriate. Children with an indeterminate concentration after a booster dose should be revaccinated with a complete series.

### Hepatitis A Vaccine

Children aged 12–23 months without documentation of hepatitis A vaccination or serologic evidence of immunity should be vaccinated on arrival in the United States (202). Persons who have received 1 dose should receive the second dose if 6–18 months have passed since the first dose was administered.

### Hepatitis B Vaccine

Persons not known to be vaccinated for hepatitis B should receive an age-appropriate series of hepatitis B vaccine. A person whose records indicate receipt of  $\geq 3$  doses of vaccine are considered protected, and additional doses are not needed if  $\geq 1$  dose was administered at age  $\geq 24$  weeks. Persons who received their last hepatitis B vaccine dose at an age <24 weeks should receive an additional dose at age  $\geq 24$  weeks. People who have received <3 doses of vaccine should complete the series at the recommended intervals and ages.

All foreign-born persons and immigrants, refugees, and internationally adopted children born in Asia, the Pacific Islands, Africa, and other regions of high or intermediate endemicity should be tested for HBsAg, regardless of vaccination status (212). Those determined to be HBsAg-positive should be monitored for development of liver disease. Household members of HBsAg-positive children or adults should be vaccinated if they are not already immune.

### Hib Vaccine

Interpretation of a serologic test to verify whether children who were vaccinated >2 months previously are protected against Hib bacteria can be difficult. Because the number of vaccinations needed for protection decreases with age and because adverse events are rare (22), age-appropriate vaccination should be provided. Hib vaccination is not recommended routinely for persons aged  $\geq 5$  years (20).

<sup>¶¶</sup> Enzyme immunoassay tests are available. Physicians should contact the laboratory performing the test for interpretive standards and limitations. Protective concentrations for antibody to diphtheria and tetanus toxins are defined as >0.1 IU/mL.



## MMR Vaccine

The simplest approach to resolving concerns about MMR vaccination is to revaccinate with 1 or 2 doses of MMR vaccine, depending on age. Serious adverse events after MMR vaccinations are rare (2). No evidence indicates that administering MMR vaccine increases the risk for adverse reactions among persons who are already immune to measles, mumps, or rubella as a result of previous vaccination or natural disease. Doses of measles-containing vaccine administered before the first birthday should not be counted as part of the series (2). Alternatively, serologic testing for IgG antibody to vaccine viruses indicated on the vaccination record can be considered. Serologic testing is widely available for measles and rubella IgG antibody. A person whose record indicates receipt of monovalent measles or measles-rubella vaccine on or after the first birthday and who has protective antibody against measles and rubella should receive 1 or 2 doses of MMR or MMRV as age appropriate to ensure protection against mumps and varicella (and rubella if measles vaccine alone had been administered). If a person whose record indicates receipt of MMR at age  $\geq 12$  months has a protective concentration of antibody to measles, no additional vaccination is needed unless a second dose is required for school entry.

## Pneumococcal Vaccines

Many industrialized countries are now routinely using pneumococcal vaccines. Although recommendations for pneumococcal polysaccharide vaccine also exist in many countries, the vaccine might not be routinely administered. PCV and PPSV should be administered according to age-appropriate vaccination schedules or as indicated by the presence of underlying medical conditions (25,49).

## Poliovirus Vaccine

The simplest approach to vaccinating with poliovirus vaccine is to revaccinate persons aged  $< 18$  years with IPV according to the U.S. schedule. Adverse events after IPV are rare (201). Children appropriately vaccinated with 3 doses of OPV in economically developing countries might have suboptimal seroconversion, including to type 3 poliovirus (201). Serologic testing for neutralizing antibody to poliovirus types 1, 2, and 3 can be obtained commercially and at certain state health department laboratories. Persons with protective titers against all three types do not need to repeat doses but should complete the schedule as age appropriate.

## Rotavirus Vaccine

Rotavirus vaccination should not be initiated for infants aged  $\geq 15$  weeks, 0 days. Infants who began the rotavirus vaccine series outside the United States but who did not complete

the series and who are still aged  $\leq 8$  months, 0 days, should follow the routine schedule and receive doses to complete the series. If the brand of a previously administered dose is RV5 or unknown, a total of 3 doses of rotavirus vaccine should be documented for series completion. All doses should be administered by age 8 months, 0 days.

## Td and Tdap Vaccines

Children aged  $\geq 7$  years who need the primary series doses of tetanus-toxoid-containing vaccine should receive Td or Tdap as age appropriate.

## Varicella Vaccine

Varicella vaccine is not available in the majority of countries. A person who lacks reliable evidence of varicella immunity should be vaccinated as age appropriate (4,20).

## Zoster Vaccine

Zoster vaccination is recommended for all persons aged  $\geq 60$  years who have no contraindications, including persons who report a previous episode of zoster or who have chronic medical conditions. The vaccine should be offered at the patient's first clinical encounter with the health-care provider. The vaccine is administered as a single 0.65-mL subcutaneous dose. Zoster vaccination is not indicated to treat acute zoster, to prevent persons with acute zoster from developing postherpetic neuralgia, or to treat ongoing postherpetic neuralgia. Before administration of zoster vaccine, patients do not need to be asked about their history of varicella or to have serologic testing conducted to determine zoster immunity.

## Vaccinating Persons with Bleeding Disorders

Because of the risk for hematoma formation after injections, intramuscular injections are often avoided among persons with bleeding disorders by using the subcutaneous or intradermal routes for vaccines that normally are administered intramuscularly. In one study, hepatitis B vaccine was administered intramuscularly to 153 persons with hemophilia. The vaccination was administered with a 23-gauge or smaller caliber needle, followed by application of steady pressure to the site for 1–2 minutes. The vaccinations resulted in a low (4%) bruising rate, and no patients required factor supplementation (213). Whether antigens that produce more local reactions (e.g., pertussis) would produce an equally low rate of bruising is unknown.

When hepatitis B or any other intramuscularly administered vaccine is indicated for a patient with a bleeding disorder, the vaccine should be administered intramuscularly if a physician

familiar with the patient's bleeding risk determines that the vaccine can be administered by this route with reasonable safety. If the patient receives antihemophilia or similar therapy, intramuscularly administered vaccinations can be scheduled shortly after such therapy is administered. A fine-gauge needle (23 gauge or smaller caliber) should be used for the vaccination, followed by firm pressure on the site, without rubbing, for at least 2 minutes. The patient or family should be given information on the risk for hematoma from the injection. Patients receiving anticoagulation therapy presumably have the same bleeding risk as patients with clotting factor disorders and should follow the same guidelines for intramuscular administration.

## Vaccination Records

### Records of Health-Care Providers

Appropriate and timely vaccination documentation helps ensure not only that persons in need of recommended vaccine doses receive them but also that adequately vaccinated patients do not receive excess doses. Curtailing the number of excess doses administered to patients controls costs incurred by patients, providers, insurers, vaccination programs, and other stakeholders. In addition, excess doses of inactivated vaccines might increase the risk for an adverse reaction. Health-care providers who administer vaccines covered by the National Childhood Vaccine Injury Act are required to ensure that the permanent medical record of the recipient (or a permanent office log or file) indicates the date the vaccine was administered, the vaccine manufacturer, the vaccine lot number, and the name, address, and title of the person administering the vaccine. In addition, the provider is required to record the edition date of the VIS distributed and the date those materials were provided. The act considers a health-care provider to be any licensed health-care professional, organization, or institution, whether private or public (including federal, state, and local departments and agencies), under whose authority a specified vaccine is administered. This information should be kept for all vaccines, not just for those required by the act. Providers and staff members also should systematically update patient's permanent medical records to reflect any documented episodes of adverse events after vaccination and any serologic test results related to vaccine-preventable diseases (e.g., those for rubella screening and antibody to HBsAg).

### Personal Records of Patients

Official childhood vaccination records have been adopted by every state and territory and the District of Columbia to

encourage uniformity of records and to facilitate assessment of vaccination status by schools and child-care centers. The records also are key tools in vaccination education programs aimed at increasing parental and patient awareness of the need for vaccines. A permanent vaccination record card should be established for each newborn infant and maintained by the parent or guardian. The parent or guardian should be educated about the importance of keeping the record up to date and instructed to keep the record indefinitely as part of the child's permanent medical record. These cards should be distributed to new mothers before discharge from the hospital. Using vaccination record cards for adolescents and adults also is encouraged. Standardized adult vaccination records are available at <http://www.immunize.org>.

## Immunization Information Systems

IISs (formerly referred to as immunization registries) are confidential, population-based, computerized information systems that collect and consolidate vaccination data from multiple health-care providers within a geographic area. IISs are a critical tool that can increase and sustain vaccination coverage by consolidating vaccination records from multiple providers, generating reminder and recall vaccination notices for each person, and providing official vaccination forms and vaccination coverage assessments (214).

Changing vaccination providers during the course of an individual's vaccination series is common in the United States. The 2007 National Health Interview Survey Summary Health Statistics for U.S. Children documented that 95% of children have a usual place of health care; 6% go to more than one health venue most of the time. Individual eligibility for Medicaid and resulting enrollment in Medicaid managed-care health plans tends to be sporadic, with an average duration of 9 months and a median of <12 months in 2000 (215). In addition to changes in providers, the vaccination records of persons who have changed vaccination providers often are unavailable or incomplete or might not have been entered into an IIS (214). Missing or inaccurate information regarding vaccines received previously might preclude accurate determination of which vaccines are indicated at the time of a visit, resulting in administration of extra doses.

A fully operational IIS also can prevent duplicate vaccinations, limit missed appointments, reduce vaccine waste, and reduce staff time required to produce or locate vaccination records or certificates. Most IISs have additional capabilities, such as vaccine management, maintenance of lifetime vaccination histories, and interoperability with other health information systems. The National Vaccine Advisory Committee strongly encourages development of community- or state-based IISs

and recommends that vaccination providers participate in these systems when possible. One of the national health objectives for 2010 was 95% participation of children aged <6 years in a fully operational population-based IIS (objective 20.1) (216). Participating in an IIS means having two or more vaccinations recorded in the IIS. 2008 IIS data indicate that approximately 75% of children aged <6 years with two or more vaccinations were participating in IISs (217). Inclusion of adults into IISs also would be worthwhile. A new national health objective for 2020 is 80% of adolescents (aged 11–18 years) with two or more age-appropriate vaccinations recorded in IISs (<http://www.healthypeople.gov/hp2020/objectives/topicarea.aspx?id=30&topicarea=immunization+and+infectious+diseases>).

## Vaccination Programs

In the United States, vaccination programs have eliminated many vaccine-preventable diseases and reduced the incidence of several others (218). Because infants and young children were the principle recipients of most vaccines developed during the twentieth century (e.g., poliovirus vaccine), many persons in the United States might believe that vaccinations are solely for the young; however, vaccinations are recommended for persons of all ages (20,28). Improved vaccination coverage can result in additional reductions in the incidence of vaccine-preventable diseases and decrease associated morbidity and mortality. Universal vaccination is a critical part of quality health care and should be accomplished through routine and catch-up vaccination provided in physicians' offices, public health clinics, and other appropriate complementary settings. Every patient encounter represents an opportunity to review and, when needed, improve a patient's vaccination status through administration of recommended vaccines.

## Vaccination of Children and Adolescents

Physicians and other pediatric vaccination providers should adhere to the standards for child and adolescent vaccination practices (8). These standards were published by the National Vaccine Advisory Committee and define appropriate vaccination practices for both public and private sectors. The standards provide guidance on practices that eliminate barriers to vaccination, including eliminating unnecessary prerequisites for receiving vaccinations, eliminating missed opportunities to vaccinate, improving procedures to assess vaccination needs, enhancing knowledge about vaccinations among parents and providers, and improving management and reporting of adverse events. In addition, the standards address the importance of recall and reminder systems and using assessments to monitor clinic or office vaccination coverage levels. Health-care providers should

simultaneously administer as many vaccine doses as possible as indicated on the *Recommended Immunization Schedules for Persons Aged 0 Through 18 Years* (20).

Community health-care providers, as well as staff members at both state and local vaccination programs, should coordinate with partners to maximize outreach to populations at risk for undervaccination and vaccine-preventable diseases. For example, the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) is a categorical federal grant program administered by the U.S. Department of Agriculture through state health departments. The program provides supplemental foods, health-care referrals, and nutrition education to low-income pregnant, breastfeeding, or postpartum women, as well as to infants and children aged <5 years. More than 8.7 million people participated in this program in 2008 (<http://www.fns.usda.gov/pd/wicmain.htm>). In collaboration, WIC and state vaccination programs should assess regularly the vaccination coverage levels of WIC participants and develop new strategies and aggressive outreach procedures in sites with coverage levels <90%. Vaccination programs and private providers are encouraged to refer eligible children to obtain WIC nutritional services (219).

## Adolescents

Vaccinations are recommended throughout life, including during adolescence. The age range for adolescence is defined as 11–21 years by many professional associations, including the American Academy of Pediatrics and the American Medical Association (220,221). Definitions of these age cutoffs differ depending on the source of the definition and the source's purpose for creating a definition. Vaccination of adolescents is critical for preventing diseases for which adolescents are at particularly high or increasing risk, such as meningococcal disease and human papillomavirus infection. Three vaccines recommended for adolescents have been licensed since 2005: MCV4, HPV, and the Tdap vaccine. A second dose of varicella vaccine is recommended for persons who received 1 dose of varicella vaccine after age 12 months, and this group includes many adolescents. In addition, annual seasonal influenza vaccination is recommended for persons aged >6 months who have no contraindications. To ensure vaccine coverage, clinicians and other health-care providers who treat adolescents must screen for a complete vaccination history on every occasion that an adolescent has an office visit.

National goals for vaccination coverage for adolescents aged 13–15 years were included in *Healthy People 2010* (216). Targets for 90% coverage were specified for established vaccine recommendations including those for 3 doses of hepatitis B vaccine, 1 dose of MMR vaccine, 1 dose of varicella vaccine (excluding persons with a history of varicella), and 1 dose of



Td vaccine. Results of the published 2008 National Immunization Survey—Teen indicate that, for the first time, coverage targets for hepatitis B and MMR vaccines were met. For  $\geq 1$  dose of varicella, coverage increased to 86%. However, coverage for  $\geq 1$  dose of either Td or Tdap was unchanged at 71%, remaining below the coverage target of 90%. Coverage for MCV4 is 42%. New objectives from *Healthy People 2020* include 1 dose of Tdap and  $\geq 2$  doses of varicella vaccine (excluding persons who have had varicella disease) (<http://www.healthypeople.gov/hp2020/objectives/topicarea.aspx?id=30&topicarea=immunization+and+infectious+diseases>).

Ensuring adolescents receive routine and catch-up vaccination and increasing vaccination coverage in this age group present challenges. In general, adolescents do not visit health-care providers frequently. Health-care providers should promote annual preventive visits (217), including one specifically for adolescents aged 11 and 12 years. The annual visits should be used as opportunities to provide routinely recommended vaccine doses, additional catch-up doses needed for lapsed vaccine series, vaccines recommended for high-risk groups, additional doses that might have been recently recommended, and other recommended health-care services.

All vaccine doses should be administered according to ACIP vaccine-specific statements and with the most recent schedules for both routine and catch-up vaccination. Before leaving any visit for medical care, adolescents should be encouraged to schedule return visits for any additional vaccine doses needed. During visits that occur outside of influenza season, providers should discuss and recommend seasonal influenza vaccination and make explicit plans for vaccination, including timing and anticipated setting (e.g., health-care provider's office, school, or pharmacy). Catch-up vaccination with multidose adolescent vaccines generally can occur according to the routine dosing schedule for these vaccines, although in some circumstances the clinician or health-care provider might use minimum intervals for vaccine doses. These circumstances include an outbreak that increases risk for disease or the likelihood that doses will be missed in the future (e.g., because of an impending loss of health-care coverage or transportation challenges). Because of lack of efficacy data for HPV vaccine administration using minimum intervals, providers are encouraged, when possible, to use routine dosing intervals for females aged 11–26 years who have not yet received 3 HPV vaccine doses as recommended (20,28).

One of the challenges of adolescent vaccination is ensuring that current, complete vaccination histories are available. Insurers, covered services, or reimbursement levels can change, and these changes might affect reimbursement for vaccine doses and vaccination services directly while also causing disruptions

in an adolescent's access to vaccination providers or venues. In circumstances in which a vaccination record is unavailable, vaccination providers should attempt to obtain this information from various sources (e.g., parent, previous providers, or school records). More detail about how to obtain these records is available at from CDC at <http://www.cdc.gov/vaccines/recs/immuniz-records.htm>. With the exception of influenza and pneumococcal polysaccharide vaccines, if documentation of a vaccine dose is not available, the adolescent should be considered unvaccinated for that dose. Regardless of the venue in which an adolescent receives a dose of vaccine, that vaccine dose should be documented in the patient's chart or in an office log, and the information should be entered into an IIS. The adolescent also should be provided with a record card that documents the vaccination history.

## Adult Vaccination

The incidence of vaccine-preventable diseases in adults in the United States is high. Approximately 45,000 adults die each year from vaccine-preventable diseases, the majority from influenza (222). In 2008, an estimated 44,000 cases of invasive pneumococcal disease were reported with approximately 4,500 deaths, the majority occurring among persons aged  $>35$  years (<http://www.cdc.gov/abcs/survreports/spneu08.htm>). Because of recent licensure of new vaccines approved for adults and new ACIP recommendations for the use of many vaccines in adults, providers of adult health care now share a greater responsibility for putting these recommendations into practice. In 2009, an estimated 4,070 deaths were caused by infection with the HPV strains causing the majority of cervical cancers in this country that are preventable with HPV vaccine and routine Papanicolaou smear testing (<http://www.cancer.org/docroot/home/index.asp>). Herpes zoster causes considerable morbidity in adults aged  $>50$  years (55). A painful complication of herpes zoster infection is postherpetic neuralgia, which is characterized by severe pain that can persist for up to a year after the herpes zoster rash has subsided. A vaccine to prevent herpes zoster was licensed in 2006.

In 2003, the National Vaccine Advisory Committee published standards for adult vaccination (222). These standards include ensuring vaccine availability, review of records, communicating the risks and benefits of vaccination, use of standing orders, and recommending simultaneous administration of all indicated doses according to the *Recommended Adult Immunization Schedule* (28).

Vaccination with vaccines recommended for all adults or for those in specific age groups is generally cost-effective, if not cost-saving, for society. The National Commission on Prevention Priorities (NCPP) ranked clinical preventive services based on



clinically preventable disease effects and cost-effectiveness (223). In the NCPP report, influenza vaccination for adults aged  $\geq 50$  years and pneumococcal vaccination for adults aged  $\geq 65$  years ranked high, with 8 of 10 possible points in the scoring system used. Most other studies have found influenza vaccination reduces or minimizes health care, societal, and individual costs or the productivity losses and absenteeism associated with influenza illness (224–226). Economic analyses among adults aged  $\geq 65$  years have found influenza vaccination to be cost-effective (225–227).

A 2008 study of the cost-effectiveness of PPSV demonstrated that vaccination resulted in a gain of \$3,341 per quality-adjusted life year; the result is sensitive to vaccine uptake assumptions (228). PPSV administered at ages 50–65 years might be clinically favorable and, depending on cost-effectiveness criteria used, economically favorable (228).

Hepatitis B vaccine is not recommended routinely for all adults. However, multiple studies have established the cost-effectiveness of providing hepatitis B vaccinations at counseling and testing sites for HIV and other sexually transmitted diseases, correctional institutions, drug-abuse treatment centers, and other settings serving adults at risk for hepatitis B virus infection (229–230).

Four studies have estimated the cost-effectiveness of a routine herpes zoster vaccination program of immunocompetent persons aged  $\geq 60$  years (231–234). At a vaccine cost of \$150 per dose, the societal costs of routinely vaccinating immunocompetent persons aged  $\geq 60$  years range from \$27,000 to \$112,000 per quality-adjusted life year gained (231–234). The estimated cost per quality-adjusted life year for zoster vaccination covers a wide range that appears acceptable compared with either standard thresholds or other established interventions but is at the intermediate to high end of that range.

Vaccination rates in adults are considered suboptimal (235–238). *Healthy People 2010* goals for adult vaccination coverage with influenza and pneumococcal polysaccharide vaccines are 90% for each vaccine. For the 2007–2008 season, influenza vaccination coverage among adults aged 50–64 years was 34%, and coverage among adults aged  $\geq 65$  years was 66% (67). In 2008, 60% of adults aged  $\geq 65$  years received a dose of PPSV ([http://www.cdc.gov/nchs/data/hestat/vaccine\\_coverage.htm](http://www.cdc.gov/nchs/data/hestat/vaccine_coverage.htm)). New *Healthy People 2020* goals for influenza and pneumococcal polysaccharide vaccines include specific subsets of adults, including institutionalized adults aged  $\geq 18$  years (for both influenza and pneumococcal polysaccharide vaccines) and noninstitutionalized adults at high risk aged  $> 18$  years (for pneumococcal polysaccharide vaccine) (<http://www.healthypeople.gov/hp2020/objectives/topicarea.aspx?id=30&topicarea=immunization+and+infectious+diseases>).

The most substantial barrier to vaccination coverage is lack of knowledge about these vaccines among adult patients and adult

providers. Other barriers are cost (lack of additional insurance to Medicare) (239) and the lack of financing mechanisms for newly licensed and recommended vaccines.

A common challenge for health-care providers is vaccinating adults with unknown vaccination records. In general (except for influenza and pneumococcal polysaccharide vaccines), adults should receive a vaccine dose if the dose is recommended and no record of previous administration exists. If an adult has a record of military service and does not have records available, providers can assume that the person has received all vaccines recommended by the military at the time of service entry. Serologic testing might be helpful in clarifying immune status if questions remain because at different times and depending on military assignments, there might be interservice and individual differences.

## Evidence-Based Interventions to Increase Vaccination Coverage

The independent, nonfederal Task Force on Community Preventive Services, whose membership is appointed by CDC, provides public health decision-makers with recommendations on population-based interventions to promote health and prevent disease, injury, disability, and premature death. The recommendations are based on systematic reviews of the scientific literature about effectiveness and cost-effectiveness of these interventions. In addition, the task force identifies critical information about the other effects of these interventions, the applicability to specific populations and settings, and the potential barriers to implementation. Additional information, including updates of published reviews, is available from *The Community Guide* at <http://www.thecommunityguide.org>.

Beginning in 1996, the task force systematically reviewed published evidence on the effectiveness and cost-effectiveness of population-based interventions to increase coverage of vaccines recommended for routine use among children, adolescents, and adults. A total of 197 articles were identified that evaluated a relevant intervention, met inclusion criteria, and were published during 1980–1997. Reviews of 17 specific interventions were published in 1999 (235–238). Using the results of their review, the task force made recommendations about the use of these interventions (238). Several interventions were identified and recommended on the basis of published evidence. Follow-up reviews were published in 2000, and a review of interventions to improve the coverage of adults at high risk was conducted in 2005 (238,239). The interventions and the recommendations are summarized in this report (Table 15).

In 1997, the task force categorized as a recommended strategy vaccination requirements for child care, school, and college (236). When appropriate, health agencies should take necessary steps to develop and enforce these requirements.

A 2008 update of the original task force systematic review of the evidence on the effectiveness of provider assessment and feedback for increasing coverage rates found that this strategy remains an effective intervention. A later update reviewed 19 new studies published during 1997–2007. The updated review supports the original task force recommendation for use of assessment and feedback based on strong evidence of effectiveness. The task force reviewed studies of assessment and feedback as a strategy that were conducted in a range of settings, including private practice, managed care, public health, community health settings, and academic centers. Studies have assessed the effectiveness of this intervention to improve coverage with MMR, DTP, DTaP, Hib, influenza, pneumococcal, and Td vaccines (237). The most updated information on this review is available at <http://www.thecommunityguide.org/vaccines/universally/providerassessment.html>. As recognized by the task force, routine assessment and feedback of vaccination rates obtained at the provider site is one of the most effective strategies for achieving high, sustainable vaccine coverage. Since 1995, all states receiving federal funds for vaccination programs have been required to conduct annual assessments of vaccination rates both in public health clinics and in private provider offices. Primarily to aid local and state health departments in their efforts to conduct assessments and assist providers, CDC has developed numerous software applications to measure vaccination rates in provider practices.

### Other General Programmatic Issues

Programmatic challenges, evolving issues, and effective interventions related to adult and adolescent vaccination programs have been described by other advisory groups and expert groups. Additional evidence-based approaches are being developed for certain issues (e.g., settings for adolescent vaccination delivery) through ongoing research and evaluation. Among current programmatic challenges, vaccine financing is especially difficult because certain problems and solutions differ markedly from one state to another. Practitioners interested in beginning or continuing to provide vaccinations to patients are encouraged to consult with local and state public health vaccination programs to learn about publicly funded programs that might be available in their areas for patients who need vaccination but have insufficient health insurance coverage and no financial resources. If not already participating, providers who care for adolescents and children aged <19 years should enroll in the Vaccines for Children Program (<http://www.cdc.gov/vaccines/programs/vfc/default.htm>). Through this program's provision of ACIP-recommended, federally purchased vaccines, participating providers are able to fully vaccinate eligible children whose parents might not otherwise be able to afford the

vaccinations. Interested providers are encouraged to work with insurers, state and specialty-specific medical organizations, vaccine manufacturers, and other stakeholders to address financial barriers to achieving high vaccination coverage. With availability of safe and effective vaccines for 17 vaccine-preventable diseases, the capacity for realizing the potential benefits of these products in the United States depends on reaching children, adolescents, and adults through dedicated, knowledgeable vaccination providers and efficient, strong vaccination programs at local, state, and federal levels.

## Vaccine Information Sources

In addition to these general recommendations, the following sources contain specific and updated vaccine information.

### CDC-INFO Contact Center

The CDC-INFO contact center is supported by CDC and provides public health-related information, including vaccination information, for health-care providers and the public, 24 hours a day, 7 days a week (telephone [English and Spanish]: 800-232-4636; telephone [TTY]: 800-232-6348).

### CDC's National Center for Immunization and Respiratory Diseases

CDC's National Center for Immunization and Respiratory Diseases website provides direct access to vaccination recommendations of ACIP, vaccination schedules, automated child schedulers, an adult immunization scheduler, vaccine safety information, publications, provider education and training, and links to other vaccination-related websites (<http://www.cdc.gov/vaccines>).

### MMWR

ACIP recommendations regarding vaccine use, statements of vaccine policy as they are developed, and reports of specific disease activity are published by CDC in the *MMWR* series and can be found at <http://www.cdc.gov/vaccines/pubs/ACIP-list.htm>. Electronic subscriptions are free (<http://www.cdc.gov/mmwr/mmwrsubscribe.html>). Subscriptions to print versions also are available from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402-9235 (telephone: 202-512-1800).

### American Academy of Pediatrics (AAP)

Every 3 years, AAP issues the *Red Book: Report of the Committee on Infectious Diseases*, which contains a composite summary of AAP and ACIP recommendations concerning infectious diseases and vaccinations for infants, children, and

adolescents (telephone: 888-227-1770; website: <http://www.aap.org>).

### **American Academy of Family Physicians (AAFP)**

Information from the professional organization of family physicians is available at <http://www.aafp.org>.

### **Immunization Action Coalition**

The Immunization Action Coalition provides extensive free provider and patient information, including translations of VISs into multiple languages. Printed materials are reviewed by CDC for technical accuracy (<http://www.immunize.org> and <http://www.vaccineinformation.org>).

### **National Network for Immunization Information**

This National Network for Immunization Information is an affiliation of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, AAP, the American Nurses Association, AAFP, the National Association of Pediatric Nurse Practitioners, the American College of Obstetricians and Gynecologists, the University of Texas Medical Branch, the Society for Adolescent Medicine, and the American Medical Association. This source provides the public, health professionals, policy makers, and the media with up-to-date, scientifically valid information (<http://www.immunizationinfo.org>).

### **Vaccine Education Center**

Located at the Children's Hospital of Philadelphia, the Vaccine Education Center provides patient and provider vaccine information (<http://www.vaccine.chop.edu>).

### **Institute for Vaccine Safety**

Located at Johns Hopkins University School of Public Health, the Institute for Vaccine Safety provides information about vaccine safety concerns and objective and timely information to physicians and health-care providers and parents (<http://www.vaccinesafety.edu>).

### **Group on Immunization Education of the Society of Teachers of Family Medicine**

The Group on Immunization Education of the Society of Teachers of Family Medicine provides information for clinicians, including the free program Shots. Shots includes the childhood, adolescent, and adult schedules for iPhone, Palm, and Windows devices, as well as online versions (<http://www.immunizationed.org>).

### **State and Local Health Departments**

State and local health departments provide technical advice through hotlines, e-mail, and websites, including printed information regarding vaccines and immunization schedules, posters, and other educational materials.

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TABLE 1. 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
HepB-1 <sup>§</sup>	Birth	Birth	1–4 months	4 weeks
HepB-2	1–2 months	4 weeks	2–17 months	8 weeks
HepB-3 <sup>¶</sup>	6–18 months	24 weeks	—	—
DTaP-1 <sup>§</sup>	2 months	6 weeks	2 months	4 weeks
DTaP-2	4 months	10 weeks	2 months	4 weeks
DTaP-3	6 months	14 weeks	6–12 months	6 months <sup>**</sup> ,††
DTaP-4	15–18 months	12 months	3 years	6 months <sup>**</sup>
DTaP-5	4–6 years	4 years	—	—
Hib-1 <sup>§,§§</sup>	2 months	6 weeks	2 months	4 weeks
Hib-2	4 months	10 weeks	2 months	4 weeks
Hib-3 <sup>¶¶</sup>	6 months	14 weeks	6–9 months	8 weeks
Hib-4	12–15 months	12 months	—	—
IPV-1 <sup>§</sup>	2 months	6 weeks	2 months	4 weeks
IPV-2	4 months	10 weeks	2–14 months	4 weeks
IPV-3	6–18 months	14 weeks	3–5 years	6 months
IPV-4 <sup>***</sup>	4–6 years	4 years	—	—
PCV-1 <sup>§§</sup>	2 months	6 weeks	8 weeks	4 weeks
PCV-2	4 months	10 weeks	8 weeks	4 weeks
PCV-3	6 months	14 weeks	6 months	8 weeks
PCV-4	12–15 months	12 months	—	—
MMR-1 <sup>†††</sup>	12–15 months	12 months	3–5 years	4 weeks
MMR-2 <sup>†††</sup>	4–6 years	13 months	—	—
Varicella-1 <sup>†††</sup>	12–15 months	12 months	3–5 years	12 weeks <sup>§§§</sup>
Varicella-2 <sup>†††</sup>	4–6 years	15 months	—	—
HepA-1	12–23 months	12 months	6–18 months <sup>**</sup>	6 months <sup>**</sup>
HepA-2	≥18 months	18 months	—	—
Influenza, inactivated <sup>¶¶¶</sup>	≥6 months	6 months <sup>****</sup>	1 month	4 weeks
LAIV (intranasal) <sup>¶¶¶</sup>	2–49 years	2 years	1 month	4 weeks
MCV4-1 <sup>††††</sup>	11–12 years	2 years	5 years	8 weeks
MCV4-2	16 years	11 years (+8 weeks)	—	—
MPSV4-1 <sup>††††</sup>	—	2 years	5 years	5 years
MPSV4-2	—	7 years	—	—
Td	11–12 years	7 years	10 years	5 years
Tdap <sup>§§§§</sup>	≥11 years	7 years	—	—
PPSV-1	—	2 years	5 years	5 years
PPSV-2 <sup>¶¶¶¶</sup>	—	7 years	—	—
HPV-1 <sup>*****</sup>	11–12 years	9 years	2 months	4 weeks
HPV-2	11–12 years (+2 months)	9 years (+4 weeks)	4 months	12 weeks <sup>††††</sup>
HPV-3 <sup>††††</sup>	11–12 years (+6 months)	9 years (+24 weeks)	—	—
Rotavirus-1 <sup>§§§§§</sup>	2 months	6 weeks	2 months	4 weeks
Rotavirus-2	4 months	10 weeks	2 months	4 weeks
Rotavirus-3 <sup>¶¶¶¶¶</sup>	6 months	14 weeks	—	—
Herpes zoster <sup>*****</sup>	≥60 years	60 years	—	—

See table footnotes on page 37



**TABLE 1. (Continued) Recommended and minimum ages and intervals between vaccine doses\*<sup>†</sup>**

**Abbreviations:** DTaP = diphtheria and tetanus toxoids and acellular pertussis; HepA = hepatitis A; HepB = hepatitis B; Hib = *Haemophilus influenzae* type b; HPV = human papillomavirus; IPV = inactivated poliovirus; LAIV = live, attenuated influenza vaccine; MCV4 = quadrivalent meningococcal conjugate vaccine; MMR = measles, mumps, and rubella; MMRV = measles, mumps, rubella, and varicella; MPSV4 = quadrivalent meningococcal polysaccharide vaccine; PCV = pneumococcal conjugate vaccine; PPSV = pneumococcal polysaccharide vaccine; PRP-OMB = polyribosylribitol phosphate-meningococcal outer membrane protein conjugate; Td = tetanus and diphtheria toxoids; TIV = trivalent inactivated influenza vaccine; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; Var = varicella vaccine.

- \* Combination vaccines are available. Use of licensed combination vaccines is generally preferred to separate injections of their equivalent component vaccines. 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 components.
- <sup>†</sup> Information on travel vaccines, including typhoid, Japanese encephalitis, and yellow fever, is available at <http://www.cdc.gov/travel>. Information on other vaccines that are licensed in the United States but not distributed, including anthrax and smallpox, is available at <http://www.bt.cdc.gov>.
- <sup>§</sup> Combination vaccines containing the hepatitis B component are available (see Table 2). These vaccines should not be administered to infants aged <6 weeks because of the other components (i.e., Hib, DTaP, HepA, and IPV).
- <sup>¶</sup> HepB-3 should be administered at least 8 weeks after HepB-2 and at least 16 weeks after HepB-1 and should not be administered before age 24 weeks.
- \*\* Calendar months.
- <sup>††</sup> The minimum recommended interval between DTaP-3 and DTaP-4 is 6 months. However, DTaP-4 need not be repeated if administered at least 4 months after DTaP-3.
- <sup>§§</sup> For Hib and PCV, children receiving the first dose of vaccine at age ≥7 months require fewer doses to complete the series.
- <sup>¶¶</sup> If PRP-OMP (Pedvax-Hib, Merck Vaccine Division) was administered at ages 2 and 4 months, a dose at age 6 months is not necessary.
- \*\*\* A fourth dose is not needed if the third dose was administered at ≥4 years and at least 6 months after the previous dose.
- <sup>†††</sup> Combination MMRV vaccine can be used for children aged 12 months–12 years. See text for details.
- <sup>§§§</sup> The minimum interval from Varicella-1 to Varicella-2 for persons beginning the series at age ≥13 years is 4 weeks.
- <sup>¶¶¶</sup> One dose of influenza vaccine per season is recommended for most persons. Children aged <9 years who are receiving influenza vaccine for the first time or who received only 1 dose the previous season (if it was their first vaccination season) should receive 2 doses this season.
- \*\*\*\* The minimum age for inactivated influenza vaccine varies by vaccine manufacturer. See package insert for vaccine-specific minimum ages.
- <sup>††††</sup> Revaccination with meningococcal vaccine is recommended for previously vaccinated persons who remain at high risk for meningococcal disease. (Source: CDC. Updated recommendations from the Advisory Committee on Immunization Practices (ACIP) for revaccination of persons at prolonged increased risk for meningococcal disease. MMWR 2009;58:[1042–3]).
- <sup>§§§§</sup> Only 1 dose of Tdap is recommended. Subsequent doses should be given as Td. For one brand of Tdap, the minimum age is 11 years. For management of a tetanus-prone wound in persons who have received a primary series of tetanus-toxoid-containing vaccine, the minimum interval after a previous dose of any tetanus-containing vaccine is 5 years.
- <sup>¶¶¶¶</sup> A second dose of PPSV 5 years after the first dose is recommended for persons aged ≤65 years at highest risk for serious pneumococcal infection and those who are likely to have a rapid decline in pneumococcal antibody concentration. (Source: CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 1997;46[No. RR-8]).
- \*\*\*\*\* Bivalent HPV vaccine is approved for females aged 10–25 years. Quadrivalent HPV vaccine is approved for males and females aged 9–26 years.
- <sup>†††††</sup> The minimum age for HPV-3 is based on the baseline minimum age for the first dose (i.e., 108 months) and the minimum interval of 24 weeks between the first and third dose. Dose 3 need not be repeated if it is administered at least 16 weeks after the first dose.
- <sup>§§§§§</sup> The first dose of rotavirus must be administered at age 6 weeks through 14 weeks and 6 days. The vaccine series should not be started for infants aged ≥15 weeks, 0 days. Rotavirus should not be administered to children older than 8 months, 0 days of age regardless of the number of doses received between 6 weeks and 8 months, 0 days of age.
- <sup>¶¶¶¶¶</sup> If 2 doses of Rotarix (GlaxoSmithKline) are administered as age appropriate, a third dose is not necessary.
- \*\*\*\*\* Herpes zoster vaccine is recommended as a single dose for persons aged ≥60 years.

**TABLE 2. FDA-licensed combination vaccines\***

Vaccine <sup>†</sup>	Trade name (year licensed)	Age range	Routinely recommended ages
Hib-HepB	Comvax (1996)	6 weeks–71 months	Three-dose schedule at 2, 4, and 12–15 months of age
DTaP/Hib	TriHIBit (1996)	15–18 months	Fourth dose of Hib and DTaP series
HepA-HepB	Twinrix (2001)	≥18 years	Three doses on a schedule of 0, 1, and 6 months
DTaP-HepB-IPV	Pediarix (2002)	6 weeks–6 years	Three-dose series at 2, 4 and 6 months of age
MMRV	ProQuad (2005)	12 months–12 years	Two doses, the first at 12–15 months, the second at 4–6 years
DTaP-IPV	Kinrix (2008)	4–6 years	Fifth dose of DTaP and fourth dose of IPV
DTaP-IPV/Hib	Pentacel (2008)	6 weeks–4 years	Four-dose schedule at 2, 4, 6, and 15–18 months of age

**Abbreviations:** DT = diphtheria and tetanus toxoids; DTaP = diphtheria and tetanus toxoids and acellular pertussis; FDA = Food and Drug Administration; HepA = hepatitis A; HepB = hepatitis B; Hib = *Haemophilus influenzae* type b; IPV = inactivated poliovirus; MMR = measles, mumps, and rubella; MMRV = measles, mumps, rubella, and varicella; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

**Source:** American Academy of Pediatrics. Passive immunization. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. Red book: 2009 report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.

\* Although MMR, DTaP, DT, Td, and Tdap are combination vaccines, they are not included on this list because they are not available in the United States as single-antigen products.

<sup>†</sup> A dash ( - ) between vaccine products indicates that products are supplied in their final form by the manufacturer and do not require mixing or reconstitution by the user. A slash ( / ) indicates that the products must be mixed or reconstituted by the user.

**TABLE 3. Guidelines for spacing of live and inactivated antigens**

Antigen combination	Recommended minimum interval between doses
Two or more inactivated*	May be administered simultaneously or at any interval between doses
Inactivated and live	May be administered simultaneously or at any interval between doses
Two or more live injectable <sup>†</sup>	28 days minimum interval, if not administered simultaneously

**Source:** American Academy of Pediatrics. Pertussis. In: Pickering LK, Baker, CJ, Kimberlin DW, Long SS, eds. Red book: 2009 report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009:22.

\* Certain experts suggest a 28-day interval between tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine and tetravalent meningococcal conjugate vaccine if they are not administered simultaneously.

<sup>†</sup> Live oral vaccines (e.g., Ty21a typhoid vaccine and rotavirus vaccine) may be administered simultaneously or at any interval before or after inactivated or live injectable vaccines.

**TABLE 4. Guidelines for administering antibody-containing products\* and vaccines**

Type of administration	Products administered		Recommended minimum interval between doses
Simultaneous (during the same office visit)	Antibody-containing products and inactivated antigen		Can be administered simultaneously at different anatomic sites or at any time interval between doses
	Antibody-containing products and live antigen		Should not be administered simultaneously. <sup>†</sup> If simultaneous administration of measles-containing vaccine or varicella vaccine is unavoidable, administer at different sites and revaccinate or test for seroconversion after the recommended interval (see Table 5)
Nonsimultaneous	<b>Administered first</b>		
	Antibody-containing products	<b>Administered second</b>	
	Inactivated antigen	Inactivated antigen	No interval necessary
	Antibody-containing products	Antibody-containing products	No interval necessary
	Antibody-containing products	Live antigen	Dose related <sup>†,§</sup>
	Live antigen	Antibody-containing products	2 weeks <sup>†</sup>

\* Blood products containing substantial amounts of immune globulin include intramuscular and intravenous immune globulin, specific hyperimmune globulin (e.g., hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, and rabies immune globulin), whole blood, packed red blood cells, plasma, and platelet products.

<sup>†</sup> Yellow fever vaccine; rotavirus vaccine; oral Ty21a typhoid vaccine; live, attenuated influenza vaccine; and zoster vaccine are exceptions to these recommendations. These live, attenuated vaccines can be administered at any time before or after or simultaneously with an antibody-containing product.

<sup>§</sup> The duration of interference of antibody-containing products with the immune response to the measles component of measles-containing vaccine, and possibly varicella vaccine, is dose related (see Table 5).

**TABLE 5. Recommended intervals between administration of antibody-containing products and measles- or varicella-containing vaccine, by product and indication for vaccination**

Product/Indication	Dose (mg IgG/kg) and route*	Recommended interval before measles- or varicella-containing vaccine <sup>†</sup> administration (months)
<b>Tetanus IG</b>	250 units (10 mg IgG/kg) IM	3
<b>Hepatitis A IG</b>		
Contact prophylaxis	0.02 mL/kg (3.3 mg IgG/kg) IM	3
International travel	0.06 mL/kg (10 mg IgG/kg) IM	3
<b>Hepatitis B IG</b>	0.06 mL/kg (10 mg IgG/kg) IM	3
<b>Rabies IG</b>	20 IU/kg (22 mg IgG/kg) IM	4
<b>Varicella IG</b>	125 units/10 kg (60–200 mg IgG/kg) IM, maximum 625 units	5
<b>Measles prophylaxis IG</b>		
Standard (i.e., nonimmunocompromised) contact	0.25 mL/kg (40 mg IgG/kg) IM	5
Immunocompromised contact	0.50 mL/kg (80 mg IgG/kg) IM	6
<b>Blood transfusion</b>		
RBCs, washed	10 mL/kg, negligible IgG/kg IV	None
RBCs, adenine-saline added	10 mL/kg (10 mg IgG/kg) IV	3
Packed RBCs (hematocrit 65%) <sup>§</sup>	10 mL/kg (60 mg IgG/kg) IV	6
Whole blood (hematocrit 35%–50%) <sup>§</sup>	10 mL/kg (80–100 mg IgG/kg) IV	6
Plasma/platelet products	10 mL/kg (160 mg IgG/kg) IV	7
<b>Cytomegalovirus IGIV</b>	150 mg/kg maximum	6
<b>IGIV</b>		
Replacement therapy for immune deficiencies <sup>¶</sup>	300–400 mg/kg IV <sup>¶</sup>	8
Immune thrombocytopenic purpura treatment	400 mg/kg IV	8
Postexposure varicella prophylaxis**	400 mg/kg IV	8
Immune thrombocytopenic purpura treatment	1000 mg/kg IV	10
Kawasaki disease	2 g/kg IV	11
<b>Monoclonal antibody to respiratory syncytial virus F protein (Synagis [MedImmune])<sup>††</sup></b>	15 mg/kg IM	None

**Abbreviations:** HIV = human immunodeficiency virus; IG = immune globulin; IgG = immune globulin G; IGIV = intravenous immune globulin; mg IgG/kg = milligrams of immune globulin G per kilogram of body weight; IM = intramuscular; IV = intravenous; RBCs = red blood cells.

\* This table is not intended for determining the correct indications and dosages for using antibody-containing products. Unvaccinated persons might not be protected fully against measles during the entire recommended interval, and additional doses of IG or measles vaccine might be indicated after measles exposure. Concentrations of measles antibody in an IG preparation can vary by manufacturer's lot. Rates of antibody clearance after receipt of an IG preparation also might vary. Recommended intervals are extrapolated from an estimated half-life of 30 days for passively acquired antibody and an observed interference with the immune response to measles vaccine for 5 months after a dose of 80 mg IgG/kg.

<sup>†</sup> Does not include zoster vaccine. Zoster vaccine may be given with antibody-containing blood products.

<sup>§</sup> Assumes a serum IgG concentration of 16 mg/mL.

<sup>¶</sup> Measles and varicella vaccinations are recommended for children with asymptomatic or mildly symptomatic HIV infection but are contraindicated for persons with severe immunosuppression from HIV or any other immunosuppressive disorder.

\*\* The investigational VariZIG, similar to licensed varicella-zoster IG (VZIG), is a purified human IG preparation made from plasma containing high levels of antiviral antibodies (IgG). The interval between VariZIG and varicella vaccine (Var or MMRV) is 5 months.

<sup>††</sup> Contains antibody only to respiratory syncytial virus

TABLE 6. Contraindications and precautions\* to commonly used vaccines

Vaccine	Contraindications	Precautions
DTaP	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Encephalopathy (e.g., coma, decreased level of consciousness, or prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP or DTaP	Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy; defer DTaP until neurologic status clarified and stabilized Temperature of $\geq 105^{\circ}\text{F}$ ( $\geq 40.5^{\circ}\text{C}$ ) within 48 hours after vaccination with a previous dose of DTP or DTaP Collapse or shock-like state (i.e., hypotonic hypo-responsive episode) within 48 hours after receiving a previous dose of DTP/DTaP Seizure $\leq 3$ days after receiving a previous dose of DTP/DTaP Persistent, inconsolable crying lasting $\geq 3$ hours within 48 hours after receiving a previous dose of DTP/DTaP GBS $< 6$ weeks after previous dose of tetanus toxoid-containing vaccine History of arthus-type hypersensitivity reactions after a previous dose of tetanus toxoid-containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus toxoid-containing vaccine Moderate or severe acute illness with or without fever
DT, Td	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	GBS $< 6$ weeks after previous dose of tetanus toxoid-containing vaccine History of arthus-type hypersensitivity reactions after a previous dose of tetanus toxoid-containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid-containing vaccine Moderate or severe acute illness with or without fever
Tdap	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Encephalopathy (e.g., coma, decreased level of consciousness, or prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP, DTaP, or Tdap	GBS $< 6$ weeks after a previous dose of tetanus toxoid-containing vaccine Progressive or unstable neurological disorder, uncontrolled seizures, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized History of arthus-type hypersensitivity reactions after a previous dose of tetanus toxoid-containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus toxoid-containing vaccine Moderate or severe acute illness with or without fever
IPV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Pregnancy Moderate or severe acute illness with or without fever
MMR <sup>†,§</sup>	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Pregnancy Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, or long-term immunosuppressive therapy <sup>¶</sup> or patients with HIV infection who are severely immunocompromised) <sup>§</sup>	Recent ( $\leq 11$ months) receipt of antibody-containing blood product (specific interval depends on product)** History of thrombocytopenia or thrombocytopenic purpura Need for tuberculin skin testing <sup>††</sup> Moderate or severe acute illness with or without fever
Hib	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Age $< 6$ weeks	Moderate or severe acute illness with or without fever
Hepatitis B	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Infant weight $< 2,000$ gm <sup>§§</sup> Moderate or severe acute illness with or without fever
Hepatitis A	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Pregnancy Moderate or severe acute illness with or without fever
Varicella	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, or long-term immunosuppressive therapy <sup>¶</sup> or patients with HIV infection who are severely immunocompromised) <sup>§</sup> Pregnancy	Recent ( $\leq 11$ months) receipt of antibody-containing blood product (specific interval depends on product) <sup>¶¶</sup> Moderate or severe acute illness with or without fever

See table footnotes on page 41



TABLE 6. (Continued) Contraindications and precautions\* to commonly used vaccines

Vaccine	Contraindications	Precautions
PCV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose (of PCV7, PCV13, or any diphtheria toxoid-containing vaccine) or to a component of a vaccine (PCV7, PCV13, or any diphtheria toxoid-containing vaccine)	Moderate or severe acute illness with or without fever
TIV	Severe allergic reaction (e.g., anaphylaxis) after previous dose or to vaccine component, including egg protein	GBS <6 weeks after a previous dose of influenza vaccine Moderate or severe acute illness with or without fever
LAIV	Severe allergic reaction (e.g., anaphylaxis) after previous dose or to vaccine component, including egg protein Pregnancy Immunosuppression Certain chronic medical conditions***	GBS <6 weeks after a previous dose of influenza vaccine Moderate or severe acute illness with or without fever
PPSV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever
MCV4	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever
MPSV4	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever
HPV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Pregnancy Moderate or severe acute illness with or without fever
Rotavirus	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component SCID	Altered immunocompetence other than SCID History of intussusception Chronic gastrointestinal disease <sup>††</sup> Spina bifida or bladder exstrophy <sup>†††</sup> Moderate or severe acute illness with or without fever
Zoster	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Substantial suppression of cellular immunity Pregnancy	Moderate or severe acute illness with or without fever

**Abbreviations:** DT = diphtheria and tetanus toxoids; DTaP = diphtheria and tetanus toxoids and acellular pertussis; GBS = Guillian-Barré syndrome; HBsAg = hepatitis B surface antigen; Hib = *Haemophilus influenzae* type b; HIV = human immunodeficiency virus; HPV = human papillomavirus; IPV = inactivated poliovirus; LAIV = live, attenuated influenza vaccine; MCV4 = quadrivalent meningococcal conjugate vaccine; MMRV = measles, mumps, rubella, and varicella; MPSV4 = quadrivalent meningococcal polysaccharide vaccine; PCV = pneumococcal conjugate vaccine; PPSV = pneumococcal polysaccharide vaccine; SCID = severe combined immunodeficiency; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; TIV = trivalent inactivated influenza vaccine.

\* Events or conditions listed as precautions should be reviewed carefully. Benefits of and risks for administering a specific vaccine to a person under these circumstances should be considered. If the risk from the vaccine is believed to outweigh the benefit, the vaccine should not be administered. If the benefit of vaccination is believed to outweigh the risk, the vaccine should be administered. Whether and when to administer DTaP to children with proven or suspected underlying neurologic disorders should be decided on a case-by-case basis.

† HIV-infected children may receive varicella and measles vaccine if CD4<sup>+</sup> T-lymphocyte count is >15%. (Source: Adapted from American Academy of Pediatrics. Passive immunization. In: Pickering LK, ed. Red book: 2009 report of the committee on infectious diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.)

§ MMR and varicella vaccines can be administered on the same day. If not administered on the same day, these vaccines should be separated by at least 28 days.

¶ Substantially immunosuppressive steroid dose is considered to be ≥2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent.

\*\* See text and Table 5 for details.

†† Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine can be administered on the same day as tuberculin skin testing. If testing cannot be performed until after the day of MMR vaccination, the test should be postponed for ≥4 weeks after the vaccination. If an urgent need exists to skin test, do so with the understanding that reactivity might be reduced by the vaccine.

§§ Hepatitis B vaccination should be deferred for infants weighing <2,000 g if the mother is documented to be HBsAg-negative at the time of the infant's birth. Vaccination can commence at chronological age 1 month or at hospital discharge. For infants born to HBsAg-positive women, hepatitis B immune globulin and hepatitis B vaccine should be administered within 12 hours after birth, regardless of weight.

¶¶ Vaccine should be deferred for the appropriate interval if replacement immune globulin products are being administered (see Table 5).

\*\*\* Source: CDC. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR 2010;59(No. RR-8).

††† For details, see CDC. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices. MMWR 2009;58(No. RR-2).

**TABLE 7. Conditions commonly misperceived as contraindications to vaccination**

Vaccine	Conditions commonly misperceived as contraindications (i.e., vaccination may be administered under these conditions)
General for all vaccines, including DTaP, pediatric DT, adult Td, adolescent-adult Tdap, IPV, MMR, Hib, hepatitis A, hepatitis B, varicella, rotavirus, PCV, TIV, LAIV, PPSV, MCV4, MPSV4, HPV, and herpes zoster	<ul style="list-style-type: none"> <li>Mild acute illness with or without fever</li> <li>Mild-to-moderate local reaction (i.e., swelling, redness, soreness); low-grade or moderate fever after previous dose</li> <li>Lack of previous physical examination in well-appearing person</li> <li>Current antimicrobial therapy*</li> <li>Convalescent phase of illness</li> <li>Preterm birth (hepatitis B vaccine is an exception in certain circumstances)<sup>†</sup></li> <li>Recent exposure to an infectious disease</li> <li>History of penicillin allergy, other nonvaccine allergies, relatives with allergies, or receiving allergen extract immunotherapy</li> </ul>
DTaP	<ul style="list-style-type: none"> <li>Fever of &lt;105°F (&lt;40.5°C), fussiness or mild drowsiness after a previous dose of DTP/DTaP</li> <li>Family history of seizures</li> <li>Family history of sudden infant death syndrome</li> <li>Family history of an adverse event after DTP or DTaP administration</li> <li>Stable neurologic conditions (e.g., cerebral palsy, well-controlled seizures, or developmental delay)</li> </ul>
Tdap	<ul style="list-style-type: none"> <li>Fever of ≥105°F (≥40.5°C) for &lt;48 hours after vaccination with a previous dose of DTP or DTaP</li> <li>Collapse or shock-like state (i.e., hypotonic hyporesponsive episode) within 48 hours after receiving a previous dose of DTP/DTaP</li> <li>Seizure &lt;3 days after receiving a previous dose of DTP/DTaP</li> <li>Persistent, inconsolable crying lasting &gt;3 hours within 48 hours after receiving a previous dose of DTP/DTaP</li> <li>History of extensive limb swelling after DTP/DTaP/Td that is not an arthus-type reaction</li> <li>Stable neurologic disorder</li> <li>History of brachial neuritis</li> <li>Latex allergy that is not anaphylactic</li> <li>Breastfeeding</li> <li>Immunosuppression</li> </ul>
IPV	<ul style="list-style-type: none"> <li>Previous receipt of ≥1 dose of oral polio vaccine</li> </ul>
MMR <sup>§,¶</sup>	<ul style="list-style-type: none"> <li>Positive tuberculin skin test</li> <li>Simultaneous tuberculin skin testing**</li> <li>Breastfeeding</li> <li>Pregnancy of recipient's mother or other close or household contact</li> <li>Recipient is female of child-bearing age</li> <li>Immunodeficient family member or household contact</li> <li>Asymptomatic or mildly symptomatic HIV infection</li> <li>Allergy to eggs</li> </ul>
Hepatitis B	<ul style="list-style-type: none"> <li>Pregnancy</li> <li>Autoimmune disease (e.g., systemic lupus erythematosus or rheumatoid arthritis)</li> </ul>
Varicella	<ul style="list-style-type: none"> <li>Pregnancy of recipient's mother or other close or household contact</li> <li>Immunodeficient family member or household contact<sup>††</sup></li> <li>Asymptomatic or mildly symptomatic HIV infection</li> <li>Humoral immunodeficiency (e.g., agammaglobulinemia)</li> </ul>
TIV	<ul style="list-style-type: none"> <li>Nonsevere (e.g., contact) allergy to latex, thimerosal, or egg</li> <li>Concurrent administration of coumadin or aminophylline</li> </ul>
LAIV	<ul style="list-style-type: none"> <li>Health-care providers that see patients with chronic diseases or altered immunocompetence (an exception is providers for severely immunocompromised patients requiring care in a protected environment)</li> <li>Breastfeeding</li> <li>Contacts of persons with chronic disease or altered immunocompetence (an exception is contacts of severely immunocompromised patients requiring care in a protected environment)</li> </ul>
PPSV	<ul style="list-style-type: none"> <li>History of invasive pneumococcal disease or pneumonia</li> </ul>
HPV	<ul style="list-style-type: none"> <li>Immunosuppression</li> <li>Previous equivocal or abnormal Papanicolaou test</li> <li>Known HPV infection</li> <li>Breastfeeding</li> <li>History of genital warts</li> </ul>

See table footnotes on page 43.

**TABLE 7. (Continued) Conditions commonly misperceived as contraindications to vaccination**

Vaccine	Conditions commonly misperceived as contraindications (i.e., vaccination may be administered under these conditions)
Rotavirus	Prematurity Immunosuppressed household contacts Pregnant household contacts
Zoster	Therapy with low-dose methotrexate ( $\leq 0.4$ mg/kg/week), azathioprine ( $\leq 3.0$ mg/kg/day), or 6-mercaptopurine ( $\leq 1.5$ mg/kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarcoidosis, inflammatory bowel disease, or other conditions Health-care providers of patients with chronic diseases or altered immunocompetence Contacts of patients with chronic diseases or altered immunocompetence Unknown or uncertain history of varicella in a U.S.-born person

**Abbreviations:** DT = diphtheria and tetanus toxoids; DTP = diphtheria toxoid, tetanus toxoid, and pertussis; DTaP = diphtheria and tetanus toxoids and acellular pertussis; HBsAg = hepatitis B surface antigen; Hib = *Haemophilus influenzae* type b; HPV = human papillomavirus; IPV = inactivated poliovirus; LAIV = live, attenuated influenza vaccine; MCV4 = quadrivalent meningococcal conjugate vaccine; MMR = measles, mumps, and rubella; MPSV4 = quadrivalent meningococcal polysaccharide vaccine; PCV = pneumococcal conjugate vaccine; PPSV = pneumococcal polysaccharide vaccine; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; TIV = trivalent inactivated influenza vaccine.

- \* Antibacterial drugs might interfere with Ty21a oral typhoid vaccine, and certain antiviral drugs might interfere with varicella-containing vaccines and LAIV.
- † Hepatitis B vaccination should be deferred for infants weighing <2,000 g if the mother is documented to be HBsAg-negative at the time of the infant's birth. Vaccination can commence at chronological age 1 month or at hospital discharge. For infants born to HBsAg-positive women, hepatitis B immune globulin and hepatitis B vaccine should be administered within 12 hours after birth, regardless of weight.
- § MMR and varicella vaccines can be administered on the same day. If not administered on the same day, these vaccines should be separated by at least 28 days.
- ¶ HIV-infected children should receive immune globulin after exposure to measles. HIV-infected children can receive varicella and measles vaccine if CD4<sup>+</sup> T-lymphocyte count is >15%. (Source: Adapted from American Academy of Pediatrics. Passive immunization. In: Pickering LK, ed. Red book: 2009 report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.)
- \*\* Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine can be administered on the same day as tuberculin skin testing. If testing cannot be performed until after the day of MMR vaccination, the test should be postponed for at least 4 weeks after the vaccination. If an urgent need exists to skin test, do so with the understanding that reactivity might be reduced by the vaccine.
- †† If a vaccinee experiences a presumed vaccine-related rash 7–25 days after vaccination, the person should avoid direct contact with immunocompromised persons for the duration of the rash.

**TABLE 8. Treatment of anaphylaxis in children and adults with drugs administered intramuscularly or orally**

Drug	Dosage
<b>Children</b>	
Primary regimen	
Epinephrine 1:1000 (aqueous) (1 mg/mL)*	0.01 mg/kg up to 0.5 mg (administer 0.01 mL/kg/dose up to 0.5 mL) IM repeated every 10–20 minutes up to 3 doses
Secondary regimen	
Diphenhydramine	1–2 mg/kg oral, IM, or IV, every 4–6 hours (100 mg, maximum single dose)
Hydroxyzine	0.5–1 mg/kg oral, IM, every 4–6 hours (100 mg, maximum single dose)
Prednisone	1.5–2 mg/kg oral (60 mg, maximum single dose); use corticosteroids as long as needed
<b>Adults</b>	
Primary regimen	
Epinephrine 1:1000 (aqueous)*	0.01 mg/kg up to 0.5 mg (administer 0.01 mL/kg/dose up to 0.5 mL) IM repeated every 10–20 minutes up to 3 doses
Secondary regimen	
Diphenhydramine	1–2 mg/kg up to 100 mg IM or oral, every 4–6 hours

**Abbreviations:** IM = intramuscular; IV = intravenous.

**Sources:** Adapted from American Academy of Pediatrics. Passive immunization. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS. Red book: 2009 report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2009:66–7; Immunization Action Coalition. Medical management of vaccine reactions in adult patients (available at [www.immunize.org/catg.d/p3082.pdf](http://www.immunize.org/catg.d/p3082.pdf)); and Mosby's Drug Consult. St. Louis, MO: Elsevier; 2005.

\*If the agent causing the anaphylactic reaction was administered by injection, epinephrine may be injected into the same site to slow absorption.

**TABLE 9. Dose and route of administration for selected vaccines**

Vaccine	Dose	Route
DTaP, DT, Td, Tdap	0.5 mL	IM
DTaP-HepB-IPV	0.5 mL	IM
DTaP/Hib	0.5 mL	IM
DTaP-IPV/Hib	0.5 mL	IM
DTaP-IPV	0.5 mL	IM
Hib	0.5 mL	IM
Combination Hib/HepB	0.5 mL	IM
HepA	≤18 years: 0.5 mL ≥19 years: 1.0 mL	IM
HepB	≤19 years: 0.5 mL* ≥20 years: 1.0 mL	IM
HepA-HepB	≥18 years: 1.0 mL	IM
LAIV	0.2 mL divided dose between nares	Intranasal spray
TIV	6–35 months: 0.25 mL ≥3 years: 0.5 mL	IM
MMR	0.5 mL	SC
MMRV	0.5 mL	SC
MCV4	0.5 mL	IM
MPSV4	0.5 mL	SC
PCV	0.5 mL	IM
PPSV	0.5 mL	IM or SC
HPV (HPV2 or HPV4)	0.5 mL	IM
IPV	0.5 mL	IM or SC
Rotavirus (RV1 or RV5)	(1.0 mL or 2.0 mL)	Oral
Varicella	0.5 mL	SC
Herpes zoster	0.65 mL	SC

**Abbreviations:** DT = diphtheria and tetanus toxoids; DTP = diphtheria toxoid, tetanus toxoid, and pertussis; DTaP = diphtheria and tetanus toxoids and acellular pertussis; HepA = hepatitis A; HepB = hepatitis B; Hib = *Haemophilus influenzae* type b; HPV = human papillomavirus; HPV2 = bivalent HPV vaccine; HPV4 = quadrivalent HPV vaccine; IM = intramuscular; IPV = inactivated poliovirus; LAIV = live, attenuated influenza vaccine; MCV4 = quadrivalent meningococcal conjugate vaccine; MMR = measles, mumps, and rubella; MMRV = measles, mumps, rubella, and varicella; MPSV4 = quadrivalent meningococcal polysaccharide vaccine; PCV = pneumococcal conjugate vaccine; PPSV = pneumococcal polysaccharide vaccine; SC = subcutaneous; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; TIV = trivalent inactivated influenza vaccine.

**Source:** Adapted from Immunization Action Coalition: <http://www.immunize.org>.

\* Persons aged 11–15 years may be administered Recombivax HB (Merck), 1.0 mL (adult formulation) on a 2-dose schedule.



**TABLE 10. Needle length and injection site of IM injections for children aged ≤18 years (by age) and adults aged ≥19 years (by sex and weight)**

Age group	Needle length	Injection site
<b>Children (birth–18 yrs)</b>		
Neonates*	5/8 inch (16 mm) <sup>†</sup>	Anterolateral thigh
Infants, 1–12 mos	1 inch (25 mm)	Anterolateral thigh
Toddlers, 1–2 yrs	1–1¼ inch (25–32 mm) 5/8 <sup>†</sup> –1 inch (16–25 mm)	Anterolateral thigh <sup>§</sup> Deltoid muscle of arm
Children, 3–18 yrs	5/8 <sup>†</sup> –1 inch (16–25 mm) 1–1¼ inches (25–32 mm)	Deltoid muscle of arm <sup>§</sup> Anterolateral thigh
<b>Adults (≥19 yrs)</b>		
Men and women, <60 kg (130 lbs)	1 inch (25 mm) <sup>¶</sup>	Deltoid muscle of arm
Men and women, 60–70 kg (130–152 lbs)	1 inch (25 mm)	
Men, 70–118 kg (152–260 lbs)	1–1½ inches (25–38 mm)	
Women, 70–90 kg (152–200 lbs)		
Men, >118 kg (260 lbs)	1½ inches (38 mm)	
Women, >90 kg (200 lbs)		

**Abbreviation:** IM = intramuscular.

**Source:** Adapted from Poland GA, Borrud A, Jacobsen RM, et al. Determination of deltoid fat pad thickness: implications for needle length in adult immunization. *JAMA* 1997;277:1709–11.

\* First 28 days of life.

<sup>†</sup> If skin is stretched tightly and subcutaneous tissues are not bunched.

<sup>§</sup> Preferred site.

<sup>¶</sup> Some experts recommend a 5/8-inch needle for men and women who weigh <60 kg.

**TABLE 11. Vaccine storage temperature recommendations**

Vaccines	Vaccine storage temperature	Diluent storage temperature	Comments
<b>Nonlyophilized, aluminum-adjuvanted vaccines</b>			
Diphtheria-tetanus-containing vaccines (DT, Td) or pertussis-containing vaccines (DTaP, Tdap)	35°F–46°F (2°C–8°C) Do not freeze.	No diluent*	Irreversible loss of potency occurs with exposure to freezing temperatures.
HepA and HepB	35°F–46°F (2°C–8°C) Do not freeze.	No diluent	Irreversible loss of potency occurs with exposure to freezing temperatures.
PCV	35°F–46°F (2°C–8°C) Do not freeze.	No diluent	Irreversible loss of potency occurs with exposure to freezing temperatures.
HPV†	35°F–46°F (2°C–8°C) Do not freeze.	No diluent	Irreversible loss of potency occurs with exposure to freezing temperatures.
<b>Nonlyophilized, non-aluminum-adjuvanted vaccines</b>			
PRP-OMP Hib	35°F–46°F (2°C–8°C)	No diluent	—
IPV	35°F–46°F (2°C–8°C)	No diluent	Data on thermostability properties of these vaccines are lacking.
MCV4‡,§	35°F–46°F (2°C–8°C)	No diluent	Data on thermostability properties of these vaccines are lacking.
PPSV	35°F–46°F (2°C–8°C)	No diluent	Data on thermostability properties of these vaccines are lacking.
TIV†	35°F–46°F (2°C–8°C)	No diluent	Data on thermostability properties of these vaccines are lacking.
<b>Lyophilized (nonvaricella) vaccines</b>			
PRP-T Hib†	35°F–46°F (2°C–8°C)¶	35°F–46°F (2°C–8°C) Do not freeze.	—
MMR†	35°F–46°F (2°C–8°C)¶	35°F–77°F (2°C–25°C) Can be refrigerated or stored at room temperature	Do not expose to light or temperatures above the recommended range.
MPSV4	35°F–46°F (2°C–8°C)¶	Data are lacking on ideal pre-reconstitution storage requirements. After reconstitution, vaccine should be stored at 35°F–46°F (2°C–8°C). Do not freeze.	Freeze dried (lyophilized) vaccine. Data on the effect of freezing temperatures on potency are lacking.
<b>Varicella-containing vaccines</b>			
MMRV†	-58°F–5°F (-50°C to -15°C)	35°F–77°F (2°C–25°C) Can be refrigerated or stored at room temperature	—
Varicella†	≤5°F (≤-15°C)	35°F–77°F (2°C–25°C) Can be refrigerated or stored at room temperature	—
Herpes zoster†	≤5°F (≤-15°C)	35°F–77°F (2°C–25°C) Can be refrigerated or stored at room temperature	—
<b>Noninjectable vaccines</b>			
RV5 vaccine†	35°F–46°F (2°C–8°C) Do not freeze.	No diluent	—
RV1 vaccine†	35°F–46°F (2°C–8°C) Do not freeze.	The diluent may be stored at a controlled room temperature 20°C–25°C (68°F–77°F). Do not freeze.	—
LAIV	35°F–46°F (2°C–8°C)	No diluent	Do not expose to temperatures above the recommended range.

**Abbreviations:** DT = diphtheria and tetanus toxoids; DTaP = diphtheria and tetanus toxoids and acellular pertussis; HepA = hepatitis A; HepB = hepatitis B; Hib = *Haemophilus influenzae* type b; HPV = human papillomavirus; IPV = inactivated poliovirus; LAIV = live, attenuated influenza vaccine; MCV4 = quadrivalent meningococcal conjugate vaccine; MMR = measles, mumps, and rubella; MMRV = measles, mumps, rubella, and varicella; MPSV4 = quadrivalent meningococcal polysaccharide vaccine; PCV = pneumococcal conjugate vaccine; PPSV = pneumococcal polysaccharide vaccine; PRP-OMB = polyribosylribitol phosphate-meningococcal outer membrane protein conjugate; PRP-T = polyribosylribitol phosphate polysaccharide conjugated to a tetanus toxoid; RV = rotavirus; RV1 = live, attenuated monovalent rotavirus vaccine; RV5 = live, reassortment pentavalent rotavirus vaccine; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; TIV = trivalent inactivated influenza vaccine.

**Source:** Adapted from Atkinson WL, Kroger AT, Pickering LK. General immunization practices. In: Plotkin SA, Orenstein WA, editors. *Vaccines*. 35th ed. Philadelphia, PA: Elsevier; 2008; and CDC. Guidelines for maintaining and managing the vaccine cold chain. *MMWR* 2003;52:1023–5.

\* DTaP–Tripedia is sometimes used as a diluent for ActHib.

† Protect from light.

‡ There are two meningococcal conjugate vaccines; Menactra is nonlyophilized, and Menveo is lyophilized. Both powder and diluent should be stored at 35°F–46°F.

¶ The lyophilized pellet may be stored at freezer temperature; the reconstituted vaccine should be stored at refrigerator temperature.

**TABLE 12. Comparison of thermometers used to monitor vaccine temperatures**

Thermometer type	Advantages	Disadvantages
Continuous chart recorder	Most accurate Continuous 24-hour readings of temperature range and duration Can be recalibrated at regular intervals	Most expensive Requires most training and maintenance
Minimum-maximum	Inexpensive Monitors temperature range	Accurate within a range of +/-1°C. No information about the duration of out-of-range temperature Cannot be recalibrated at routine intervals
Standard fluid filled	Inexpensive and simple to use Because thermometers encased in biosafe liquids, can reflect vaccine temperatures more accurately than those directly exposed to the air	Accurate within a range of +/-1°C No information about duration of out-of-temperature exposure No information on minimum/maximum temperatures Cannot be recalibrated at routine intervals Might experience poor performance from inexpensive models

**Source:** Adapted from CDC. Guidelines for maintaining and managing the vaccine cold chain. MMWR 2003;52:1023–5; and Langley A, Grant S, eds. Proceedings of the National Vaccine Storage Workshop; June 28–30; Brisbane, Australia. Maroochydore: Queensland Health; 2004.

**TABLE 13. Vaccination of persons with primary and secondary immunodeficiencies**

Primary	Specific immunodeficiency	Contraindicated vaccines*	Risk-specific recommended vaccines*	Effectiveness and comments
B-lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV† Smallpox LAIV BCG Ty21a (live typhoid) Yellow fever	Pneumococcal Consider measles and varicella vaccination	The effectiveness of any vaccine is uncertain if it depends only on the humoral response (e.g., PPSV or MPSV4). IGIV interferes with the immune response to measles vaccine and possibly varicella vaccine.
	Less severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)	OPV† BCG Yellow fever Other live vaccines appear to be safe.	Pneumococcal	All vaccines likely effective; immune response might be attenuated.
T-lymphocyte (cell-mediated and humoral)	Complete defects (e.g., severe combined immunodeficiency [SCID] disease, complete DiGeorge syndrome)	All live vaccines <sup>§,¶,**</sup>	Pneumococcal	Vaccines might be ineffective.
	Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines <sup>§,¶,**</sup>	Pneumococcal Meningococcal Hib (if not administered in infancy)	Effectiveness of any vaccine depends on degree of immune suppression.
Complement	Persistent complement, properdin, or factor B deficiency	None	Pneumococcal Meningococcal	All routine vaccines likely effective.
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defect, and myeloperoxidase deficiency.	Live bacterial vaccines <sup>§</sup>	Pneumococcal††	All inactivated vaccines safe and likely effective. Live viral vaccines likely safe and effective.
Secondary	HIV/AIDS	OPV† Smallpox BCG LAIV Withhold MMR and varicella in severely immunocompromised persons. Yellow fever vaccine might have a contraindication or a precaution depending on clinical parameters of immune function***	Pneumococcal Consider Hib (if not administered in infancy) and meningococcal vaccination.	MMR, varicella, rotavirus, and all inactivated vaccines, including inactivated influenza, might be effective. <sup>§§</sup>
	Malignant neoplasm, transplantation, immunosuppressive or radiation therapy	Live viral and bacterial, depending on immune status <sup>§,¶</sup>	Pneumococcal	Effectiveness of any vaccine depends on degree of immune suppression.
	Asplenia	None	Pneumococcal Meningococcal Hib (if not administered in infancy)	All routine vaccines likely effective.
	Chronic renal disease	LAIV	Pneumococcal Hepatitis B <sup>¶¶</sup>	All routine vaccines likely effective.

**Abbreviations:** AIDS = acquired immunodeficiency syndrome; BCG = bacille Calmette-Guérin; Hib = *Haemophilus influenzae* type b; HIV = human immunodeficiency virus; IG = immunoglobulin; IGIV = immune globulin intravenous; LAIV = live, attenuated influenza vaccine; MMR = measles, mumps, and rubella; MPSV4 = quadrivalent meningococcal polysaccharide vaccine; OPV = oral poliovirus vaccine (live); PPSV = pneumococcal polysaccharide vaccine; TIV = trivalent inactivated influenza vaccine.

**Source:** Adapted from American Academy of Pediatrics. Passive immunization. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS eds. Red book: 2009 report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009:74–5.

\* Other vaccines that are universally or routinely recommended should be given if not contraindicated.

† OPV is no longer available in the United States.

§ Live bacterial vaccines: BCG and oral Ty21a *Salmonella Typhi* vaccine.

¶ Live viral vaccines: MMR, MMRV, OPV, LAIV, yellow fever, zoster, rotavirus, varicella, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.

\*\* Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for severe combined immunodeficiency.

†† Pneumococcal vaccine is not indicated for children with chronic granulomatous disease beyond age-based universal recommendations for PCV. Children with chronic granulomatous disease are not at increased risk for pneumococcal disease.

§§ HIV-infected children should receive IG after exposure to measles and may receive varicella and measles vaccine if CD4+ T-lymphocyte count is ≥15%.

¶¶ Indicated based on the risk from dialysis-based bloodborne transmission.

\*\*\* Symptomatic HIV infection or CD4+ T-lymphocyte count of <200/mm<sup>3</sup> or <15% of total lymphocytes for children aged <6 years is a contraindication to yellow fever vaccine administration. Asymptomatic HIV infection with CD4+ T-lymphocyte count of 200–499/mm<sup>3</sup> for persons aged ≥6 years or 15%–24% of total lymphocytes for children aged <6 years is a precaution for yellow fever vaccine administration. Details of yellow fever vaccine recommendations are available from CDC. (CDC. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2010;59[No. RR-7].)



**TABLE 14. Approaches to evaluation and vaccination of persons vaccinated outside the United States who have no (or questionable) vaccination records**

Vaccine	Recommended approach	Alternative approach*
MMR	Revaccination with MMR	Serologic testing for IgG antibodies to measles, mumps, and rubella
Hib	Age-appropriate revaccination	—
Hepatitis A	Age-appropriate revaccination	Serologic testing for IgG antibodies to hepatitis A
Hepatitis B	Age-appropriate revaccination and serologic testing for HBsAg <sup>†</sup>	—
Poliovirus	Revaccination with inactivated poliovirus vaccine	Serologic testing for neutralizing antibody to poliovirus types 1, 2, and 3 (limited availability)
DTaP	Revaccination with DTaP, with serologic testing for specific IgG antibody to tetanus and diphtheria toxins in the event of a severe local reaction	Persons whose records indicate receipt of $\geq 3$ doses: serologic testing for specific IgG antibody to diphtheria and tetanus toxins before administering additional doses (see text), or administer a single booster dose of DTaP, followed by serological testing after 1 month for specific IgG antibody to diphtheria and tetanus toxins with revaccination as appropriate (see text)
Tdap	Age-appropriate vaccination of persons who are candidates for Tdap vaccine on the basis of time since last diphtheria and tetanus-toxoid-containing vaccines.	—
Varicella	Age-appropriate vaccination of persons who lack evidence of varicella immunity	—
Pneumococcal conjugate	Age-appropriate vaccination	—
Rotavirus	Age-appropriate vaccination	—
HPV	Age-appropriate vaccination	—
Zoster	Age-appropriate vaccination	—

**Abbreviations:** DTaP = diphtheria and tetanus toxoids and acellular pertussis; HBsAg = hepatitis B surface antigen; Hib = *Haemophilus influenzae* type b; HPV = human papillomavirus; IgG = immune globulin G; MMR = measles, mumps, and rubella; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

\* There is a recommended approach for all vaccines and an alternative approach for some vaccines.

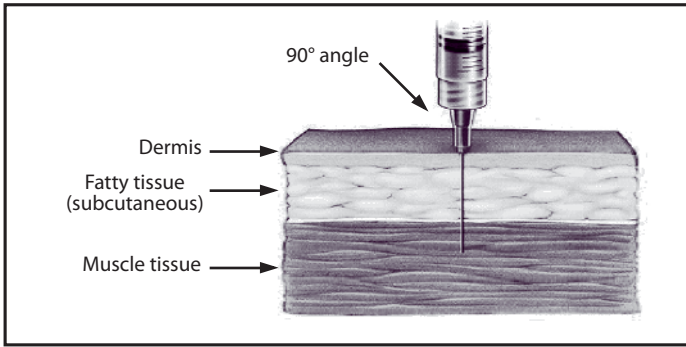
<sup>†</sup> In rare instances, hepatitis B vaccine can give a false-positive HBsAg result up to 18 days after vaccination; therefore, blood should be drawn to test for HBsAg before vaccinating (Source: CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices [ACIP]; Part I: Immunization in Infants, Children, and Adolescents. MMWR 2005;54(No. RR-16.)

**TABLE 15. Recommendations regarding interventions to improve coverage of vaccines recommended for routine use among children, adolescents, and adults**

Intervention	Recommendation
<b>Increase community demand for vaccination</b>	
Client reminder or recall systems	Strongly recommended
Multicomponent interventions, including education	Strongly recommended
Requirements for entry to schools, child-care facilities, and colleges	Recommended
Community education alone	Insufficient evidence
Clinic-based education	Insufficient evidence
Patient or family incentives or sanctions	Insufficient evidence
Client-held medical records	Insufficient evidence
<b>Enhance access to vaccination services</b>	
Reducing out-of-pocket costs	Strongly recommended
Enhancing access through the U.S. Department of Agriculture's Women, Infants, and Children program	Recommended
Home visits, outreach, and case management	Recommended
Enhancing access at schools	Recommended
Expanding access in health care settings	Recommended as part of multicomponent interventions only
Enhancing access at child care centers	Insufficient evidence
<b>Focus on providers</b>	
Reminder or recall systems	Strongly recommended
Assessment and feedback	Strongly recommended
Standing orders	Strongly recommended
Provider education alone	Insufficient evidence

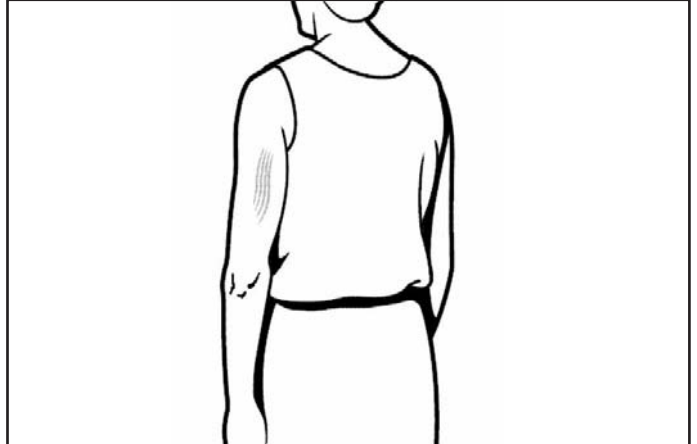
**Source:** Adapted from Task Force on Community Preventive Services. Recommendations regarding interventions to improve vaccination coverage in children, adolescents and adults. *Am J Prev Med* 2000;18:92–6, and Task Force on Community Preventive Services. Recommendations to improve targeted vaccination coverage among high-risk adults. *Am J Prev Med* 2005;28:231–7.

FIGURE 1. Intramuscular needle insertion



Source: Adapted from California Immunization Branch.

FIGURE 4. Subcutaneous site of administration: triceps



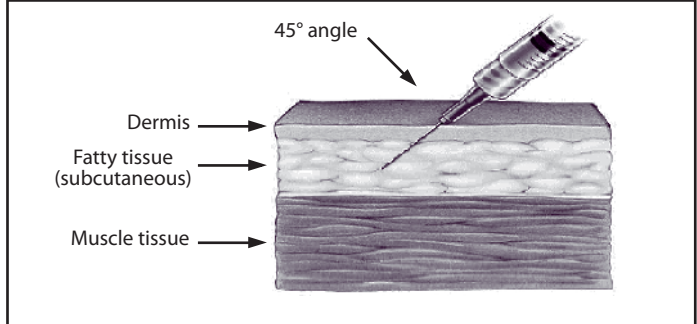
Source: Adapted from Minnesota Department of Health.

FIGURE 2. Intramuscular/subcutaneous site of administration: ante-rolateral thigh



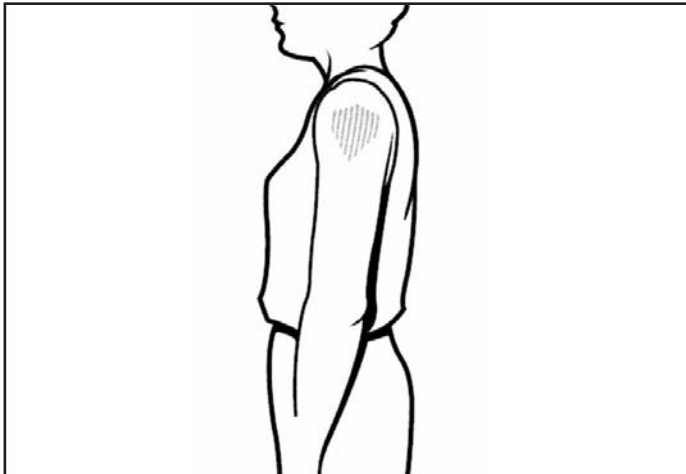
Source: Adapted from Minnesota Department of Health.

FIGURE 5. Subcutaneous needle insertion



Source: Adapted from California Immunization Branch.

FIGURE 3. Intramuscular site of administration: deltoid



Source: Adapted from Minnesota Department of Health.

FIGURE 6. Sample temperature log

Temperature Log for Vaccines (Fahrenheit)													Month/Year: _____			Days 1–15		
Day of Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			
Staff Initials																		
Room Temp.																		
Exact Time																		
°F Temp	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm		
Too warm	49°																	
	48°	Take immediate action if temperature is in shaded section*																
	47°																	
Refrigerator temperature	46°																	
	45°																	
	44°																	
	43°																	
	42°																	
	41°																	
	40°																	
	39°																	
	38°																	
	37°																	
Too cold	36°																	
	35°																	
	34°	Take immediate action if temperature is in shaded section*																
	33°																	
	32°																	
Freezer temp	8°																	
	7°	Take immediate action if temperature is in shaded section*																
	6°																	
	5°																	
	4°																	
	3°																	

Source: Adapted from Immunization Action Coalition. Available at <http://www.immunize.org/catg.d/p3039.pdf>. Accessed December 1, 2010.

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## Abbreviations

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
DT	pediatric diphtheria-tetanus toxoid
DTaP	pediatric diphtheria and tetanus toxoids and acellular pertussis
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
Hib	<i>Haemophilus influenzae</i> type b
HIV	human immunodeficiency virus
HPV	human papillomavirus
HCT	hematopoietic cell transplant
IgG	immunoglobulin G
IGIV	intravenous immune globulin
IPV	inactivated poliovirus
LAIV	live, attenuated influenza vaccine
MCV4	quadrivalent meningococcal conjugate vaccine
MMR	measles, mumps, and rubella
MMRV	measles, mumps, rubella, and varicella
MPSV4	quadrivalent meningococcal polysaccharide vaccine
OPV	oral poliovirus
OSHA	Occupational Safety and Health Administration
PCV	pneumococcal conjugate vaccine
PRP-OMP	<i>Haemophilus influenzae</i> type b-polyribosylribitol phosphate-meningococcal outer membrane protein conjugate
PPSV	pneumococcal polysaccharide vaccine
RV1	live, attenuated monovalent rotavirus vaccine
RV5	live, reassortant pentavalent rotavirus vaccine
Td	adult tetanus and diphtheria toxoids
Tdap	tetanus and reduced diphtheria toxoids and acellular pertussis (for adolescents and adults)
TIV	trivalent inactivated influenza vaccine
TST	tuberculin skin test
VAERS	Vaccine Adverse Event Reporting System
VIS	vaccine information statement
ZOS	herpes zoster vaccine

## Glossary

**Adverse event.** An untoward event that occurs after a vaccination that might be caused by the vaccine product or vaccination process. Adverse events include those that have the following characteristics: 1) vaccine induced (caused by the intrinsic characteristic of the vaccine preparation and the individual response of the vaccinee); these events would not have occurred without vaccination (e.g., vaccine-associated paralytic poliomyelitis); 2) vaccine potentiated: the events would have occurred anyway but were precipitated by the vaccination (e.g., first febrile seizure in a predisposed child); 3) programmatic error: the event was caused by technical errors in vaccine preparation, handling, or administration; and 4) coincidental: the event was associated temporally with vaccination by chance or caused by underlying illness. Special studies are needed to determine whether an adverse event is a reaction to the vaccine or the result of another cause (**Sources:** Chen RT. Special methodological issues in pharmacoepidemiology studies of vaccine safety. In: Strom BL, ed. *Pharmacoepidemiology*. 3rd ed. Sussex, England: John Wiley & Sons; 2000:707–32; and Fenichel GM, Lane DA, Livengood JR, Horwitz SJ, Menkes JH, Schwartz JF. Adverse events following immunization: assessing probability of causation. *Pediatr Neurol* 1989;5:287–90).

**Adverse reaction.** An undesirable medical condition that has been demonstrated to be caused by a vaccine. Evidence for the causal relation is usually obtained through randomized clinical trials, controlled epidemiologic studies, isolation of the vaccine strain from the pathogenic site, or recurrence of the condition with repeated vaccination (i.e., rechallenge); synonyms include side effect and adverse effect.

**Adjuvant.** A vaccine component distinct from the antigen that enhances the immune response to the antigen.

**Antitoxin.** A solution of antibodies against a toxin. Antitoxin can be derived from either human (e.g., tetanus immune globulin) or animal (usually equine) sources (e.g., diphtheria and botulism antitoxin). Antitoxins are used to confer passive immunity and for treatment.

**Hyperimmune globulin (specific).** Special preparations obtained from blood plasma from donor pools preselected for a high antibody content against a specific antigen (e.g., hepatitis B immune globulin, varicella-zoster immune globulin, rabies immune globulin, tetanus immune globulin, vaccinia immune globulin, cytomegalovirus immune globulin, botulism immune globulin).

**Immune globulin.** A sterile solution containing antibodies, which are usually obtained from human blood. It is obtained by cold ethanol fractionation of large pools of blood plasma and contains 15%–18% protein. Intended for intramuscular administration, immune globulin is primarily indicated for routine maintenance of immunity among certain immunodeficient persons and for passive protection against measles and hepatitis A.

**Immunobiologic.** Antigenic substances (e.g., vaccines and toxoids) or antibody-containing preparations (e.g., globulins and antitoxins) from human or animal donors. These products are used for active or passive immunization or therapy. Examples of immunobiologics include antitoxin, immune globulin and hyperimmune globulin, monoclonal antibodies, toxoids, and vaccines.

**Intravenous immune globulin.** A product derived from blood plasma from a donor pool similar to the immune globulin pool, but prepared so that it is suitable for intravenous use. Intravenous immune globulin is used primarily for replacement therapy in primary antibody-deficiency disorders, for treatment of Kawasaki disease, immune thrombocytopenic purpura, hypogammaglobulinemia in chronic lymphocytic leukemia, and certain cases of human immunodeficiency virus infection (Table 5).

**Monoclonal antibody.** An antibody product prepared from a single lymphocyte clone, which contains only antibody against a single antigen.

**Simultaneous.** In the context of vaccine timing and spacing, occurring on the same clinic day, at different anatomic sites, and not combined in the same syringe.

**Toxoid.** A modified bacterial toxin that has been made nontoxic, but retains the ability to stimulate the formation of antibodies to the toxin.

**Vaccination and immunization.** The terms vaccine and vaccination are derived from *vacca*, the Latin term for cow. Vaccine was the term used by Edward Jenner to describe material used (i.e., cowpox virus) to produce immunity to smallpox. The term vaccination was used by Louis Pasteur in the 19th century to include the physical act of administering any vaccine or toxoid. Immunization is a more inclusive term, denoting the process of inducing or providing immunity by administering an immunobiologic. Immunization can be active or passive. Active immunization is the production of antibody or other immune responses through administration of a vaccine or toxoid. Passive immunization means the provision of temporary immunity by the administration of preformed antibodies. Although persons often use the terms vaccination and immunization interchangeably in reference to active immunization, the terms are not synonymous because the administration of an immunobiologic cannot be equated automatically with development of adequate immunity.

**Vaccine.** A suspension of live (usually attenuated) or inactivated microorganisms (e.g., bacteria or viruses) or fractions thereof administered to induce immunity and prevent infectious disease or its sequelae. Some vaccines contain highly defined antigens (e.g., the polysaccharide of *Haemophilus influenzae* type b or the surface antigen of hepatitis B); others have antigens that are complex or incompletely defined (e.g., *Bordetella pertussis* antigens or live, attenuated viruses).



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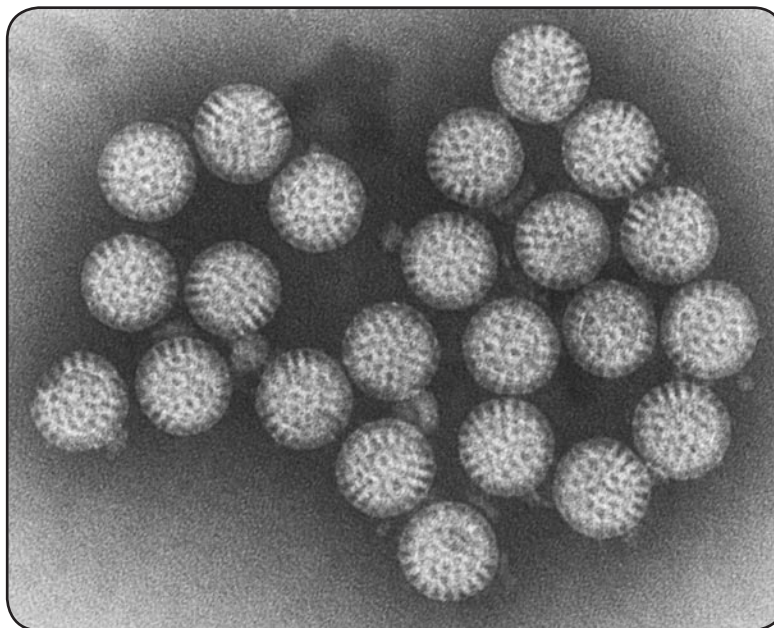
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Recommendations and Reports

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### **Prevention of Rotavirus Gastroenteritis Among Infants and Children Recommendations of the Advisory Committee on Immunization Practices (ACIP)**



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**On the cover:** Negative-stain electron micrograph of rotavirus A. Courtesy of Charles D. Humphrey, CDC.

# Prevention of Rotavirus Gastroenteritis Among Infants and Children

## Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Prepared by  
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### Summary

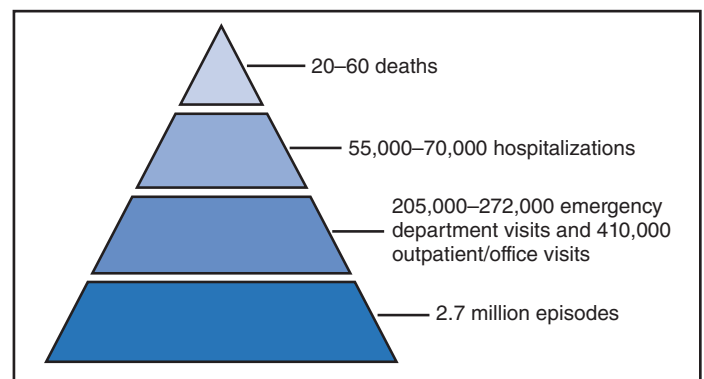
*Rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide. Before initiation of the rotavirus vaccination program in the United States in 2006, approximately 80% of U.S. children had rotavirus gastroenteritis by age 5 years. Each year during the 1990s and early 2000s, rotavirus resulted in approximately 410,000 physician visits, 205,000–272,000 emergency department visits, and 55,000–70,000 hospitalizations among U.S. infants and children, with total annual direct and indirect costs of approximately \$1 billion. In February 2006, a live, oral, human-bovine reassortant rotavirus vaccine (RotaTeq® [RV5]) was licensed as a 3-dose series for use among U.S. infants for the prevention of rotavirus gastroenteritis, and the Advisory Committee on Immunization Practices (ACIP) recommended routine use of RV5 among U.S. infants (CDC. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2006;55[No. RR-12]). In April 2008, a live, oral, human attenuated rotavirus vaccine (Rotarix® [RV1]) was licensed as a 2-dose series for use among U.S. infants, and in June 2008, ACIP updated its rotavirus vaccine recommendations to include use of RV1. This report updates and replaces the 2006 ACIP statement for prevention of rotavirus gastroenteritis. ACIP recommends routine vaccination of U.S. infants with rotavirus vaccine. RV5 and RV1 differ in composition and schedule of administration. RV5 is to be administered orally in a 3-dose series, with doses administered at ages 2, 4, and 6 months. RV1 is to be administered orally in a 2-dose series, with doses administered at ages 2 and 4 months. ACIP does not express a preference for either RV5 or RV1. The recommendations in this report also address the maximum ages for doses, contraindications, precautions, and special situations for the administration of rotavirus vaccine.*

### Introduction

Rotavirus is the most common cause of severe gastroenteritis in infants and young children worldwide. Rotavirus causes approximately half a million deaths each year among children aged <5 years, with >80% of deaths occurring in developing countries (1). In the United States during the prevaccine era, rotavirus gastroenteritis resulted in relatively few childhood deaths (approximately 20–60 deaths per year among children aged <5 years) (2–5). However, before initiation of the rotavirus vaccination program in 2006, nearly every child in the United States was infected with rotavirus by age 5 years; the majority had gastroenteritis, resulting annually during the 1990s and early 2000s in approximately 410,000 physician

visits, 205,000–272,000 emergency department (ED) visits, 55,000–70,000 hospitalizations, and total annual direct and indirect costs of approximately \$1 billion (5–9) (Figure 1). This report presents the recommendations of the Advisory Committee on Immunization Practices (ACIP) for use of two

**FIGURE 1. Estimated number of annual deaths, hospitalizations, emergency department visits, and episodes of rotavirus gastroenteritis among children aged <5 years before introduction of rotavirus vaccine — United States**



The material in this report originated in the National Center for Immunization and Respiratory Diseases, Anne Schuchat, MD, Director, and the Division of Viral Diseases, Larry Anderson, MD, Director.

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rotavirus vaccines among U.S. infants: RotaTeq® (RV5) (Merck and Company, Whitehouse Station, New Jersey), which was licensed by the Food and Drug Administration (FDA) in February 2006 (10) and Rotarix® (RV1) (GlaxoSmithKline [GSK] Biologicals, Rixensart, Belgium), which was licensed by FDA in April 2008 (11). This report updates and replaces the 2006 ACIP statement for prevention of rotavirus gastroenteritis (12).

## Background

### Clinical and Epidemiologic Features of Rotavirus Disease in the Prevalence Era

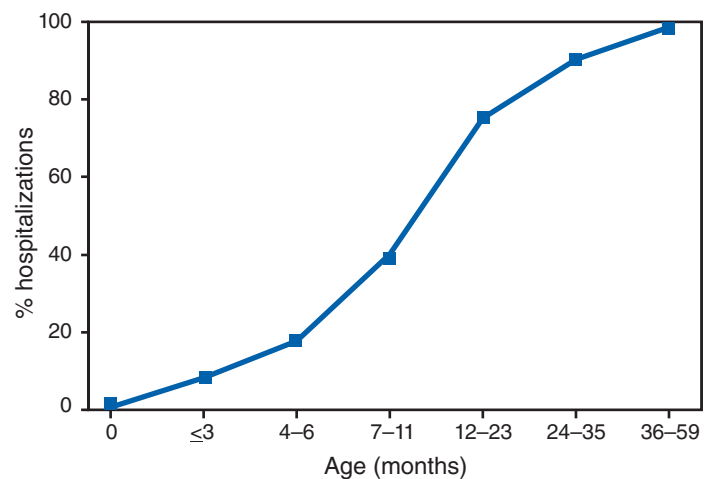
In the prevaccine era, rotavirus infected almost all children by age 5 years; severe dehydrating gastroenteritis caused by rotavirus occurred primarily among children aged 4–23 months (13–15). Rotavirus infects the proximal small intestine, where it elaborates an enterotoxin and destroys the epithelial surface, resulting in blunted villi, extensive damage, and shedding of massive quantities of virus in stool (13). The estimated incubation period for rotavirus diarrheal illness is <48 hours (16). Under experimental conditions, adults who became ill had symptoms 1–4 days after receiving rotavirus orally (17,18). The clinical spectrum of rotavirus illness in children ranges from mild, watery diarrhea of limited duration to severe diarrhea with vomiting and fever that can result in dehydration with shock, electrolyte imbalance, and death (19). The illness usually begins with acute onset of fever and vomiting, followed 24–48 hours later by frequent, watery stools (20,21). Up to one third of children with rotavirus illness have a temperature of >102°F (>39°C) (22,23). Vomiting usually lasts ≤24 hours; other gastrointestinal symptoms generally resolve in 3–7 days. Rotavirus protein and ribonucleic acid (RNA) have been detected in blood, organs, and cerebrospinal fluid, but the clinical implications of these findings are not clear (20,24).

Rotaviruses are shed in high concentrations (i.e.,  $10^{12}$  virus particles per gram of stool during the acute illness) in the stools of infected children before and several days after clinical disease (25). Rotavirus is transmitted primarily by the fecal-oral route, both through close person-to-person contact and through fomites (26). Very few infectious virions are needed to cause disease in susceptible hosts (25). Spread is common within families. Of adult contacts of infected children, 30%–50% become infected, although infections in adults often are asymptomatic because of immunity from previous exposure (27–29). Transmission of rotavirus through contaminated water or food is likely to be rare (30,31). Transmission through

airborne droplets also has been hypothesized but remains unproven (21,30,32).

In the United States, rotavirus causes winter seasonal peaks of gastroenteritis, with activity beginning usually in the southwestern states during December–January, moving across the country, and ending in the northeastern states in April–May (33–35). Rotavirus might account for up to 10% of gastroenteritis episodes among children aged <5 years (36). Infants and children with rotavirus gastroenteritis are likely to have more severe symptoms than those with nonrotavirus gastroenteritis (22,23,37,38). In the prevaccine era, rotavirus accounted for 30%–50% of all hospitalizations for gastroenteritis among U.S. children aged <5 years and up to 70% of hospitalizations for gastroenteritis during the seasonal peak months (7,14,39–44). Of all the rotavirus hospitalizations that occurred among children aged <5 years in the United States during the prevaccine era, 17% occurred during the first 6 months of life, 40% by age 1 year, and 75% by age 2 years (Figure 2). Rotavirus accounted for 20%–40% of outpatient clinic visits during the rotavirus season (14,45,46). Before the initiation of the rotavirus vaccination program, four of five children in the United States had rotavirus gastroenteritis by age 5 years (36,39,47), one in seven required a clinic or ED visit, one in 70 were hospitalized, and one in 200,000 died from this disease (3,8). Active, population-based surveillance from early 2006 and before vaccine was used provided annual rotavirus hospitalization and ED visit rates of 22.4 and 301

**FIGURE 2. Cumulative proportion of children hospitalized with an International Classification of Diseases, Ninth Revision-Clinical Modifications code for rotavirus gastroenteritis among children aged <5 years, by age group — United States, National Hospital Discharge Survey, 1993–2002\***



\* Calculated from the database used in Charles MD, Holman RC, Curns AT, Parashar UD, Glass RI, Bresee JS. Hospitalizations associated with rotavirus gastroenteritis in the United States, 1993–2002. *Pediatr Infect Dis J* 2006;25:489–93.



per 10,000 children aged <3 years, respectively (14). Rotavirus also was an important cause of hospital-acquired gastroenteritis among children (48).

In a recent study, factors associated with increased risk for hospitalization for rotavirus gastroenteritis among U.S. children included lack of breastfeeding, low birth weight (a likely proxy for prematurity), daycare attendance, the presence of another child aged <24 months in the household, and either having Medicaid insurance or having no medical insurance (49). Another study identified low birth weight, maternal factors (e.g., young age, having Medicaid insurance, and maternal smoking), and male gender as risk factors for hospitalization with viral gastroenteritis (50). These studies suggest that preterm infants are at higher risk for severe rotavirus disease. Children and adults who are immunocompromised because of congenital immunodeficiency or because of bone marrow or solid organ transplantation sometimes experience severe or prolonged rotavirus gastroenteritis (51–56). The severity of rotavirus disease among children infected with human immunodeficiency virus (HIV) might be similar to that among children without HIV infection (57). Whether the incidence rate of severe rotavirus disease among HIV-infected children is similar to or greater than that among children without HIV infection is not known.

## Laboratory Testing for Rotavirus

Because the clinical features of rotavirus gastroenteritis do not differ distinctly from those of gastroenteritis caused by other pathogens, confirmation of rotavirus infection by laboratory testing of fecal specimens is necessary for reliable rotavirus surveillance and can be useful (e.g., for infection-control purposes) in clinical settings. The most widely used diagnostic laboratory method is antigen detection in the stool by an enzyme immunoassay (EIA) directed at an antigen common to all group A rotaviruses (i.e., those that are the principal cause of human disease). Certain commercial EIA kits are available that are easy to use, rapid, and highly sensitive, making them suitable for rotavirus surveillance and clinical diagnosis. Other techniques, including electron microscopy, RNA electrophoresis, reverse transcription–polymerase chain reaction (RT-PCR), sequence analysis, and culture are used primarily in research settings.

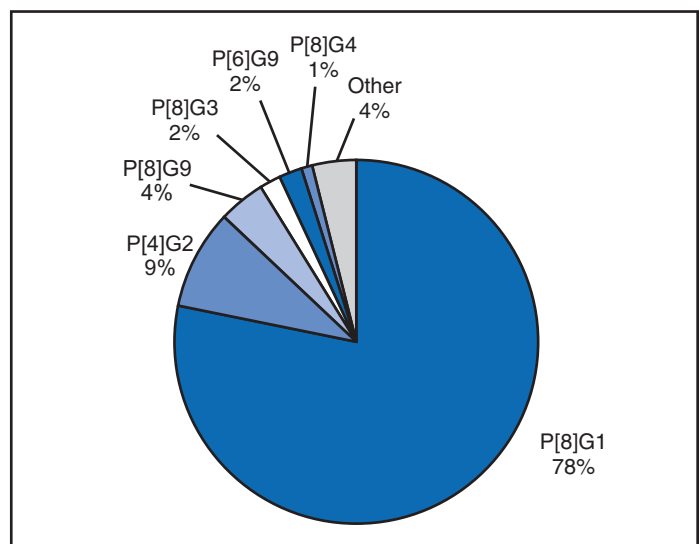
Serologic methods that detect a rise in serum antibodies, primarily EIA for rotavirus serum immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies, have been used to confirm recent infections primarily in the research setting. In vaccine trials, the immunogenicity of rotavirus vaccines has been assessed by measuring rotavirus-specific IgG, IgA and neutralizing antibodies to the serotypes of the vaccine strains (58–60).

## Morphology, Antigen Composition, and Immune Response

Rotaviruses are 70-nm nonenveloped RNA viruses in the family *Reoviridae* (61,62). The viral nucleocapsid is composed of three concentric shells that enclose 11 segments of double-stranded RNA. The outermost layer contains two structural viral proteins (VP): VP4, the protease-cleaved protein (P protein) and VP7, the glycoprotein (G protein). These two proteins define the serotype of the virus and are considered critical to vaccine development because they are targets for neutralizing antibodies that are believed to be important for protection (61,62). Because the two gene segments that encode these proteins can segregate independently, a typing system consisting of both P and G types has been developed (63). Although characterizing G serotypes by traditional methods is straightforward, using these methods for determining P serotypes is more difficult. Consequently, molecular methods are used almost exclusively to define genetically distinct P genotypes by nucleotide sequencing. These genotypes correlate well with known serotypes, but they are designated in brackets (e.g., P[8]) to distinguish them from P serotypes determined by antigenic analyses. In the United States, viruses containing six distinct P and G combinations are most prevalent: P[8]G1, P[4]G2, P[8]G3, P[8]G4, P[8]G9, P[6]G9 (64–67) (Figure 3).

Several animal species (e.g., primates and cows) are susceptible to rotavirus infection and suffer from rotavirus diarrhea, but animal strains of rotavirus differ from those that infect humans. Although human rotavirus strains that possess a high degree of genetic homology with animal strains have been identified (63,68–71), animal-to-human transmission appears

**FIGURE 3. Prevalent strains of rotavirus — United States, 1996–2005**



to be uncommon. However, natural reassortant animal-human strains have been identified in humans (63), and some are being developed as vaccine candidates (72).

Although children can be infected with rotavirus several times during their lives, initial infection after age 3 months is most likely to cause severe gastroenteritis and dehydration (15,73–75). After a single natural infection, 38% of children are protected against subsequent infection with rotavirus, 77% are protected against subsequent rotavirus gastroenteritis, and 87% are protected against severe rotavirus gastroenteritis; second and third infections confer progressively greater protection against rotavirus gastroenteritis (75). Rotavirus infection in healthy full-term neonates often is asymptomatic or results in only mild disease, perhaps because of protection from passively transferred maternal antibody (13,76).

The immune correlates of protection from rotavirus infection and disease are not understood fully. Both serum and mucosal antibodies probably are associated with protection, and in some studies, serum antibodies against VP7 and VP4 have correlated with protection (58,59). However, in other studies, including vaccine studies, correlation between serum antibody and protection has been poor (77). First infections with rotavirus generally elicit a predominantly homotypic, serum-neutralizing antibody response, and subsequent infections typically elicit a broader, heterotypic response (21,78). The influence of cell-mediated immunity is understood less clearly but probably is related both to recovery from infection and to protection against subsequent disease (79,80).

## Rotavirus Vaccines

### Background

In 1998, ACIP recommended Rotashield® (RRV-TV) (Wyeth Lederle Vaccines and Pediatrics, Marietta, Pennsylvania) (81), a rhesus-based tetravalent rotavirus vaccine, for routine vaccination of U.S. infants, with 3 doses administered at ages 2, 4, and 6 months (82). However, RRV-TV was withdrawn from the U.S. market within 1 year of its introduction because of its association with intussusception (83). At the time of its withdrawal, RRV-TV had not yet been introduced in any other national vaccination program globally. The risk for intussusception was most elevated (>20-fold increase) within 3–14 days after receipt of dose 1 of RRV-TV, with a smaller (approximately fivefold) increase in risk within 3–14 days after receipt of dose 2 (84). Overall, the estimated risk associated with dose 1 of RRV-TV was approximately one case per 10,000 vaccine recipients (85). After they reassessed the data on RRV-TV and intussusception, certain researchers suggested

that the risk for intussusception was age-dependent and that the absolute number of intussusception events, and possibly the relative risk for intussusception associated with dose 1 of RRV-TV increased with increasing age at vaccination (86,87). However, after reviewing all the available data, the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS) concluded that the risk for RRV-TV-associated intussusception was high in infants vaccinated after age 60 days and that insufficient evidence was available to conclude that the use of RRV-TV at age <60 days was associated with a lower risk (88). GACVS noted that the possibility of an age-dependent risk for intussusception should be taken into account in assessing rotavirus vaccines.

### Methodology

The ACIP rotavirus vaccine workgroup was reestablished in July 2007, after submission of the Biologics License Application (BLA) for RV1 to FDA in June 2007. The workgroup held teleconferences at least monthly to review published and unpublished data on the burden and epidemiology of rotavirus disease in the United States, the safety and efficacy of RV1 and RV5, and cost-effectiveness analyses. Recommendation options were developed and discussed by ACIP's rotavirus vaccine workgroup. The opinions of workgroup members and other experts were considered when data were lacking. Programmatic aspects related to implementation of the recommendations were taken into account. Presentations were made to ACIP during meetings in October 2007 and February 2008. The final proposed recommendations were presented to ACIP at the June 2008 ACIP meeting; after discussion, minor modifications were made, and the recommendations were approved.

### Pentavalent Human-Bovine Reassortant Rotavirus Vaccine (RotaTeq® [RV5])

RV5, which was licensed in the United States in 2006, is a live, oral vaccine that contains five reassortant rotaviruses developed from human and bovine parent rotavirus strains (Box) (10,89). Four reassortant rotaviruses express one of the outer capsid proteins (G1, G2, G3, or G4) from the human rotavirus parent strains and the attachment protein (P7[5]) from the bovine rotavirus parent strain. The fifth reassortant virus expresses the attachment protein (P1A[8]) from the human rotavirus parent strain and the outer capsid protein (G6) from the bovine rotavirus parent strain. The parent bovine rotavirus strain, Wistar Calf 3 (WC3), was isolated in 1981 from a calf with diarrhea in Chester County, Pennsylvania,

**BOX. Characteristics of RotaTeq® (RV5) and Rotarix® (RV1)**

<b>Characteristic</b>	<b>RV5</b>	<b>RV1</b>
Parent rotavirus strain	Bovine strain WC3 (type G6P7[5])	Human strain 89-12 (type G1P1A[8])
Vaccine composition	Reassortant strains G1 x WC3; G2 x WC3; G3 x WC3; G4 x WC3; P1A[8] x WC3	Human strain 89-12 (type G1P1A[8])
Vaccine titer	$\geq 2.0\text{--}2.8 \times 10^6$ infectious units (IU) per dose, depending on serotype	$\geq 10^{6.0}$ median cell culture infective dose (CCID <sub>50</sub> ) after reconstitution, per dose
Cell culture substrate	Vero cells	Vero cells
Formulation	Liquid requiring no reconstitution	Vial of lyophilized vaccine with a prefilled oral applicator of liquid diluent (1 ml)
Applicator	Latex-free dosing tube	Tip cap and rubber plunger of the oral applicator contain dry natural latex rubber. The vial stopper and transfer adapter are latex-free.
Other content	Sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, and trace amounts of fetal bovine serum.	Lyophilized vaccine: amino acids, dextran, Dulbecco's Modified Eagle Medium, sorbitol, and sucrose. Liquid diluent contains calcium carbonate, sterile water, and xanthan
Preservatives	None	None
Shelf life	24 months	24 months
Storage	Store refrigerated at 36°F–46°F (2°C–8°C). Administer as soon as possible after being removed from refrigeration. Protect from light.	Storage before reconstitution: Refrigerate vials of lyophilized vaccine at 36°F–46°F (2°C–8°C); diluent may be stored at a controlled room temperature of 68°F–77°F (20°C–25°C). Protect vials from light. Storage after reconstitution: Administer within 24 hours of reconstitution. May be stored refrigerated at 36°F–46°F (2°C–8°C) or at room temperature up to 77°F (25°C), after reconstitution.
Volume per dose	2 ml	1 ml

and was passaged 12 times in African green monkey kidney cells (90). The reassortants are propagated in Vero cells using standard tissue culture techniques in the absence of antifungal agents. The licensed vaccine is a ready-to-use 2 ml solution that contains  $\geq 2.0\text{--}2.8 \times 10^6$  infectious units (IUs) per individual reassortant dose, depending on serotype.

The RV5 BLA contained three phase III trials (91). Data from these trials on the immunogenicity, efficacy, and safety of RV5 are summarized below.

## Immunogenicity

A relation between antibody responses to rotavirus vaccination and protection against rotavirus gastroenteritis has not been established. In clinical trials, a rise in titer of rotavirus group-specific serum IgA antibodies was used as one of the measures of the immunogenicity of RV5. Sera were collected before vaccination and at 2–6 weeks after dose 3, and seroconversion was defined as a threefold or greater rise in antibody titer from baseline. Seroconversion rates for IgA antibody to rotavirus were 93%–100% among 439 RV5 recipients compared with 12%–20% in 397 placebo recipients in phase III studies (91).

Antibody responses to concomitantly administered vaccines were evaluated in a study with a total of 662 RV5 recipients and 696 placebo recipients. Different subsets of infants were evaluated for specific antibody responses. A 3-dose series of RV5 did not diminish the immune response to concomitantly administered *Haemophilus influenzae* type b conjugate (Hib) vaccine, inactivated poliovirus vaccine (IPV), hepatitis B (HepB) vaccine, pneumococcal conjugate vaccine (PCV), and diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine (10,91).

## Efficacy

The efficacy of the final formulation of RV5 has been evaluated in two phase III trials among healthy infants (92,93). Administration of oral polio vaccine (OPV) was not allowed; concomitant administration of other vaccines was not restricted. The large Rotavirus Efficacy and Safety Trial (REST) included a clinical efficacy substudy (Tables 1 and 2). In this substudy, 4,512 infants from Finland and the United States were included in the primary per-protocol efficacy analysis (consisting of evaluable subjects for whom there was no protocol violation) through one rotavirus season. The primary efficacy endpoint was the prevention of wild type G1–G4 rotavirus gastroenteritis occurring  $\geq 14$  days after completion of a 3-dose series through the first full rotavirus season after vaccination. A case of rotavirus gastroenteritis was defined as production of three or more watery or looser-than-normal stools within a 24-hour period or forceful vomiting, along with rotavirus detection by EIA in a stool specimen obtained within 14 days after the onset of symptoms. G serotypes were identified by RT-PCR followed by sequencing. Severe gastroenteritis was defined as a score of  $> 16$  on an established 24-point severity scoring system (Clark score) on the basis of intensity and duration of fever, vomiting, diarrhea, and changes in behavior.

The efficacy of RV5 against G1–G4 rotavirus gastroenteritis of any grade of severity through the first full rotavirus season after vaccination was 74.0% (95% confidence interval

[CI] = 66.8–79.9) and against severe G1–G4 rotavirus gastroenteritis was 98.0% (CI = 88.3–100.0) (Table 2). RV5 reduced office or clinic visits for G1–G4 rotavirus gastroenteritis by 86.0% (CI = 73.9–92.5). In a trial that evaluated RV5 at the end of its shelf life, the efficacy estimates for RV5 based on per-protocol analysis of data from 551 RV5 recipients and 564 placebo recipients were similar to those identified in the clinical efficacy substudy (10,92,93). Among the limited number of infants from phase III trials who received at least 1 dose of RV5 ( $n = 144$ ) or placebo ( $n = 135$ )  $> 10$  weeks after a previous dose, the estimate of efficacy of the RV5 series for protection against G1–G4 rotavirus gastroenteritis of any severity was 63% (CI = 53%–94%) (94).

In the health-care utilization cohort of REST, data from 57,134 infants from 11 countries were included in the per-protocol analysis of the efficacy of RV5 in reducing the need for hospitalization or ED care for rotavirus gastroenteritis (93). The efficacy of the RV5 series against ED visits for G1–G4 rotavirus gastroenteritis was 93.7% (CI = 88.8–96.5), and efficacy against hospitalization for G1–G4 rotavirus gastroenteritis was 95.8% (CI = 90.5–98.2) (Table 2). Efficacy was observed against all G1–G4 and G9 serotypes (Table 3); relatively few non-G1 rotavirus cases were detected. The efficacy of RV5 against all gastroenteritis-related hospitalizations was 58.9% (CI = 51.7–65.0) for the period that started after dose 1.

Breastfeeding did not appear to diminish the efficacy of a 3-dose series of RV5. Post-hoc analyses of the clinical efficacy substudy found that the efficacy of RV5 against G1–G4 rotavirus gastroenteritis of any severity through the first rotavirus season was similar among the 1,632 infants (815 in the vaccine group and 817 in the placebo group) who never were breastfed (68.3%; CI = 46.1–82.1) and the 1,566 infants (767 in the vaccine group and 799 in the placebo group) who were exclusively breastfed (68.0%; CI = 53.8–78.3) (95). Efficacy against severe G1–G4 rotavirus gastroenteritis also was similar among infants who never were breastfed (100.0%; CI = 48.3–100.0) and those who were exclusively breastfed (100.0%; CI = 79.3–100.0).

In posthoc analyses of data from the clinical efficacy substudy of REST, efficacy also was estimated among 73 healthy preterm infants (gestational age of  $< 37$  weeks) who received RV5 and 78 healthy preterm infants who received placebo (96). The efficacy through the first full season against rotavirus gastroenteritis of any severity (all serotypes combined) was 73.0% (CI = -2.2–95.2); three cases occurred among RV5 recipients, and 11 cases occurred among placebo recipients. In the health-care utilization cohort, the efficacy against rotavirus gastroenteritis-attributable hospitalizations (all serotypes combined) for healthy preterm infants was 100.0% (CI = 53.0–100.0); no cases were identified among 764 preterm infants who received



**TABLE 1. Characteristics of the major efficacy trials of Rotarix® (RV1) and RotaTeq® (RV5)**

Characteristic	RV1 Latin America*			RV1 Europe†			RV5 REST§¶		
	Vaccine	Placebo	Total	Vaccine	Placebo	Total	Vaccine	Placebo	Total
Study locations (Vaccine:placebo enrollment ratio)	Latin America (1:1)			Europe (2:1)			Primarily United States and Finland (1:1)		
No. of infants included in efficacy analyses									
Year 1 ATP**	9,009	8,858	17,867	2,572	1,302	3,874	2,207	2,305	4,512
Year 2 ATP	7,175	7,062	14,237	2,554	1,294	3,848	813	756	1,569
Health-care use cohort	—	—	—	—	—	—	28,646	28,488	57,134
Age at doses, per protocol	Dose 1: 6–12 wks 6 days (for one country, 6–13 wks 6 days) Dose 2: 1–2 mos later, at age ≤24 wks 6 days			Dose 1: 6–14 wks 6 days Dose 2: 1–2 mos later, at age ≤24 wks 6 days			Dose 1: 6–12 wks 0 days Subsequent doses: 4–10 wks apart Dose 3: age ≤32 wks 0 days		
Primary efficacy endpoint	Prevention of severe rotavirus gastroenteritis caused by circulating wild-type strains from 2 wks after dose 2 until age 1 year			Prevention of rotavirus gastroenteritis of any severity caused by circulating wild-type strains from 2 wks after dose 2 until end of first rotavirus season			Prevention of wild-type G1–G4 rotavirus gastroenteritis ≥14 days after dose 3 through first full rotavirus season after vaccination		

\* **SOURCES:** Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006;354:11–22. Food and Drug Administration. Rotarix clinical review. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2008. Available at <http://www.fda.gov/cber/products/rotarix/rotarix031008rev.pdf>.

† **SOURCE:** Vesikari T, Karvonen A, Prymula R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. *Lancet* 2007;370:1757–63.

§ Rotavirus Efficacy and Safety Trial. Efficacy was evaluated among two cohorts: clinical efficacy cohort (the United States and Finland) and health-care utilization cohort (11 countries, with 80% of infants from the United States and Finland).

¶ **SOURCES:** Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006;354:23–33. Food and Drug Administration. Product approval information-licensing action, package insert: RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent), Merck. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research; 2006.

\*\* According to protocol.

RV5 and nine cases were identified among 818 preterm infants who received placebo. Efficacy against rotavirus gastroenteritis-attributable ED visits was 100% (CI = 66.6–100.0), with no cases identified among RV5 recipients and 12 cases identified among placebo recipients (96).

## Adverse Events After Vaccination

### Intussusception

REST was designed as a large trial to permit evaluation of safety with respect to intussusception; 69,625 enrolled infants received at least 1 dose of RV5 or placebo (10,93). No increased risk for intussusception was observed in this trial after administration of RV5 when compared with placebo. For the prespecified period of days 0–42 after any dose, six confirmed intussusception cases occurred among 34,837 infants who received RV5, and five confirmed intussusception cases occurred among 34,788 infants who received placebo (relative risk adjusted for group sequential design: 1.6; CI = 0.4–6.4). None of the infants with confirmed intussusception in either treatment group had onset during days 1–21 after dose 1.

### Other Adverse Events

Serious adverse events (SAEs) and deaths were evaluated in infants enrolled in phase III trials (10,97). Among RV5 and placebo recipients, the incidence of SAEs within 42 days of any dose (2.4% of 36,150 and 2.6% of 35,536, respectively)

was similar. Across the studies, the incidence of death was similar among RV5 recipients (<0.1% [n = 25]) and placebo recipients (<0.1% [n = 27]). The most common cause of death (accounting for 17 ([32.7%]) of 52 deaths) was sudden infant death syndrome (SIDS), which was observed in eight RV5 recipients and nine placebo recipients.

Gastroenteritis occurring anytime after a dose was reported as an SAE in 76 (0.2%) RV5 recipients and in 129 (0.4%) placebo recipients. Seizures reported as SAEs occurred in 27 (<0.1%) vaccine recipients and in 18 (<0.1%) placebo recipients (difference not statistically significant). Pneumonia occurring anytime after a dose was reported as an SAE in 59 (0.2%) of RV5 recipients and in 62 (0.2%) of placebo recipients; hospitalization for pneumonia within 7 days after any dose occurred in 11 (<0.1%) RV5 recipients and in 14 (<0.1%) placebo recipients (91).

A subset of 11,711 infants was studied in detail to assess other potential adverse experiences (10). In the 42-day period postvaccination of any dose of RV5, the incidence of fever reported by parents and guardians of RV5 recipients and placebo recipients (42.6% and 42.8%, respectively) was similar, as was the incidence of hematochezia reported as an adverse experience (0.6% in both RV5 recipients and placebo recipients). Some (e.g., diarrhea, vomiting) adverse events occurred at a statistically higher incidence within 42 days of any dose in RV5 recipients (Table 4). Statistical significance was determined using 95% CIs on the risk difference; intervals with a



**TABLE 2. Efficacy of Rotarix® (RV1) and RotaTeq® (RV5) against rotavirus gastroenteritis (GE) in major efficacy trials, by severity and season\***

Rotavirus disease severity	No. of cases <sup>†</sup>		% efficacy	(95% CI <sup>§</sup> )
	Vaccine	Placebo		
<b>Rotavirus GE of any severity</b>				
<b>RV1 Europe<sup>¶</sup></b>				
Through 1st season	24 (2,572)	94 (1,302)	87.1	(79.6–92.1)
2nd season	61 (2,554)	110 (1,294)	71.9	(61.2–79.8)
Through 2nd season**	85 (2,572)	204 (1,302)	78.9	(72.7–83.8)
<b>RV5 REST<sup>††§§</sup></b>				
Through 1st full season (types G1–G4)	82 (2,207)	315 (2,305)	74.0	(66.8–79.9)
2nd full season (types G1–G4)	36 (813)	88 (756)	62.6	(44.3–75.4)
<b>Severe rotavirus GE</b>				
<b>RV1 Latin America<sup>¶¶</sup></b>				
To age 1 year: clinical <sup>***</sup>	12 (9,009)	77 (8,858)	84.7	(71.7–92.4)
To age 1 year: Vesikari ≥11 <sup>†††</sup>	11 (9,009)	71 (8,858)	84.8	(71.1–92.7)
2nd year: Vesikari ≥11	19 (7,175)	101 (7,062)	81.5	(69.6–89.3)
To age 2 years: Vesikari ≥11 <sup>§§§</sup>	28 (7,205)	154 (7,081)	82.1	(73.1–88.5)
<b>RV1 Europe</b>				
Through 1st season: Vesikari ≥11	5 (2,572)	60 (1,302)	95.8	(89.6–98.7)
2nd season: Vesikari ≥11	19 (2,554)	67 (1,294)	85.6	(75.8–91.9)
Through 2nd season: Vesikari ≥11	24 (2,572)	127 (1,302)	90.4	(85.1–94.1)
<b>RV5 REST</b>				
Through 1st full season: Clark>16 (types G1–G4) <sup>¶¶¶</sup>	1 (2,207)	51 (2,305)	98.0	(88.3–100)
2nd full season: Clark>16 (types G1–G4)	2 (813)	17 (756)	88.0	(49.4–98.7)
<b>Hospitalization for rotavirus GE</b>				
<b>RV1 Latin America</b>				
To age 1 year	9 (9,009)	59 (8,858)	85.0	(69.6–93.5)
2nd year	15 (7,175)	80 (7,062)	81.5	(67.7–90.1)
To age 2 years	22 (7,205)	127 (7,081)	83.0	(73.1–89.7)
<b>RV1 Europe</b>				
Through 1st season	0 (2,572)	12 (1,302)	100.0	(81.8–100)
2nd season	2 (2,554)	13 (1,294)	92.2	(65.6–99.1)
Through 2nd season	2 (2,572)	25 (1,302)	96.0	(83.8–99.5)
<b>RV5 REST</b>				
Health-care use cohort (types G1–G4) <sup>****</sup>	6 (28,646)	144 (28,488)	95.8	(90.5–98.2)

\* Because trials were conducted in different countries and have other differences (including different case definitions and durations of follow-up), efficacy results between trials cannot be directly compared. Efficacy assessment periods began 2 weeks after the last dose of the series in the per-protocol analyses. The number of persons with rotavirus cases and the number of infants who contributed to the analyses are presented; vaccine efficacy results are based on analyses using the follow-up time contributed by each subject. Selected results are presented.

<sup>†</sup> Numbers in parentheses represent the number of persons who received either vaccine or placebo and were included in the per-protocol analysis.

<sup>§</sup> Confidence interval.

<sup>¶</sup> **SOURCES:** Vesikari T, Karvonen A, Prymula R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. *Lancet* 2007;370:1757–63.

\*\* Efficacy results for “through second season” based on 2,572 RV1 recipients and 1,302 placebo recipients who entered the first efficacy period (from 2 weeks after dose 2 up to the end of the first rotavirus season) and on 2,554 RV1 recipients and 1,294 placebo recipients who entered the second efficacy period (from the visit at the end of the first rotavirus season up to the visit at the end of the second rotavirus season).

<sup>††</sup> Rotavirus Efficacy and Safety Trial.

<sup>§§</sup> **SOURCES:** Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006;354:23–33. Vesikari T, Karvonen A, Ferrante SA et al. Efficacy of the pentavalent rotavirus vaccine, RotaTeq, against hospitalizations and emergency department visits up to 3 years postvaccination: the Finnish Extension Study. Presented at the 13th International Congress on Infectious Diseases, Kuala Lumpur, Malaysia; June 19–22, 2008. Food and Drug Administration. Product approval information-licensing action, package insert: RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent), Merck. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research; 2006.

<sup>¶¶</sup> **SOURCES:** Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006;354:11–22. Food and Drug Administration. Rotarix clinical review. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2008. Available at <http://www.fda.gov/cber/products/rotarix/rotarix031008rev.pdf>.

<sup>\*\*\*</sup> Defined as diarrhea (three or more loose or watery stools within 24 hours), with or without vomiting, that required overnight hospitalization or rehydration therapy equivalent to World Health Organization plan B (oral rehydration) or plan C (intravenous rehydration) in a medical facility.

<sup>†††</sup> Defined as ≥11 on this 20-point clinical scoring system, based on the intensity and duration of symptoms of fever, vomiting, diarrhea, degree of dehydration, and treatment needed.

<sup>§§§</sup> Efficacy results for “to age 2 years” are based on 7,205 RV1 recipients and 7,081 placebo recipients who entered the first efficacy period (from 2 weeks after dose 2 up to age 1 year) and on 7,175 RV1 recipients and 7,062 placebo recipients who entered the second efficacy period (from age 1 year up to age 2 years).

<sup>¶¶¶</sup> Defined as >16 on this 24-point clinical scoring system, based on the intensity and duration of symptoms of fever, vomiting, diarrhea, and behavioral changes.

<sup>\*\*\*\*</sup> Efficacy results are based on G1–G4 rotavirus-related hospitalizations among 28,646 RV5 recipients and 28,488 placebo recipients in the health-care utilization cohort analysis contributing approximately 35,000 person-years of total follow-up during the first year and on a subset of the cohort (2,502 infants total) contributing approximately 1,000 person-years of follow-up during the second year.

**TABLE 3. Efficacy of Rotarix® (RV1) and RotaTeq® (RV5) against G type-specific rotavirus gastroenteritis in major efficacy trials, by severity and season\***

Rotavirus type	No. of cases†		% Efficacy	(95% CI§)
	Vaccine	Placebo		
<b>G1</b>				
<b>Any severity</b>				
<b>RV5 REST¶**</b>				
Through 1st full season	72 (2,207)	286 (2,305)	74.9	(67.3–80.9)
<b>Severe</b>				
<b>RV1 Latin America††</b>				
To age 1 yr: clinical§§	3 (9,009)	36 (8,858)	91.8	(74.1–98.4)
To age 1 yr: Vesikari ≥11¶¶	3 (9,009)	32 (8,858)	90.8	(70.5–98.2)
To age 2 yrs: clinical***	10 (7,205)	55 (7,081)	82.1	(64.6–91.9)
<b>RV1 Europe†††</b>				
Through 1st season: Vesikari ≥11	2 (2,572)	28 (1,302)	96.4	(85.7–99.6)
Through 2nd season: Vesikari ≥11§§§	4 (2,572)	57 (1,302)	96.4	(90.4–99.1)
<b>RV5 REST</b>				
Hospitalization/ED¶¶¶ visits****	16 (28,646)	328 (28,488)	95.1	(91.6–97.1)
<b>G2</b>				
<b>Any severity</b>				
<b>RV5 REST</b>				
Through 1st full season	6 (2,207)	17 (2,305)	63.4	(2.6–88.2)
<b>Severe</b>				
<b>RV1 Latin America</b>				
To age 1 yr: clinical	6 (9,009)	10 (8,858)	41.0	(<0–82.4)
To age 1 yr: Vesikari ≥11	5 (9,009)	9 (8,858)	45.4	(<0–85.6)
To age 2 yrs: clinical	5 (7,205)	8 (7,081)	38.6	(<0–84.2)
<b>RV1 Europe</b>				
Through 1st season: Vesikari ≥11	1 (2,572)	2 (1,302)	74.7	(<0–99.6)
Through 2nd season: Vesikari ≥11	2 (2,572)	7 (1,302)	85.5	(24.0–98.5)
<b>RV5 REST</b>				
Hospitalization/ED visits	1 (28,646)	8 (28,488)	87.6	(<0–98.5)
<b>G3</b>				
<b>Any severity</b>				
<b>RV5 REST</b>				
Through 1st full season	1 (2,207)	6 (2,305)	82.7	(<0–99.6)
<b>Severe</b>				
<b>RV1 Latin America</b>				
To age 1 yr: clinical	1 (9,009)	8 (8,858)	87.7	(8.3–99.7)
To age 2 yrs: clinical	3 (7,205)	14 (7,081)	78.9	(24.5–96.1)
<b>RV1 Europe</b>				
Through 1st season: Vesikari ≥11	0 (2,572)	5 (1,302)	100.0	(44.8–100.0)
Through 2nd season: Vesikari ≥11	1 (2,572)	8 (1,302)	93.7	(52.8–99.9)
<b>RV5 REST</b>				
Hospitalization/ED visits	1 (28,646)	15 (28,488)	93.4	(49.4–99.1)
<b>G4</b>				
<b>Any severity</b>				
<b>RV5 REST</b>				
Through 1st full season	3 (2,207)	6 (2,305)	48.1	(<0–91.6)
<b>Severe</b>				
<b>RV1 Latin America</b>				
To age 1 yr: clinical	1 (9,009)	2 (8,858)	NA††††	
To age 2 yrs: clinical	7 (7,205)	18 (7,081)	61.8	(4.1–86.5)
<b>RV1 Europe</b>				
Through 1st season: Vesikari ≥11	0 (2,572)	7 (1,302)	100.0	(64.9–100.0)
Through 2nd season: Vesikari ≥11	1 (2,572)	11 (1,302)	95.4	(68.3–99.9)
<b>RV5 REST</b>				
Hospitalization/ED visits	2 (28,646)	18 (28,488)	89.1	(52.0–97.5)
<b>G9</b>				
<b>Any severity</b>				
<b>RV5 REST</b>				
Through 1st full season	1 (2,207)	3 (2,305)	65.4	(<0–99.3)
<b>Severe</b>				
<b>RV1 Latin America</b>				
To age 1 yr: clinical	2 (9,009)	21 (8,858)	90.6	(61.7–98.9)
To age 2 yrs: clinical	9 (7,205)	66 (7,081)	86.6	(73.0–94.1)
<b>RV1 Europe</b>				
Through 1st season: Vesikari ≥11	2 (2,572)	19 (1,302)	94.7	(77.9–99.4)
Through 2nd season: Vesikari ≥11	13 (2,572)	44 (1,302)	85.0	(71.7–92.6)
<b>RV5 REST</b>				
Hospitalization/ED visits	0 (28,646)	14 (28,488)	100.0	(69.6–100.0)

See Table 3 footnotes on next page.

**TABLE 3. (Continued) Efficacy of Rotarix® (RV1) and RotaTeq® (RV5) against G type-specific rotavirus gastroenteritis in major efficacy trials, by severity and season\***

\* Because trials were conducted in different countries and have other differences (including different case definitions and durations of follow-up), efficacy results between trials cannot be directly compared. Efficacy assessment periods began 2 weeks after the last dose of the series in the per-protocol analyses. The number of persons with rotavirus cases and the number of infants who contributed to the analyses are presented; vaccine efficacy results are based on analyses using the follow-up time contributed by each subject. Selected results are presented.

† Numbers in parentheses represent the number of persons who received either vaccine or placebo and were included in the per-protocol analysis.

§ Confidence interval.

¶ Rotavirus Efficacy and Safety Trial.

\*\* **SOURCES:** Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006;354:23–33. Food and Drug Administration. Product approval information-licensing action, package insert: RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent), Merck. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research; 2006. Vesikari T, Karvonen A, Ferrante SA et al. Efficacy of the pentavalent rotavirus vaccine, RotaTeq, against hospitalizations and emergency department visits up to 3 years postvaccination: the Finnish Extension Study. Presented at the 13th International Congress on Infectious Diseases, Kuala Lumpur, Malaysia; June 19–22, 2008.

†† **SOURCES:** Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006;354:11–22. Food and Drug Administration. Rotarix clinical review. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2008. Available at <http://www.fda.gov/cber/products/rotarix/rotarix031008rev.pdf>.

§§ Defined as diarrhea (three or more loose or watery stools within 24 hours), with or without vomiting, that required overnight hospitalization or rehydration therapy equivalent to World Health Organization plan B (oral rehydration) or plan C (intravenous rehydration) in a medical facility.

¶¶ Defined as  $\geq 11$  on this 20-point clinical scoring system, based on the intensity and duration of symptoms of fever, vomiting, diarrhea, degree of dehydration, and treatment needed.

\*\*\* Efficacy results for “to age 2 years” are based on 7,205 RV1 recipients and 7,081 placebo recipients who entered the first efficacy period (from 2 weeks after dose 2 up to age 1 year) and on 7,175 RV1 recipients and 7,062 placebo recipients who entered the second efficacy period (from age 1 year up to age 2 years).

††† **SOURCE:** Vesikari T, Karvonen A, Prymula R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. *Lancet* 2007;370:1757–63.

§§§ Efficacy results for “through second season” based on 2,572 RV1 recipients and 1,302 placebo recipients who entered the first efficacy period (from 2 weeks after dose 2 up to the end of the first rotavirus season) and 2,554 RV1 recipients and 1,294 placebo who entered the second efficacy period (from the visit at the end of the first rotavirus season up to the visit at the end of the second rotavirus season).

¶¶¶ Emergency department.

\*\*\*\* Hospitalization/ED results based on 28,646 RV5 recipients and 28,488 placebo recipients in the healthcare utilization cohort analysis contributing ~35,000 person-years of total follow-up during the first year, and a subset of the cohort (2,502 infants total) contributing ~1,000 person-years of follow-up during the second year.

†††† Not available.

lower bound above zero were considered statistically significant. Adverse events also were solicited from parents and guardians within the first week after each dose. RV5 recipients had a small but statistically significantly greater ( $p$ -value  $< 0.05$ ) rate of diarrhea and vomiting after specific doses or after any dose (Table 5). Among the limited number of infants from phase III trials who received at least 1 dose of RV5 or placebo  $> 10$  weeks after a previous dose (depending on dose number and specific adverse event monitored, the number of infants evaluated in either the RV5 or placebo group ranged from 211–1,182), the proportion of infants with adverse events appeared generally similar among the RV5 and placebo recipients (94).

In the phase III clinical trials, infants were followed for up to 42 days of vaccine dose. Kawasaki disease was reported in five of 36,160 RV5 recipients and in one of 35,536 placebo recipients (unadjusted relative risk: 4.9; CI = 0.6–239.1) (10).

### Preterm Infants

In posthoc analyses of data from REST, adverse events were examined among healthy preterm infants with gestational age of 25–36 weeks (median: 34 weeks) (10,96). At least one SAE was reported within 42 days after any dose in 55 (5.5%) of the 1,005 preterm infants who received RV5 and in 62 (5.8%) of the 1,061 preterm infants who received placebo. Among the preterm infants with gestational age of  $< 32$  weeks, at least

one SAE was reported within 42 days of any dose in 6 (8.1%) of the 74 RV5 recipients and in 9 (9.8%) of the 92 placebo recipients. No confirmed intussusception occurred in a preterm infant during the study. Two deaths occurred in the RV5 group (one from SIDS and one from a motor-vehicle crash), and two occurred in the placebo group (one from SIDS and one from an unknown cause). The incidence of solicited adverse events (fever, vomiting, diarrhea, and irritability) within 7 days after each dose administration was assessed in preterm infants; depending on dose number and specific adverse event monitored, the number of infants evaluable in either the RV5 or placebo group varied (range: 108–154). The rates appeared generally similar between the RV5 and placebo recipients.

### Shedding and Transmission of Vaccine Virus

Fecal shedding of rotavirus vaccine virus was evaluated by plaque assays with electrophenotyping in a subset of infants enrolled in the large phase III trial by obtaining a single stool sample during days 4–6 after each dose of RV5 (93). Vaccine virus was detected in 17 (12.7%) of 134 infants after dose 1, zero of 109 infants after dose 2, and zero of 99 infants after dose 3. Shedding of vaccine virus also was assessed for phase III studies overall, including that detected by plaque assays

**TABLE 4. Number and percentage of infants with adverse events that occurred at a statistically higher incidence among recipients of RotaTeq® (RV5) compared with placebo, by event\***

Event	RV5†		Placebo§	
	No.	(%)	No.	(%)
Diarrhea	1,479	(24.1)	1,186	(21.3)
Vomiting	929	(15.2)	758	(13.6)
Otitis media	887	(14.5)	724	(13.0)
Nasopharyngitis	422	(6.9)	325	(5.8)
Bronchospasm	66	(1.1)	40	(0.7)

**SOURCE:** Food and Drug Administration. Product approval information—licensing action, package insert: RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent), Merck. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research; 2006.

\* Events that occurred at a statistically higher incidence within 42 days of any dose. Statistical significance was determined using 95% confidence intervals on the risk difference; intervals with a lower bound above zero were considered statistically significant. Coadministration of routine infant vaccines was allowed in studies that provided these data. Parents and guardians were asked to report adverse events on a vaccination report card.

† N = 6,138.

§ N = 5,573.

of rotavirus-antigen positive stools from infants evaluated for possible gastroenteritis. Shedding was observed as early as 1 day and as late as 15 days after a dose (10). The potential for transmission of vaccine virus to other persons was not assessed.

## Postlicensure Rotavirus Surveillance Data from the United States

Rotavirus surveillance data from two systems, the National Respiratory and Enteric Virus Surveillance System (NREVSS) and the New Vaccine Surveillance Network (NVSN), indicated that the 2007–08 season was substantially delayed in onset and diminished in magnitude compared to the seasons before substantial uptake of RV5 among U.S. infants (98). NREVSS is a voluntary network of U.S. laboratories that provides CDC with

weekly reports of the number of tests performed and positive results obtained for a variety of pathogens. For rotavirus, results of EIAs are reported. Compared with the 15 previous seasons spanning 1991–2006, rotavirus activity during the 2007–08 season appeared delayed in onset by 2–4 months (Figure 4). Further, data from the 32 laboratories that consistently reported results during July 2000–May 2008 indicated that the number of tests positive for rotavirus during the 2007–08 season (January 1, 2008–May 3, 2008) was lower by more than two thirds compared with the median number positive during the same weeks in the seven preceding rotavirus seasons.

Since 2006, NVSN has conducted prospective, population-based surveillance for rotavirus gastroenteritis among children aged <3 years residing in three U.S. counties. Among children with gastroenteritis enrolled during January–April of each year, the overall percentage of fecal specimens testing positive for rotavirus was 51% in 2006, 54% in 2007, and 6% in 2008.

Although nationally representative data on vaccine coverage are not yet available, information from population-based immunization information system sentinel sites indicates that mean coverage with 1 dose of rotavirus vaccine among infants aged 3 months was 49.1% in May 2007 and 56.0% in March 2008. Additional surveillance and epidemiologic studies are underway to monitor the impact of rotavirus vaccination in the United States.

## Postlicensure Safety Monitoring Data from the United States

During February 2006–March 2008, approximately 14 million doses of RV5 were distributed in the United States (99). Results from two safety monitoring systems have been reported. The U.S. Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance system managed

**TABLE 5. Solicited adverse events within the first week after doses 1, 2, and 3 of RotaTeq® (RV5) and placebo, by event and dose\***

Event	Dose 1		Dose 2		Dose 3		Any dose	
	RV5 (n = 6,130)	Placebo (n = 5,560)	RV5 (n = 5,703)	Placebo (n = 5,173)	RV5 (n = 5,496)	Placebo (n = 4,989)	RV5 (n = 6,130)	Placebo (n = 5,560)
Vomiting	6.7%†	5.4%	5.0%	4.4%	3.6%	3.2%	11.6%†	9.9%
Diarrhea	10.4%†	9.1%	8.6%†	6.4%	6.1%	5.4%	18.1%†	15.3%
Irritability	7.1%	7.1%	6.0%	6.5%	4.3%	4.5%	12.9%	13.0%
Elevated temperature§	17.1%	16.2%	20.0%	19.4%	18.2%	17.6%	35.3%	34.1%
	(n = 5, 616)	(n = 5,077)	(n = 5,215)	(n = 4,725)	(n = 4,865)	(n = 4,382)	(n = 5,751)	(n = 5,209)

**SOURCES:** Food and Drug Administration. Product approval information—licensing action, package insert: RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent), Merck. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research; 2006. Merck (unpublished data, 2006).

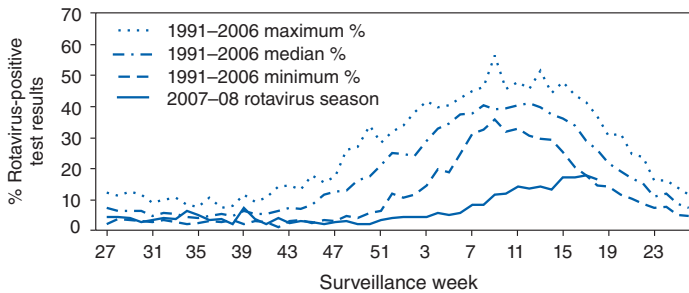
\* Coadministration of routine infant vaccines was allowed in studies that provided these data. Parents and guardians were asked to monitor for these adverse events and record information on a vaccination report card.

† Statistically significantly higher compared to rate in placebo recipients ( $p < 0.05$ ).

§ Temperature  $\geq 100.5^\circ\text{F}$  ( $\geq 38.1^\circ\text{C}$ ) rectal equivalent obtained by adding  $1^\circ\text{F}$  ( $0.55^\circ\text{C}$ ) to otic and oral temperatures and  $2^\circ\text{F}$  ( $1.1^\circ\text{C}$ ) to axillary temperatures.



**FIGURE 4. Percentage of rotavirus tests with positive results from participating laboratories, by week of year — National Respiratory and Enteric Virus Surveillance System, United States, 1991–2006 rotavirus seasons and 2007–08 rotavirus season\***



\* 2008 data current through week ending May 3, 2008. Data from July 2006–June 2007 were excluded from the (1991–2006) prevaccine baseline data because some persons tested likely received vaccine during that period.

jointly by FDA and CDC, receives reports of adverse events after vaccination from multiple sources, including health-care providers, vaccine recipients and parents and guardians of vaccine recipients, and manufacturers (100,101). Reported cases of intussusception among vaccine recipients are classified as confirmed if Brighton Collaboration Level 1 criteria are met (102). In VAERS analyses, the number of confirmed intussusception cases reported after vaccination is compared with the number of cases expected to occur by chance alone. This latter number is determined from estimates of the background rates of intussusception among infants and estimates of the total number of doses of RV5 that have been administered to infants. As of March 31, 2008, the number of confirmed cases of intussusception reported to VAERS during either the 1–21 day period or the 1–7 day period after receipt of any dose (doses 1, 2, and 3 combined) of RV5 did not exceed the number of cases expected to occur by chance alone after vaccination (99,103). A relative increase in intussusception reports in the first week after receipt of dose 1 of RV5, compared with the second and third weeks after dose 1, has been noted; whether this phenomenon is related to better reporting for intussusception during the first week after vaccination or represents a small increased risk for intussusception during the first week after dose 1 of RV5 is not clear (99,103).

Because VAERS is not designed to provide a definitive assessment of risk, the safety of RV5 also is monitored in the Vaccine Safety Datalink (VSD), a collaborative project between CDC and several large U.S. health maintenance organizations that links computerized patient-level vaccination data to medical outcomes, including potential adverse events (104). VSD is able to test hypotheses suggested by VAERS reports and prelicensure trials. With >200,000 doses of RV5 administered to infants in the VSD system during May 21, 2006–May 24,

2008, the number of cases of intussusception identified that occurred within a 30-day period after receipt of any dose of RV5 was not greater than the number of cases expected to occur by chance alone (105). No case of intussusception was identified that occurred within the first week after receipt of the first dose of RV5 in VSD (out of approximately 77,000 first doses) nor in the prelicensure REST. The data suggest that, if any associated risk exists, the risk for intussusception associated with the first dose of RV5 within the first week after vaccination is not greater than one in 25,000–50,000 first doses (105).

Other adverse events monitored in VAERS, VSD, or both include hematochezia, Kawasaki syndrome, seizures, meningitis and encephalitis, myocarditis and gram-negative sepsis. The data do not indicate that RV5 is associated with an increased risk for these adverse events (99,105).

## Monovalent Human Rotavirus Vaccine (Rotarix® [RV1])

RV1 is a live, oral vaccine licensed in 2008 for use in the United States that contains a human rotavirus strain (type G1P1A[8]) (Box). It was developed from a strain of rotavirus (termed 89-12) that was isolated in 1988 from a child in Cincinnati, Ohio, and that was first attenuated by passing 33 times in African green monkey kidney cells (106); it was then cloned and further passaged in a Vero cell line and renamed RIX 4414 (107). The licensed vaccine is prepared as a lyophilized powder that is reconstituted with 1 ml of a calcium bicarbonate buffer to a titer of  $\geq 10^{6.0}$  CCID<sub>50</sub> per dose (11). The BLA contained six phase II trials and five phase III trials (108). Data from these trials on the immunogenicity, efficacy, and safety of RV1 are summarized below.

## Immunogenicity

A relation between antibody responses to rotavirus vaccination and protection against rotavirus gastroenteritis has not been established. In two clinical trials, seroconversion was defined as the appearance of antirotavirus IgA antibodies (concentration of  $\geq 20$  U/ml) postvaccination in the serum of infants previously negative for rotavirus IgA antibodies. In the two studies, 1–2 months after a 2-dose series, 681 (86.5%) of 787 RV1 recipients seroconverted compared with 28 (6.7%) of 420 placebo recipients, and 302 (76.8%) of 393 RV1 recipients seroconverted compared with 33 (9.7%) of 341 placebo recipients, respectively (11).

One U.S. study was designed specifically to evaluate the antibody responses to vaccines (DTaP-HepB-IPV, PCV7 and Hib) coadministered with RV1. A total of 180 infants received



the 2 doses of RV1 coadministered with the other vaccines, and 137 infants who received the 2 RV1 doses 1 month after the other vaccines were included in the ATP cohort. Noninferiority criteria were met for all antigens, indicating that coadministration of RV1 with routine childhood vaccines did not diminish the immune responses to any of these vaccine antigens (11,108).

## Efficacy

The efficacy of the licensed formulation of RV1 has been evaluated in two large phase III trials among healthy infants, one conducted in 11 Latin American countries (109) and one conducted in six European countries (110) (Table 1). OPV was not coadministered; other routine childhood vaccines could be administered concomitantly. In both studies, both breast and formula feeding were permitted.

In the Latin American trial, 17,867 infants enrolled into the safety study also were part of the efficacy analysis and were included in the per-protocol efficacy analysis (Table 1) (109). The primary efficacy endpoint in this study was prevention of severe wild-type rotavirus gastroenteritis from 2 weeks after second dose until age 1 year. Wild-type rotavirus gastroenteritis was defined as an episode of gastroenteritis in which rotavirus other than vaccine strain was identified in a stool sample collected no later than 7 days after symptom onset. A clinical definition for severe rotavirus gastroenteritis was used: diarrhea (three or more loose or watery stools within 24 hours), with or without vomiting, in which rotavirus other than vaccine strain was identified in a stool sample and that required overnight hospitalization or rehydration equivalent to WHO plan B (oral rehydration) or plan C (intravenous rehydration) in a medical facility. Stools were tested for the presence of rotavirus antigen by enzyme-linked immunosorbent assay (ELISA). Stools that tested positive by ELISA were analyzed further for G and P type determination by RT-PCR, followed by reverse hybridization assay or optional sequencing (108). For certain outcomes, severe rotavirus gastroenteritis also was defined as a score of  $\geq 11$  on an established 20-point severity scoring system (Vesikari scale) on the basis of the intensity and duration of symptoms of fever, vomiting, diarrhea, degree of dehydration, and treatment needed (109).

In the Latin American trial, the efficacy of RV1 against severe rotavirus gastroenteritis (clinical definition) after completion of a 2-dose series until age 1 year was 84.7% (CI = 71.7–92.4) (109) (Table 2); the efficacy results were similar when severe rotavirus gastroenteritis was defined as an episode of rotavirus gastroenteritis with a Vesikari score of  $\geq 11$  (84.8%; CI = 71.1–92.7). The efficacy against severe rotavirus gastroenteritis (clinical definition) after completion of a 2-dose

series until age 2 years was 80.5% (CI = 71.3–87.1). Efficacy against non-G1 strains was observed; few cases from certain strains were detected (Table 3). The efficacy against G2 was greater than zero for subjects followed to age 1 year and those followed to age 2 years, but the 95% CIs included zero.

The efficacy against rotavirus gastroenteritis of any severity was not measured in the Latin American trial. For the first year follow-up period, the efficacy for 2 doses of RV1 against severe gastroenteritis (clinical definition) from any cause was 40.0% (CI = 27.7–50.4) (109).

In the European trial, efficacy was assessed among 3,874 infants who received either RV1 or placebo (110). The primary efficacy endpoint in this study was prevention of wild-type rotavirus gastroenteritis of any grade of severity occurring from 2 weeks after dose 2 until the end of the first rotavirus season. In general, efficacy results were somewhat higher in the European trial than in the Latin American trial (Tables 2 and 3). The efficacy against rotavirus gastroenteritis of any severity after the 2-dose regimen until the end of the first rotavirus season was 87.1% (CI = 79.6–92.1), and efficacy against severe rotavirus gastroenteritis (score of  $\geq 11$  on the Vesikari scale) was 95.8% (CI = 89.6–98.7) (Table 2). The efficacy after 2 doses of RV1 through the end of the second rotavirus season was 78.9% (CI = 72.7–83.8) against rotavirus gastroenteritis of any severity, and 90.4% (CI = 85.1–94.1) against severe rotavirus gastroenteritis (score of  $\geq 11$  on the Vesikari scale). Efficacy against non-G1 strains was observed; few cases from certain strains were detected (Table 3). For the second season and for the combined first and second season, the efficacy against severe disease from G2 was positive with a 95% CI that did not include zero. For the first season follow-up period, the efficacy for 2 doses of RV1 against hospitalization for gastroenteritis of any cause was 74.7% (CI = 45.5–88.9).

The efficacy of RV1 against rotavirus gastroenteritis of any severity through the first season among infants in the European trial that breastfed at the time of at least 1 dose (86.0%; CI = 76.8–91.9) was similar to the efficacy among infants not breastfed at the time of either dose (90.8%; CI = 72.5–97.7) (108). Efficacy against severe rotavirus gastroenteritis through the first season also was similar for the two groups (breastfed at the time of at least 1 dose: 95.7% [CI = 88.2–98.9] compared with not breastfed at the time of either dose: 96.2% [CI = 74.1–99.9]). Data on the efficacy of RV1 among preterm infants are not available.

## Adverse Events After Vaccination

### Intussusception

The Latin American trial was designed as a large trial to permit evaluation of safety with respect to intussusception;

63,225 infants (including 2,060 infants from Finland) received at least 1 dose of RV1 or placebo (109). No increased risk for intussusception was observed after administration of RV1 when compared with placebo. For the prespecified period days 0–30 after either dose, on the basis of the date of diagnosis, six confirmed intussusception cases occurred among 31,673 infants who received RV1 and seven occurred among 31,552 infants who received placebo (relative risk [RR]: 0.85; CI = 0.30–2.42). On the basis of the date of intussusception onset, seven confirmed intussusception cases occurred among RV1 recipients and seven occurred among placebo recipients for the period days 0–30 after either dose (108). None of the confirmed intussusception cases in either vaccine or placebo group had onset from days 0–14 after dose 1.

### Other Adverse Events

During the entire course of eight clinical studies, 68 (0.19%) deaths occurred among 36,755 RV1 recipients, and 50 (0.15%) deaths occurred among 34,454 placebo recipients (11). The most commonly reported cause of death after vaccination was pneumonia, which occurred in 19 (0.05%) RV1 recipients and 10 (0.03%) placebo recipients (RR: 1.7; CI = 0.8–4.2).

Infants were monitored for SAEs that occurred in the 31-day period after vaccination in eight clinical studies (11). Severe disease from one or more SAE occurred in 627 (1.7%) of 36,755 RV1 recipients compared with 659 (1.9%) of 34,454 placebo recipients (RR: 0.9; CI = 0.8–1.0). Diarrhea (RV1: 0.02%; placebo: 0.07%), dehydration (RV1: 0.02%; placebo: 0.06%), and gastroenteritis (RV1: 0.2%; placebo: 0.3%) occurred at a statistically higher (CI for relative risk excluded 1.0) incidence among placebo recipients compared with RV1 recipients. SAEs were coded with Medical Dictionary for Regulatory Activities (MedDRA) terms on the basis of information collected by study investigators from parental reports or medical records. Rates of SAEs were similar or the same between RV1 and placebo recipients for SAEs coded with the preferred MedDRA term “pneumonia” (RV1: 0.3%; placebo: 0.4%) and “convulsions” (RV1: 0.02%; placebo: 0.02%) (108).

In the Latin American trial, no notable differences were observed in the vaccinated versus placebo groups in rates of nonfatal pneumonia events and pneumonia hospitalizations (108). However, an increase was observed in pneumonia deaths (using combined pneumonia-related preferred terms) during the period between dose 1 and visit 3 [visit 3 took place 30–90 days after dose 2]; 16 (0.05%) such deaths occurred among RV1 recipients, and six (0.02%) occurred among placebo recipients (risk difference: 3.2 per 10,000 infants; exact  $p = 0.035$ ) (108). In the European trial, no deaths were reported (108); rates of SAEs with the preferred term “pneumonia” reported from dose 1 to the end of the second rotavirus season

were significantly greater among RV1 recipients than among placebo recipients (0.9% and 0.3%, respectively) (risk difference: 61 per 10,000 infants;  $p = 0.03$ ). In the RV1 group, 71% of the pneumonia SAEs occurred  $\geq 153$  days from the last dose of RV1 (111) (GSK, unpublished data, 2008). In all the other clinical trials in the BLA, and in the core integrated safety summary, statistically significant differences were not noted in the vaccine versus placebo groups for pneumonia or other pneumonia-related SAEs within the 31-day postvaccination period or for the full study period (111) (GSK, unpublished data, 2008). Excluding the Latin American safety and efficacy trial, for all other BLA trials combined, no statistically significant differences were noted among the vaccine versus placebo groups in pneumonia-related deaths during the full study period. The significance of these pneumonia-related findings is unclear. Additional data are expected from studies nearing completion in Asia and Africa (Leonard Friedland, GSK, personal correspondence, June 2008).

In the Latin American trial, statistically significantly more events coded with the preferred term “convulsions” were reported from dose 1 to visit 3 in RV1 recipients (16 [0.05%]) compared with placebo recipients (6 [0.02%];  $p = 0.03$ ) (108). When convulsion-related preferred terms were combined, no statistically significant difference in these events occurred in RV1 recipients compared with placebo recipients in three periods that were analyzed: from dose 1 to visit 3 (RV1: 20 [0.06%]; placebo: 12 [0.04%]), within 31 days after any dose (RV1: seven [0.02%]; placebo: nine [0.03%]), and 43 days after any dose (RV1: 12 [0.04%]; placebo: nine [0.03%]). In the European trial, no statistically significant difference was observed between convulsion-related SAEs in the RV1 group compared with the placebo group within 31 or 43 days after any dose (one event in each group; 0.04% and 0.07%, respectively) (108).

In seven clinical studies, detailed safety information for solicited adverse events was collected by parents and guardians for the day of vaccination and the next 7 days. Adverse events among RV1 recipients and placebo recipients occurred at similar rates, with the exception of Grade 3 (i.e., those that prevented normal everyday activities) cough or runny nose, which was slightly but statistically significantly higher in the RV1 group (108) (Table 6). During the 31-day period after vaccination, the following unsolicited adverse events occurred at a statistically higher incidence among RV1 recipients compared with placebo recipients: irritability (11.4% in RV1 group compared with 8.7% in the placebo group) and flatulence (2.2% in RV1 group compared with 1.3% in the placebo group) (11). No significant differences in Grade 3 irritability and flatulence were observed between the vaccine recipients and placebo recipients (108).

**TABLE 6. Percentage of infants with solicited adverse events (any intensity and Grade 3\*) within 8 days following any dose of Rotarix® (RV1) or placebo†**

Event	RV1 (n = 3,286)		Placebo (n = 2,015)	
	% Any intensity	% Grade 3	% Any intensity	% Grade 3
Fever‡	39.8	0.9	48.8	1.1
Fussiness/irritability	62.2	6.3	61.6	8.1
Loss of appetite	34.8	1.0	35.2	1.1
Vomiting	17.6	3.4	15.8	2.7
Diarrhea	6.8	1.2	5.7	1.5
Cough/runny nose¶	44.2	3.6**	47.2	3.2

**SOURCE:** Food and Drug Administration. Rotarix clinical review. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration; 2008. Available at <http://www.fda.gov/cber/products/rotarix/rotarix031008rev.pdf>.

\* Those that prevented normal everyday activities.

† Percentages are per subject. Coadministration of routine infant vaccines allowed in studies that provided these data. Parents/guardians were asked to monitor for these events and record on a diary card.

‡ Fever, any intensity defined as temperature of  $\geq 100.4^{\circ}\text{F}$  ( $\geq 38.0^{\circ}\text{C}$ ) rectally or  $\geq 99.5^{\circ}\text{F}$  ( $\geq 37.5^{\circ}\text{C}$ ) orally/axillary. Grade 3 fever is defined as temperature of  $\geq 103.1^{\circ}\text{F}$  ( $\geq 39.5^{\circ}\text{C}$ ) rectally or  $\geq 102.2^{\circ}\text{F}$  ( $\geq 39.0^{\circ}\text{C}$ ) orally/axillary.

¶ This event was solicited among 2,584 RV1 recipients and 1,899 placebo recipients.

\*\* Statistically significantly higher (95% confidence interval for relative risk excluded 1.0) in RV1 group compared with placebo group.

In the placebo-controlled trials (including some that were not 1:1 randomized), Kawasaki disease was reported in 17 (0.03%) RV1 recipients and nine (0.02%) placebo recipients (RR: 1.7; CI = 0.7–4.4); one case occurred within 30 days after study dose in RV1 recipients and one in the placebo recipients (RR: 1.0; CI = 0.01–78.4) (11). Among RV1 recipients, the time of onset after study dose varied (range: 3 days–19 months).

## Preterm Infants

A limited number of preterm infants (reported gestational age of  $\leq 36$  weeks) who received RV1 were followed for serious adverse events up to 30–90 days after dose 2. Serious adverse events were observed in seven (5.2%) of 134 preterm RV1 recipients compared with six (5.0%) of 120 preterm placebo recipients (11). No deaths or cases of intussusception were reported among these infants. Additional data are expected in the near future.

## Shedding and Transmission of Vaccine Virus

Rotavirus antigen shedding in stools postvaccination was evaluated in all or a subset of infants from seven phase II or III studies in various countries (RV1 administered at  $10^{6.5}$ – $10^{6.8}$  CCID<sub>50</sub> per dose, with 26–152 infants evaluated per study) (108). After dose 1, rotavirus antigen shedding was detected by ELISA in 50.0%–80.0% (depending on study) of infants

at approximately day 7, 19.2%–64.1% at approximately day 15, 0–24.3% at approximately day 30, and 0–2.6% at approximately day 60. After dose 2, rotavirus antigen shedding was detected in 4.2%–18.4% (depending on study) of infants at approximately day 7, 0–16.2% at approximately day 15, 0–1.2% at approximately day 30, and 0 at approximately day 45 (day 45 was assessed in only one study).

Shedding of live rotavirus was assessed in two BLA studies in which RV1 was administered at  $10^{6.5}$  CCID<sub>50</sub> per dose (108). In both studies, stool samples that were collected from a subset of infants at approximately day 7 after dose 1 were tested by ELISA. Stools that were rotavirus-antigen positive were tested subsequently for live virus by focus forming unit assay if enough sample was available. Live virus was detected in six (46.2%) of 13 and 15 (45.5%) of 33 rotavirus-antigen positive stools, for an estimated 26% of vaccinated infants shedding live virus at approximately day 7 after dose 1. The potential for transmission of vaccine virus to other persons was not assessed.

## Cost-Effectiveness of Rotavirus Vaccination

In a 2006 analysis that considered rotavirus disease burden, vaccine efficacy, vaccine coverage rates, and health costs, investigators estimated that a national rotavirus vaccination program in which 3 doses of RV5 were administered at ages 2, 4, and 6 months would result in 255,000 fewer physician visits, 137,000 fewer ED visits, 44,000 fewer hospitalizations, and 13 fewer deaths among children in one U.S. birth cohort followed to age 5 years (5). From the health-care perspective (i.e., evaluating medical costs only), the vaccination program was estimated to be cost-saving if the total cost per child (including administration costs) was less than \$66 (in 2004 dollars) for a complete series and would incur a net cost at \$143 per child. From the societal perspective (i.e., evaluating medical and nonmedical costs), vaccination was likely to be cost-saving at a total cost per child of less than \$156 and would be a net cost to society if total cost of vaccination was more than \$238 per child. At the manufacturer's price of \$62.50 (in 2006 dollars) per dose, a rotavirus vaccination program with RV5 would cost an estimated \$197,190 per life-year saved and \$138 per case averted from the societal perspective. This analysis was repeated in 2008 for RV1 administered at ages 2 and 4 months (112). A national program with either the 3-dose RV5 series or the 2-dose RV1 series will have similar cost-effectiveness estimates. Assuming a total cost of \$208 per child for RV1 and \$218 per child for RV5 (in 2006 dollars; one extra \$10 administration cost for RV5), RV1 was slightly more cost-effective than RV5 (e.g., from a societal perspective,



median estimates of \$94 compared with \$139 per case averted and \$128,400 compared with \$198,546 per life-year saved, respectively). However, because of uncertainty in cost per dose, administration, and shipping for each product and of the field vaccine effectiveness of a product's full or partial series, these differences in median estimates between the vaccines might not translate into a true difference for a program.

## Rationale for Rotavirus Vaccination and Development of Updated Recommendations

The rationale for adopting vaccination of infants as the primary public health measure for prevention of rotavirus disease, especially severe rotavirus disease, in the United States is threefold. First, rates of rotavirus illness among children in industrialized and less developed countries were similar, indicating that clean water supplies and good hygiene have little effect on virus transmission; therefore, further improvements in hygiene in the United States were unlikely to have a substantial impact on disease prevention (36,75,113–116). Second, in the United States, a high level of rotavirus morbidity continued in the prevaccine era despite available therapies. For example, the rate of hospitalizations for gastroenteritis in young children declined only modestly during 1979–1995 (8,117) despite the widespread availability of oral rehydration solutions in the treatment of dehydrating gastroenteritis (118,119). Third, studies of natural rotavirus infection indicated that initial infection protects against subsequent severe gastroenteritis, although subsequent asymptomatic infections and mild disease still might occur (75,76,120). Therefore, vaccination early in life, which mimics a child's first natural infection, will not prevent all subsequent disease but should prevent the majority of cases of severe rotavirus disease and their sequelae (e.g., dehydration, physician visits, hospitalizations, and deaths).

In drafting and updating rotavirus vaccine recommendations for consideration by ACIP, the rotavirus vaccine workgroup acknowledged that differences existed in the design of the vaccine trials and studies and that these differences and the lack of a head-to-head trial between the two licensed vaccines limited direct comparisons of some study results. One aspect that differed in the trials was the maximum ages for doses of vaccine. The maximum age for dose 1 in the trial protocols differed by approximately 3 weeks (Table 1). In addition, because the RV1 series has only 2 doses of vaccine whereas the RV5 series has 3 doses, the maximum age for the last dose for the RV1 trials was younger than that for the RV5 trial. When developing the recommendations for the maximum ages for doses, the workgroup considered the vaccines' safety and efficacy data and also the effect that having the same or different

maximum ages for the products would have on the ability of practitioners to follow the recommendations. After reviewing the options, the workgroup considered that harmonization of the maximum ages for doses of the two vaccines, as presented in the recommendations, would be unlikely to affect the safety and efficacy of the vaccines and would be programmatically advantageous.

## Changes to Recommendations from the 2006 ACIP Statement

- ACIP provides recommendations for use of a second rotavirus vaccine, RV1, to be administered in a 2-dose series at ages 2 and 4 months.
- The maximum age for dose 1 of rotavirus vaccine\* is 14 weeks and 6 days (previous recommendation: 12 weeks).
- The maximum age for the last dose of rotavirus vaccine is 8 months and 0 days (previous recommendation: 32 weeks).
- The minimum interval between doses of rotavirus vaccine is 4 weeks; no maximum interval is set (previous recommendation: interval of 4–10 weeks between doses).
- Considerations that support rotavirus vaccination of HIV-exposed or infected infants are described below.
- Rotavirus vaccine may be administered at any time before, concurrent with, or after administration of any blood product, including antibody-containing products, following the routinely recommended schedule for rotavirus vaccine (previous recommendation: defer vaccination for 42 days after receipt of an antibody-containing product, if possible).

## Recommendations for the Use of Rotavirus Vaccine

### Routine Administration

ACIP recommends routine vaccination of U.S. infants with rotavirus vaccine (Table 7). Two different rotavirus vaccine products are licensed for use in infants in the United States, RV5 and RV1. The products differ in composition and schedule of administration. Safety and efficacy were demonstrated for both vaccines in prelicensure clinical trials. Efficacy studies demonstrated that rotavirus vaccine was 85%–98% protective against severe rotavirus disease and 74%–87% protective against rotavirus disease of any severity through approximately the first rotavirus season (93,109,110). ACIP does not express a preference for either RV5 or RV1.

\* In these recommendations, the term "rotavirus vaccine" is used to refer to both RV5 and RV1.

**TABLE 7. Recommendations and quality of evidence for recommendations for use of rotavirus vaccine**

	Level of evidence*	Strength of evidence†
<b>Recommendation</b>		
Routine vaccination with RotaTeq® at ages 2, 4, and 6 mos or with Rotarix® at ages 2 and 4 mos	I	A
Administer to breastfed infants	I	A
Coadminister with DTaP,§ Hib <sup>¶</sup> vaccine, IPV,** hepatitis B vaccine, and pneumococcal conjugate vaccine	I	A
Administer to infants with mild illness, including gastroenteritis	I	B
<b>Contraindications</b>		
Severe allergic reaction to a vaccine component or a previous vaccine dose	III	B
<b>Precautions</b>		
Altered immunocompetence	III	C
Moderate or severe acute illness, including gastroenteritis	III	C
Chronic gastrointestinal disease	III	C
History of intussusception	III	C
Infants with spina bifida or bladder exstrophy	III	C
<b>Special situations</b>		
Preterm infants (<37 weeks' gestation)	I	B
Infants living in households with immunocompromised persons	III	C
Infants living in households with pregnant women	III	C
Regurgitation of vaccine	III	C
Infants hospitalized after vaccination	III	C
Infants who have received antibody-containing blood products	III	C

\* I = evidence from randomized controlled studies; II = evidence from other epidemiologic studies; and III = opinion of authorities.

† A = good evidence to support recommendation; B = fair evidence to support recommendation; and C = insufficient evidence.

§ Diphtheria and tetanus toxoids and acellular pertussis vaccine.

¶ *Haemophilus influenzae* type b conjugate.

\*\* Inactivated poliovirus vaccine.

RV5 is to be administered orally in a 3-dose series, with doses administered at ages 2, 4, and 6 months. RV1 is to be administered orally in a 2-dose series, with doses administered at ages 2 and 4 months (Table 8). The minimum age for dose 1 of rotavirus vaccine is 6 weeks; the maximum age for dose 1 is 14 weeks and 6 days. Vaccination should not be initiated for infants aged 15 weeks and 0 days or older because of insufficient data on safety of dose 1 of rotavirus vaccine in older infants. The minimum interval between doses of rotavirus vaccine is 4 weeks; no maximum interval is set. All doses should be administered by age 8 months and 0 days.

For infants to whom dose 1 of rotavirus vaccine is administered inadvertently at age 15 weeks and 0 days or older, the rest of the rotavirus vaccination series should be completed according to the schedule and by age 8 months and 0 days because timing of dose 1 should not affect the safety and efficacy of any subsequent dose(s). Infants who have had rotavirus gastroenteritis before receiving the full series of rotavirus vaccination should still start or complete the schedule according to the age and interval recommendations because the initial rotavirus infection might provide only partial protection against subsequent rotavirus disease.

No restrictions are placed on the infant's feeding before or after receipt of rotavirus vaccine. Breastfed infants should be vaccinated according to the same schedule as nonbreastfed

infants. The efficacy of the rotavirus vaccine series is similar among breastfed and nonbreastfed infants. As with all other vaccines, rotavirus vaccine can be administered to infants with minor acute illness (e.g., mild gastroenteritis or mild upper-respiratory tract infection, with or without fever).

## Simultaneous Administration

Rotavirus vaccine can be administered together with DTaP vaccine, Hib vaccine, IPV, hepatitis B vaccine, and pneumococcal conjugate vaccine. Available evidence suggests that rotavirus vaccine does not interfere with the immune response to these vaccines (for each rotavirus vaccine, see Immunogenicity). The infant's immune response to influenza vaccine administered at the same time as rotavirus vaccine has not been studied. However, ACIP has recommended previously that an inactivated vaccine (e.g., inactivated influenza vaccine) may be administered either simultaneously or at any time before or after a different inactivated vaccine or live vaccine (e.g., rotavirus vaccine) (121).

## Interchangeability of Rotavirus Vaccines

ACIP recommends that the rotavirus vaccine series be completed with the same product whenever possible. However, vaccination should not be deferred because the product used



**TABLE 8. Schedule for administration of rotavirus vaccines**

Characteristic	Vaccine	
	RV5*	RV1†
No. doses in series	3	2
Recommended ages for doses	2, 4, and 6 mos	2 and 4 mos
Minimum age for first dose	6 wks	
Maximum age for first dose	14 wks and 6 days	
Minimum interval between doses	4 wks	
Maximum age for last dose	8 mos and 0 days	

\* RotaTeq®.

† Rotarix®.

for a previous dose(s) is not available or is unknown. In these situations, the provider should continue or complete the series with the product available. If any dose in the series was RV5 or the vaccine product is unknown for any dose in the series, a total of 3 doses of rotavirus vaccine should be administered. All doses should be administered by age 8 months and 0 days.

No studies address the interchangeability of the two rotavirus vaccine products. However, no theoretic reason exists to expect that the risk for adverse events would be increased if the series included more than one product, compared with the risk for adverse events of a series containing only one product. Further, although it is possible that effectiveness of a series that contained both products could be reduced compared with a complete series with one product, the effectiveness of a series that contains both products is likely to be greater than an incomplete series with one product.

## Contraindications

Rotavirus vaccine should not be administered to infants who have a history of a severe allergic reaction (e.g., anaphylaxis) after a previous dose of rotavirus vaccine or to a vaccine component. Latex rubber is contained in the RV1 oral applicator, so infants with a severe (anaphylactic) allergy to latex should not receive RV1. The RV5 dosing tube is latex-free.

## Precautions

### Altered Immunocompetence

Practitioners should consider the potential risks and benefits of administering rotavirus vaccine to infants with known or suspected altered immunocompetence (121); consultation with an immunologist or infectious diseases specialist is advised. Children and adults who are immunocompromised because of congenital immunodeficiency, hematopoietic transplantation, or solid organ transplantation sometimes experience severe or prolonged rotavirus gastroenteritis. However, no safety or

efficacy data are available for the administration of rotavirus vaccine to infants who are immunocompromised or potentially immunocompromised, including 1) infants with primary and acquired immunodeficiency states, cellular immunodeficiencies, and hypogammaglobulinemic and dysgammaglobulinemic states; 2) infants with blood dyscrasias, leukemia, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic system; 3) infants on immunosuppressive therapy (including high-dose systemic corticosteroids); and 4) infants who are HIV-exposed or infected. However, two considerations support vaccination of HIV-exposed or infected infants: first, the HIV diagnosis might not be established in infants born to HIV-infected mothers before the age of the first rotavirus vaccine dose (only 1.5%–3% of HIV-exposed infants in the United States will be determined to be HIV-infected); and second, vaccine strains of rotavirus are considerably attenuated.

## Acute Gastroenteritis

In usual circumstances, rotavirus vaccine should not be administered to infants with acute moderate or severe gastroenteritis until the condition improves. However, infants with mild acute gastroenteritis can be vaccinated, particularly if the delay in vaccination might be substantial and might make the infant ineligible to receive vaccine (e.g., aged  $\geq 15$  weeks and 0 days before the vaccine series is started). Rotavirus vaccine has not been studied among infants with concurrent acute gastroenteritis. In these infants, the immunogenicity and efficacy of rotavirus vaccine theoretically could be compromised. For example, in some instances, infants who received OPV during an episode of acute gastroenteritis had diminished poliovirus antibody responses (122).

## Moderate or Severe Acute Illness

As with all other vaccines, the presence of a moderate or severe acute illness with or without fever is a precaution to administration of rotavirus vaccine. Infants with a moderate or severe acute illness should be vaccinated as soon as they have recovered from the acute phase of the illness. This precaution avoids superimposing any potential adverse effects of the vaccine on the underlying illness or mistakenly attributing a manifestation of the underlying illness to the vaccine. Vaccination should not be delayed because of the presence of mild respiratory tract illness or other mild acute illness with or without fever.

## Pre-existing Chronic Gastrointestinal Diseases

Infants with pre-existing gastrointestinal conditions (e.g., congenital malabsorption syndromes, Hirschsprung's disease, or short-gut syndrome) who are not undergoing immuno-

suppressive therapy should benefit from receiving rotavirus vaccine, and ACIP considers the benefits to outweigh the theoretic risks. However, no data are available on the safety and efficacy of rotavirus vaccine for infants with preexisting chronic gastrointestinal conditions.

### **Previous History of Intussusception**

Practitioners should consider the potential risks and benefits of administering rotavirus vaccine to infants with a previous history of intussusception. Available data do not indicate that RV5 or RV1 are associated with intussusception. A previously licensed rotavirus vaccine that is no longer available in the United States, RRV-TV, was associated with an increased risk for intussusception. Compared with infants who have never had intussusception, infants with a history of intussusception are at higher risk for a repeat episode of intussusception. No data are available on the administration of rotavirus vaccine to infants with a history of intussusception.

### **Infants with Spina Bifida or Bladder Exstrophy**

Latex rubber is contained in the RV1 oral applicator whereas the RV5 dosing tube is latex-free. Therefore, some experts prefer that infants with spina bifida or bladder exstrophy, who are at high risk for acquiring latex allergy, receive RV5 instead of RV1 to minimize latex exposure in these children. However, if RV1 is the only rotavirus vaccine available, it should be administered, because the benefit of vaccination is considered to be greater than the risk for sensitization.

## **Special Situations**

### **Preterm Infants (<37 Weeks' Gestation)**

ACIP considers the benefits of rotavirus vaccination of preterm infants (those born at <37 weeks' gestation) to outweigh the risks of adverse events. Data suggest that preterm infants are at increased risk for hospitalization from rotavirus or other viral pathogens associated with gastroenteritis during their first one to two years of life. In clinical trials, rotavirus vaccine appeared to be generally well tolerated in preterm infants, although a relatively small number of preterm infants have been evaluated (for each rotavirus vaccine, see Adverse Events After Immunization).

ACIP supports vaccination of preterm infants according to the same schedule and precautions as full-term infants and under the following conditions: the infant's chronological age meets the age requirements for rotavirus vaccine (e.g., age 6 weeks–14 weeks and 6 days for dose 1), the infant is clinically stable, and the vaccine is administered at the time of discharge from the neonatal intensive care unit [NICU] or nursery, or

after discharge from the NICU or nursery. Although the lower level of maternal antibody to rotavirus in very preterm infants theoretically could increase the risk for adverse reactions from rotavirus vaccine, ACIP believes the benefits of vaccinating the infant when age-eligible, clinically stable, and no longer in the hospital outweigh the theoretic risks.

Vaccine strains of rotavirus are shed in stools of vaccinated infants (for each rotavirus vaccine, see Shedding and Transmission of Vaccine Virus), so if an infant were to be vaccinated with rotavirus vaccine while still needing care in the NICU or nursery, at least a theoretic risk exists for vaccine virus being transmitted to infants in the same unit who are acutely ill (moderate or severe acute illness is a precaution for vaccination) and to preterm infants who are not age-eligible for vaccine. ACIP considers that, in usual circumstances, the risk from shedding outweighs the benefit of vaccinating the infant who is age-eligible for vaccine but who will remain in the NICU or nursery after vaccination.

### **Exposure of Immunocompromised Persons to Vaccinated Infants**

Infants living in households with persons who have or are suspected of having an immunodeficiency disorder or impaired immune status can be vaccinated. Vaccine virus (attenuated rotavirus) is shed in the stools of infants after rotavirus vaccination. However, no data are available on the risk for transmission of vaccine virus to household contacts and the risk for any subsequent disease. Vaccine virus is shed more commonly and for longer periods after RV1 than after RV5 (for each rotavirus vaccine, see Shedding and Transmission of Vaccine Virus). ACIP believes that the protection of the immunocompromised household member afforded by vaccinating the infant in the household and preventing wild-type rotavirus disease outweighs the small risk for transmitting vaccine virus to the immunocompromised household member and any subsequent theoretic risk for vaccine virus-associated disease. Vaccine virus is shed during the first weeks after administration of rotavirus vaccine; handwashing after diaper changing is always recommended.

### **Exposure of Pregnant Women to Vaccinated Infants**

Infants living in households with pregnant women should be vaccinated according to the same schedule as infants in households without pregnant women. Because the majority of women of childbearing age have preexisting immunity to rotavirus, the risk for infection and any subsequent theoretic risk for disease from potential exposure to the attenuated vaccine virus is considered to be very low.

## Regurgitation of Vaccine

The practitioner should not readminister a dose of rotavirus vaccine to an infant who regurgitates, spits out, or vomits during or after administration of vaccine. No data exist on the benefits or risks associated with readministering a dose. The infant should receive the remaining recommended doses of rotavirus vaccine following the routine schedule (with a 4-week minimum interval between doses).

## Hospitalization After Vaccination

If a recently vaccinated infant is hospitalized for any reason, no precautions other than standard precautions need to be taken to prevent spread of vaccine virus in the hospital setting.

## Infants Who Have Recently Received or Will Receive an Antibody-Containing Blood Product

Rotavirus vaccine may be administered at any time before, concurrent with, or after administration of any blood product, including antibody-containing products, following the routinely recommended schedule for rotavirus vaccine among infants who are eligible for vaccination. No data are available on the immune response to rotavirus vaccine in infants who have recently received a blood product. In theory, infants who have recently received an antibody-containing blood product might have a reduced immunologic response to a dose of oral rotavirus vaccine. However, 2 or 3 doses of vaccine are administered in the full rotavirus vaccine series, and no increased risk for adverse events is expected.

## Reporting of Adverse Events

Any clinically significant or unexpected adverse event that occurs after administration of rotavirus vaccine should be reported to VAERS, even if a causal relation to vaccination is not certain. The National Childhood Vaccine Injury Act requires health-care providers to maintain permanent immunization records and to report to VAERS occurrences of specific adverse events that follow selected vaccines, including rotavirus vaccine (available at <http://vaers.hhs.gov/reportable.htm>). VAERS reporting forms and information are available electronically at <http://vaers.hhs.gov> or by telephone, 1-800-822-7967. Web-based reporting by providers is encouraged and is available at <https://secure.vaers.org/VaersDataEntryinto.htm>.

## Enhanced Postlicensure Surveillance for Adverse Events

Monitoring for adverse events after introduction of rotavirus vaccine into routine vaccination programs is important, particularly in light of the previous experience with RRV-TV and its association with intussusception. The monitoring after introduction of RV1 will be similar to that conducted for RV5 and will include manufacturer-sponsored phase IV studies and enhanced review of adverse events reported to VAERS.

## National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program (VICP), established by the National Childhood Vaccine Injury Act of 1986, is a no-fault system through which persons thought to have suffered an injury or death as a result of administration of a covered vaccine can seek compensation. Persons of all ages who receive a VICP-covered vaccine are eligible to file a claim.

The program relies on a vaccine injury table listing the vaccines covered by the program and the injuries, disabilities, illnesses, and conditions (including death) for which compensation can be awarded. Claimants also can prevail for conditions not listed in the table if they can prove causation. For a claimant to be eligible for compensation, claims must be filed within a specific time period after the injury.

Rotavirus vaccine is covered by VICP under the general category of rotavirus vaccines in Category XI of the Vaccine Injury Table (available at <http://www.hrsa.gov/vaccinecompensation/table.htm>). In this category, no condition is specified for compensation. Additional information about the program is available at <http://www.hrsa.gov/vaccinecompensation> or by telephone, 1-800-338-2382.

## Areas for Study Related to Rotavirus Vaccination

### Surveillance of Rotavirus Gastroenteritis

Rotavirus gastroenteritis is not a reportable disease in the United States, and testing for rotavirus infection is not always performed when a child seeks medical care for acute gastroenteritis. Rotavirus disease surveillance systems need to be adequately sensitive and specific to document the effectiveness of the vaccination program. Methods of surveillance for rotavirus disease at the national level include review of national hospital discharge databases for rotavirus-specific or rotavirus-compatible diagnoses, surveillance for rotavirus disease at three sites that participate in NVSN, and reports of rotavirus detec-

tion from a sentinel system of laboratories (6,7,14). At the state and local levels, surveillance efforts at sentinel hospitals or by review of hospital discharge databases can be used to monitor the impact of the vaccine program. Special studies (e.g., case-control studies and retrospective cohort studies) will be used to measure the effectiveness of rotavirus vaccine under routine use in the United States.

### Detection of Unusual Strains of Rotavirus

CDC has established a national strain surveillance system of sentinel laboratories to monitor circulating rotavirus strains before and after the introduction of rotavirus vaccine (64–66). This system is designed to detect new or unusual strains causing gastroenteritis that might not be prevented effectively by vaccination, which might affect the success of the vaccination program.

### Research

Additional studies would be valuable to evaluate the safety and efficacy of rotavirus vaccine administered to infants who are born preterm, have immune deficiencies, live in households with immunocompromised persons, have chronic gastrointestinal disease, or start the series late. Postlicensure studies also could determine the relative effectiveness of rotavirus vaccine when less than the full series is administered and evaluate possible secondary transmission of vaccine virus.

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## Vaccines & Immunizations

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### Vaccines and Preventable Diseases:

## Statement Regarding Rotarix® and RotaTeq® Rotavirus Vaccines and Intussusception

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On October 28, 2010, summaries of post-licensure evaluations on rotavirus vaccines and intussusception were presented to the Advisory Committee on Immunization Practices. Some studies performed outside the United States have detected a low-level increased risk of intussusception following rotavirus vaccination, particularly shortly after the first dose. The level of risk observed in these post-marketing studies is substantially lower than the risk of intussusception after vaccination with RotaShield®, the previous rotavirus vaccine.

The Food and Drug Administration (FDA) licensed RotaTeq® (Merck & Co., Inc.) in February 2006 and Rotarix® (GSK Biologicals) in April 2008 for routine use in U.S. infants to prevent severe rotavirus disease in infants and children. Because a previous rotavirus vaccine, RotaShield® (Wyeth-Ayerst), was associated with intussusception, a form of bowel obstruction, the risk of this adverse event was specifically evaluated in a large pre-licensure trial for each vaccine. In these trials, each involving over 60,000 participants, conducted mainly in Finland and the United States for RotaTeq and in 11 Latin American countries for Rotarix, no increased risk for intussusception was observed. Post-marketing surveillance for intussusception is ongoing in many countries. On September 22, 2010, FDA approved a label change for Rotarix to advise practitioners of new data regarding intussusception from an evaluation in Mexico by GSK (see [Updated Vaccine Label for Rotarix® \(Vac-label-HCP.htm\)](#)).

Since 2007, the Pan American Health Organization has collaborated with ministries of health, the Centers for Disease Control and Prevention (CDC), and PATH, to evaluate, in Brazil and Mexico, the potential risk of intussusception after Rotarix immunization during routine use. Analyses of the data collected have identified a clustering of 18 hospitalizations for intussusception in the period 1–7 days after the first dose in Mexico, corresponding to a rate of intussusception that was about 4–5 times higher than in later periods after vaccination, after adjusting for age. No clustering was observed after the first dose in Brazil.

In a similar study sponsored by GSK Biologicals in a different population in Mexico, a possible increased risk of intussusception of about 1.8-fold was found in the 30-day period following the first dose of Rotarix, with a clustering of cases in the first week after vaccination.

In Australia, post-marketing surveillance studies found a possibility of an increase in intussusception cases in the first week after vaccination with both Rotarix and RotaTeq vaccines, although these findings are based on relatively few cases.

In the United States, more than 27 million doses of RotaTeq have been distributed. A study is being done through the Vaccine Safety Datalink (VSD) to see if RotaTeq, the vaccine primarily used in these practices, is associated with intussusception. This study, which includes data on more than 800,000 total doses of RotaTeq vaccine, has not found an increased risk of intussusception. However, the VSD study cannot rule out a risk of intussusception with RotaTeq as low as the risk currently reported with Rotarix in Mexico. An evaluation in the United States sponsored by Merck & Co., Inc. also did not show evidence of an increased risk of intussusception with RotaTeq; this study also could not rule out a low-level increased risk.

Rotarix has been available in the United States since 2008, and about 2.7 million doses of this vaccine have been distributed. There are not enough safety data on Rotarix from ongoing studies in the United States to allow detection of a level of risk as low as those reported in Mexico.

Some post-marketing studies from outside the United States have detected a low-level increased risk of intussusception following rotavirus vaccination, particularly shortly after the first dose. The level of intussusception risk observed in these post-marketing studies is substantially lower than the estimated risk following receipt of RotaShield (1 case/10,000 vaccinees). The documented benefits of rotavirus vaccine in U.S. children are substantial. The rotavirus vaccination program in the United States has reduced the number of infants and children needing hospitalization or emergency department care for rotavirus disease by about 85%. In the 2008 rotavirus season, 2 years after the introduction of RotaTeq, there were an estimated 40,000–60,000 fewer gastroenteritis-related hospitalizations than in the pre-vaccine seasons among children less than 5 years of age. While an increased risk of intussusception from rotavirus vaccine has not been documented in the United States, if a risk does exist of the magnitude seen in the data currently available from Mexico, 1 case of intussusception caused by rotavirus vaccine would occur per approximately 100,000 infants who are vaccinated following age recommendations. Considering that the data currently available suggest a small risk of intussusception caused by rotavirus vaccine is possible and considering that the benefits of rotavirus vaccination are great, CDC continues to recommend both Rotarix and RotaTeq to prevent severe rotavirus disease in U.S. infants and children. CDC will continue to monitor additional data on intussusception as they become available.

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### Reference

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World Health Organization, Global Advisory Committee on Vaccine Safety Statement on Rotarix and RotaTeq Vaccines and Intussusception.

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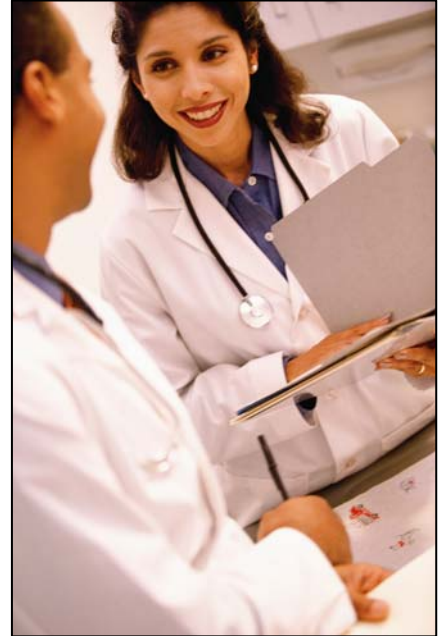
# Immunization Information Systems

## What are immunization registries?

Immunization information systems (IIS) or immunization registries are confidential, computerized systems that track vaccines given within a state or community. Registries help to ensure that correct and timely immunizations are administered by consolidating vaccination records from multiple providers, generating reminder and recall notices, and providing official vaccination forms and assessments.

Immunization registries include a child's name; date and place of birth; names and addresses of parents or guardians; date of vaccination; specific type of vaccine(s) administered; and any complications or side effects from the vaccinations. Children typically are entered into a registry at birth or at the time of their first contact with the health care system. Registries increasingly record immunizations across the lifespan.

The AAP supports the use of immunization registries, as long as they are cost effective, pay for costs incurred while entering data, support interface with electronic medical records, and do not penalize physicians for low rates (*Pediatrics* 2006; 118:1293-1295).



## What are the benefits of IIS?

One of the *Healthy People 2010* national objectives is to increase to 95% the proportion of children 6 years of age and younger who are enrolled in a fully operational, population-based immunization registry. By using registries, health care providers can promote effective immunization strategies (i.e., reminder/recall systems) while decreasing the resources needed to achieve and maintain high levels of coverage. Increasing health-care provider participation by linking Electronic Medical Records to immunization registries and/or IISs is vital to meeting the national health objective.

Studies show that families are more mobile than in the past, and approximately 23% of children visit more than one provider by 2 years of age, making it difficult to accurately assess immunization needs. Also, parents do not always have complete information about their children's immunization status. Approximately 1 in 5 US children have received at least 1 unnecessary vaccine because of incomplete immunization records, wasting approximately \$26.5 million per year on vaccine costs. Registries help address these problems by maintaining accurate immunization records and identifying children in need of vaccines so they can be called back to the health care provider's office. In addition, registries keep providers informed of new vaccines and changes in the recommended schedule.

Registries help providers fulfill school, camp, and child care immunization requirements; reduce paper work and office-based computer entries; introduce new vaccines or changes in the vaccine schedule; and generate Health Plan Employer Data and Information Set (HEDIS) reports for managed-care organizations.

Registries help communities by identifying high-risk and underimmunized populations and target interventions by providing information on community and state immunization rates. IIS may also be able to integrate immunization services with other public health functions, such as newborn and lead screening.

### **Additional Resources:**

Every Child by Two: [www.ecbt.org](http://www.ecbt.org)

Immunization Action Coalition : [www.immunize.org](http://www.immunize.org)

American Immunization Registry Association:  
[www.immregistries.org](http://www.immregistries.org)

# Immunization Information Systems

## What are some concerns about registries?

**Cost to implement.** Many providers are concerned about the cost involved in implementing registries. According to the CDC, however, the cost for a provider to manually retrieve, review, and update immunization records is 3 times the annual cost of maintaining a child in a registry until 5 years of age. Other cost-saving benefits include reducing “no-show” rates (though the use of reminders), reducing vaccine wastage, and avoiding part or all of the cost of the National Immunization Survey (currently the primary method for assessing community coverage levels).

**Time involved.** Purchasing adequate software, training staff, and ensuring that technical support is available can be expensive and time-consuming. Although entering records into a new system takes time, once the registry is in place, the need to manually search for records will be eliminated.

**Provider commitment.** A lack of patient data often is a problem when starting registries. Having a fully functional registry requires the participation of health care providers and a willingness to gather relevant information. The cost and staff time involved in implementing and maintaining registries is significant. The AAP encourages appropriate payment for these tasks.

## Are registry records confidential?

The information stored in registries is confidential, and the privacy of all users (including children, families, and providers) is protected by law. Many states dictate how registry information can be used and have strict rules about privacy. The CDC has developed the following specifications to protect the privacy of registry users and confidentiality of registry information:

- **Confidentiality policies and agreements.** All registries must have a written policy that is consistent with applicable federal, state, and local laws and regulations, and all users must sign an agreement to comply with written specifications.
- **Notification and choice.** Parents must be informed about participating in the registry, notified of the registry’s existence, the information it will contain, and how the information will be used.
- **Use of registry information.** Registry information must not be used in a punitive manner.
- **Access to and disclosure of registry information.** Policies must clearly define who has access to registry information.
- **Penalties for unauthorized disclosure.** Policies must define what constitutes a breach of confidentiality, and penalties must be enforced.
- **Data retention.** Policies must address the length of time registry information will be held.



## Where can health care providers find more information about registries?

The CDC Immunization Registry Clearinghouse (IRC) serves to collect, merge, and distribute information about immunization registries and maintains information on registry participation; privacy, confidentiality, and legislative issues; technical development; and guidance and registry funding. For more information about immunization registries, please visit [www.cdc.gov/vaccines/programs/iis/default.htm](http://www.cdc.gov/vaccines/programs/iis/default.htm). To find an IIS in your state, visit: [www.cdc.gov/vaccines/programs/iis/contact-state.htm](http://www.cdc.gov/vaccines/programs/iis/contact-state.htm).





# Recommended Immunization Schedule for Persons Aged 0 Through 6 Years—United States • 2011

For those who fall behind or start late, see the catch-up schedule

Vaccine ▼	Age ►	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B <sup>1</sup>		HepB	HepB				HepB					
Rotavirus <sup>2</sup>			RV	RV	RV	RV <sup>2</sup>						
Diphtheria, Tetanus, Pertussis <sup>3</sup>			DTaP	DTaP	DTaP	DTaP	see footnote <sup>3</sup>	DTaP				DTaP
<i>Haemophilus influenzae</i> type b <sup>4</sup>			Hib	Hib	Hib	Hib <sup>4</sup>	Hib					
Pneumococcal <sup>5</sup>			PCV	PCV	PCV	PCV	PCV				PPSV	
Inactivated Poliovirus <sup>6</sup>			IPV	IPV			IPV					IPV
Influenza <sup>7</sup>							Influenza (Yearly)					
Measles, Mumps, Rubella <sup>8</sup>							MMR			see footnote <sup>8</sup>		MMR
Varicella <sup>9</sup>							Varicella			see footnote <sup>9</sup>		Varicella
Hepatitis A <sup>10</sup>							HepA (2 doses)				HepA Series	
Meningococcal <sup>11</sup>												MCV4

Range of recommended ages for all children

Range of recommended ages for certain high-risk groups

This schedule includes recommendations in effect as of December 21, 2010. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Considerations should include provider assessment, patient preference, and the potential for adverse events. Providers should consult the relevant Advisory Committee on Immunization Practices statement for detailed recommendations: <http://www.cdc.gov/vaccines/pubs/acip-list.htm>. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS) at <http://www.vaers.hhs.gov> or by telephone, 800-822-7967. Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

## 1. Hepatitis B vaccine (HepB). (Minimum age: birth)

### At birth:

- Administer monovalent HepB to all newborns before hospital discharge.
- If mother is hepatitis B surface antigen (HBsAg)-positive, administer HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth.
- If mother's HBsAg status is unknown, administer HepB within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if HBsAg-positive, administer HBIG (no later than age 1 week).

### Doses following the birth dose:

- The second dose should be administered at age 1 or 2 months. Monovalent HepB should be used for doses administered before age 6 weeks.
- Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg 1 to 2 months after completion of at least 3 doses of the HepB series, at age 9 through 18 months (generally at the next well-child visit).
- Administration of 4 doses of HepB to infants is permissible when a combination vaccine containing HepB is administered after the birth dose.
- Infants who did not receive a birth dose should receive 3 doses of HepB on a schedule of 0, 1, and 6 months.
- The final (3rd or 4th) dose in the HepB series should be administered no earlier than age 24 weeks.

## 2. Rotavirus vaccine (RV). (Minimum age: 6 weeks)

- Administer the first dose at age 6 through 14 weeks (maximum age: 14 weeks 6 days). Vaccination should not be initiated for infants aged 15 weeks 0 days or older.
- The maximum age for the final dose in the series is 8 months 0 days
- If Rotarix is administered at ages 2 and 4 months, a dose at 6 months is not indicated.

## 3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). (Minimum age: 6 weeks)

- The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.

## 4. *Haemophilus influenzae* type b conjugate vaccine (Hib). (Minimum age: 6 weeks)

- If PRP-OMP (PedvaxHIB or Comvax [HepB-Hib]) is administered at ages 2 and 4 months, a dose at age 6 months is not indicated.
- Hiberix should not be used for doses at ages 2, 4, or 6 months for the primary series but can be used as the final dose in children aged 12 months through 4 years.

## 5. Pneumococcal vaccine. (Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV])

- PCV is recommended for all children aged younger than 5 years. Administer 1 dose of PCV to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- A PCV series begun with 7-valent PCV (PCV7) should be completed with 13-valent PCV (PCV13).
- A single supplemental dose of PCV13 is recommended for all children aged 14 through 59 months who have received an age-appropriate series of PCV7.
- A single supplemental dose of PCV13 is recommended for all children aged 60 through 71 months with underlying medical conditions who have received an age-appropriate series of PCV7.

- The supplemental dose of PCV13 should be administered at least 8 weeks after the previous dose of PCV7. See *MMWR* 2010;59(No. RR-11).

- Administer PPSV at least 8 weeks after last dose of PCV to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant.

## 6. Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)

- If 4 or more doses are administered prior to age 4 years an additional dose should be administered at age 4 through 6 years.
- The final dose in the series should be administered on or after the fourth birthday and at least 6 months following the previous dose.

## 7. Influenza vaccine (seasonal). (Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 2 years for live, attenuated influenza vaccine [LAIV])

- For healthy children aged 2 years and older (i.e., those who do not have underlying medical conditions that predispose them to influenza complications), either LAIV or TIV may be used, except LAIV should not be given to children aged 2 through 4 years who have had wheezing in the past 12 months.
- Administer 2 doses (separated by at least 4 weeks) to children aged 6 months through 8 years who are receiving seasonal influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but only received 1 dose.
- Children aged 6 months through 8 years who received no doses of monovalent 2009 H1N1 vaccine should receive 2 doses of 2010–2011 seasonal influenza vaccine. See *MMWR* 2010;59(No. RR-8):33–34.

## 8. Measles, mumps, and rubella vaccine (MMR). (Minimum age: 12 months)

- The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.

## 9. Varicella vaccine. (Minimum age: 12 months)

- The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose.
- For children aged 12 months through 12 years the recommended minimum interval between doses is 3 months. However, if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

## 10. Hepatitis A vaccine (HepA). (Minimum age: 12 months)

- Administer 2 doses at least 6 months apart.
- HepA is recommended for children aged older than 23 months who live in areas where vaccination programs target older children, who are at increased risk for infection, or for whom immunity against hepatitis A is desired.

## 11. Meningococcal conjugate vaccine, quadrivalent (MCV4). (Minimum age: 2 years)

- Administer 2 doses of MCV4 at least 8 weeks apart to children aged 2 through 10 years with persistent complement component deficiency and anatomic or functional asplenia, and 1 dose every 5 years thereafter.
- Persons with human immunodeficiency virus (HIV) infection who are vaccinated with MCV4 should receive 2 doses at least 8 weeks apart.
- Administer 1 dose of MCV4 to children aged 2 through 10 years who travel to countries with highly endemic or epidemic disease and during outbreaks caused by a vaccine serogroup.
- Administer MCV4 to children at continued risk for meningococcal disease who were previously vaccinated with MCV4 or meningococcal polysaccharide vaccine after 3 years if the first dose was administered at age 2 through 6 years.

The Recommended Immunization Schedules for Persons Aged 0 Through 18 Years are approved by the Advisory Committee on Immunization Practices (<http://www.cdc.gov/vaccines/recs/acip>), the American Academy of Pediatrics (<http://www.aap.org>), and the American Academy of Family Physicians (<http://www.aafp.org>).

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age

PERSONS AGED 4 MONTHS THROUGH 6 YEARS					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Hepatitis B <sup>1</sup>	Birth	4 weeks	8 weeks (and at least 16 weeks after first dose)		
Rotavirus <sup>2</sup>	6 wks	4 weeks	4 weeks <sup>2</sup>		
Diphtheria, Tetanus, Pertussis <sup>3</sup>	6 wks	4 weeks	4 weeks	6 months	6 months <sup>3</sup>
<i>Haemophilus influenzae</i> type b <sup>4</sup>	6 wks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose) if first dose administered at age 12–14 months No further doses needed if first dose administered at age 15 months or older	4 weeks <sup>4</sup> if current age is younger than 12 months 8 weeks (as final dose) <sup>4</sup> if current age is 12 months or older and first dose administered at younger than age 12 months and second dose administered at younger than 15 months No further doses needed if previous dose administered at age 15 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months	
Pneumococcal <sup>5</sup>	6 wks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose for healthy children) if first dose administered at age 12 months or older or current age 24 through 59 months No further doses needed for healthy children if first dose administered at age 24 months or older	4 weeks if current age is younger than 12 months 8 weeks (as final dose for healthy children) if current age is 12 months or older No further doses needed for healthy children if previous dose administered at age 24 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age	
Inactivated Poliovirus <sup>6</sup>	6 wks	4 weeks	4 weeks	6 months <sup>6</sup>	
Measles, Mumps, Rubella <sup>7</sup>	12 mos	4 weeks			
Varicella <sup>8</sup>	12 mos	3 months			
Hepatitis A <sup>9</sup>	12 mos	6 months			
PERSONS AGED 7 THROUGH 18 YEARS					
Tetanus, Diphtheria/ Tetanus, Diphtheria, Pertussis <sup>10</sup>	7 yrs <sup>10</sup>	4 weeks	4 weeks if first dose administered at younger than age 12 months 6 months if first dose administered at 12 months or older	6 months if first dose administered at younger than age 12 months	
Human Papillomavirus <sup>11</sup>	9 yrs		Routine dosing intervals are recommended (females) <sup>11</sup>		
Hepatitis A <sup>9</sup>	12 mos	6 months			
Hepatitis B <sup>1</sup>	Birth	4 weeks	8 weeks (and at least 16 weeks after first dose)		
Inactivated Poliovirus <sup>6</sup>	6 wks	4 weeks	4 weeks <sup>6</sup>	6 months <sup>6</sup>	
Measles, Mumps, Rubella <sup>7</sup>	12 mos	4 weeks			
Varicella <sup>8</sup>	12 mos	3 months if person is younger than age 13 years 4 weeks if person is aged 13 years or older			

**1. Hepatitis B vaccine (HepB).**

- Administer the 3-dose series to those not previously vaccinated.
- The minimum age for the third dose of HepB is 24 weeks.
- A 2-dose series (separated by at least 4 months) of adult formulation Recombivax HB is licensed for children aged 11 through 15 years.

**2. Rotavirus vaccine (RV).**

- The maximum age for the first dose is 14 weeks 6 days. Vaccination should not be initiated for infants aged 15 weeks 0 days or older.
- The maximum age for the final dose in the series is 8 months 0 days.
- If Rotarix was administered for the first and second doses, a third dose is not indicated.

**3. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).**

- The fifth dose is not necessary if the fourth dose was administered at age 4 years or older.

**4. *Haemophilus influenzae* type b conjugate vaccine (Hib).**

- 1 dose of Hib vaccine should be considered for unvaccinated persons aged 5 years or older who have sickle cell disease, leukemia, or HIV infection, or who have had a splenectomy.
- If the first 2 doses were PRP-OMP (PedvaxHIB or Comvax), and administered at age 11 months or younger, the third (and final) dose should be administered at age 12 through 15 months and at least 8 weeks after the second dose.
- If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a final dose at age 12 through 15 months.

**5. Pneumococcal vaccine.**

- Administer 1 dose of 13-valent pneumococcal conjugate vaccine (PCV13) to all healthy children aged 24 through 59 months with any incomplete PCV schedule (PCV7 or PCV13).
- For children aged 24 through 71 months with underlying medical conditions, administer 1 dose of PCV13 if 3 doses of PCV were received previously or administer 2 doses of PCV13 at least 8 weeks apart if fewer than 3 doses of PCV were received previously.
- A single dose of PCV13 is recommended for certain children with underlying medical conditions through 18 years of age. See age-specific schedules for details.
- Administer pneumococcal polysaccharide vaccine (PPSV) to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant, at least 8 weeks after the last dose of PCV. A single revaccination should be administered after 5 years to children with functional or anatomic asplenia or an immunocompromising condition. See *MMWR* 2010;59(No. RR-11).

**6. Inactivated poliovirus vaccine (IPV).**

- The final dose in the series should be administered on or after the fourth birthday and at least 6 months following the previous dose.
- A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months following the previous dose.
- In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk for imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).

**7. Measles, mumps, and rubella vaccine (MMR).**

- Administer the second dose routinely at age 4 through 6 years. The minimum interval between the 2 doses of MMR is 4 weeks.

**8. Varicella vaccine.**

- Administer the second dose routinely at age 4 through 6 years.
- If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

**9. Hepatitis A vaccine (HepA).**

- HepA is recommended for children aged older than age 23 months who live in areas where vaccination programs target older children, or who are at increased risk for infection, or for whom immunity against hepatitis A is desired.

**10. Tetanus and diphtheria toxoids (Td) and tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap).**

- Doses of DTaP are counted as part of the Td/Tdap series.
- Tdap should be substituted for a single dose of Td in the catch-up series for children aged 7 through 10 years or as a booster for children aged 11 through 18 years; use Td for other doses.

**11. Human papillomavirus vaccine (HPV).**

- Administer the series to females at age 13 through 18 years if not previously vaccinated or have not completed the vaccine series.
- Quadrivalent HPV vaccine (HPV4) may be administered in a 3-dose series to males aged 9 through 18 years to reduce their likelihood of genital warts.
- Use recommended routine dosing intervals for series catch-up (i.e., the second and third doses should be administered at 1 to 2 and 6 months after the first dose). The minimum interval between the first and second doses is 4 weeks. The minimum interval between the second and third doses is 12 weeks, and the third dose should be administered at least 24 weeks after the first dose.

Information about reporting reactions after immunization is available online at <http://www.vaers.hhs.gov> or by telephone, 800-822-7967. Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for immunization, is available from the National Center for Immunization and Respiratory Diseases at <http://www.cdc.gov/vaccines> or telephone, 800-CDC-INFO (800-232-4636).

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## Standing Orders for Administering Rotavirus Vaccine to Infants

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**Purpose:** To reduce morbidity and mortality from rotavirus disease by vaccinating all infants who meet the criteria established by the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices.

**Policy:** Under these standing orders, eligible nurses and other healthcare professionals (e.g., pharmacists), where allowed by state law, may vaccinate infants who meet the criteria below.

### Procedure

1. Identify infants ages 6 weeks through 7 months (not for 8 months or older) who have not completed a rotavirus (RV) vaccination series.
2. Screen all patients for contraindications and precautions to rotavirus vaccine:
  - a. **Contraindications:**
    - a history of a serious reaction (e.g., anaphylaxis) after a previous dose of RV vaccine or to an RV vaccine component (Note: latex rubber is contained in the Rotarix oral applicator). For a list of vaccine components, go to [www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/excipient-table-2.pdf](http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/excipient-table-2.pdf).
    - a diagnosis of severe combined immunodeficiency (SCID)
  - b. **Precautions:**
    - altered immunocompetence
    - chronic gastrointestinal disease
    - history of intussusception
    - moderate or severe acute illness with or without fever
3. Provide all patients (parent/legal representative) with a copy of the most current federal Vaccine Information Statement (VIS). You must document, in the patient’s medical record or office log, the publication date of the VIS and the date it was given to the patient (parent/legal representative). Provide non-English speaking patients with a copy of the VIS in their native language, if available; these can be found at [www.immunize.org/vis](http://www.immunize.org/vis).
4. Provide routine vaccination with Rotarix at ages 2 and 4 months OR provide routine vaccination with RotaTeq at ages 2, 4, and 6 months. Administer the full dose (1 mL for Rotarix; 2 mL for RotaTeq) of vaccine by administering the entire contents of the dosing applicator of the liquid vaccine into the infant’s mouth toward the inner cheek until empty. Note that Rotarix needs to be reconstituted by the end user; RotaTeq does not.
5. For infants who have not received RV vaccine by age 2 months, give the first dose at the earliest opportunity but no later than age 14 weeks 6 days. Then schedule subsequent doses by observing minimum intervals of 4 weeks between the remaining one (if Rotarix) or two (if RotaTeq) dose(s) such that the final dose can be administered by age 8 months 0 days. Do not administer any RV vaccine beyond the age of 8 months 0 days.
6. Document each patient’s vaccine administration information and follow up in the following places:
  - a. **Medical chart:** Record the date the vaccine was administered, the manufacturer and lot number, the vaccination site and route, and the name and title of the person administering the vaccine. If vaccine was not given, record the reason(s) for non-receipt of the vaccine (e.g., medical contraindication, patient refusal).
  - b. **Personal immunization record card:** Record the date of vaccination and the name/location of the administering clinic.
7. Be prepared for management of a medical emergency related to the administration of vaccine by having a written emergency medical protocol available, as well as equipment and medications.
8. Report all adverse reactions to RV vaccine to the federal Vaccine Adverse Event Reporting System (VAERS) at [www.vaers.hhs.gov](http://www.vaers.hhs.gov) or (800) 822-7967. VAERS report forms are available at [www.vaers.hhs.gov](http://www.vaers.hhs.gov).

This policy and procedure shall remain in effect for all patients of the \_\_\_\_\_ until rescinded or until \_\_\_\_\_ (date).  
(name of practice or clinic)

Medical Director’s signature: \_\_\_\_\_ Effective date: \_\_\_\_\_

Patient name: \_\_\_\_\_ Date of birth: \_\_\_\_/\_\_\_\_/\_\_\_\_  
 (mo.) (day) (yr.)

# Screening Questionnaire for Child and Teen Immunization

**For parents/guardians:** The following questions will help us determine which vaccines your child may be given today. If you answer “yes” to any question, it does not necessarily mean your child should not be vaccinated. It just means additional questions must be asked. If a question is not clear, please ask your healthcare provider to explain it.

	Yes	No	Don't Know
1. Is the child sick today?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Does the child have allergies to medications, food, a vaccine component, or latex?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Has the child had a serious reaction to a vaccine in the past?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Has the child had a health problem with lung, heart, kidney or metabolic disease (e.g., diabetes), asthma, or a blood disorder? Is he/she on long-term aspirin therapy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. If the child to be vaccinated is between the ages of 2 and 4 years, has a healthcare provider told you that the child had wheezing or asthma in the past 12 months?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Has the child, a sibling, or a parent had a seizure; has the child had brain or other nervous system problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Does the child have cancer, leukemia, AIDS, or any other immune system problem?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. In the past 3 months, has the child taken cortisone, prednisone, other steroids, or anticancer drugs, or had radiation treatments?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. In the past year, has the child received a transfusion of blood or blood products, or been given immune (gamma) globulin or an antiviral drug?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Is the child/teen pregnant or is there a chance she could become pregnant during the next month?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Has the child received vaccinations in the past 4 weeks?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Form completed by: \_\_\_\_\_ Date: \_\_\_\_\_  
 Form reviewed by: \_\_\_\_\_ Date: \_\_\_\_\_

**Did you bring your child's immunization record card with you?**      **yes**     **no**

It is important to have a personal record of your child's vaccinations. If you don't have a personal record, ask the child's healthcare provider to give you one with all your child's vaccinations on it. Keep this record in a safe place and bring it with you every time you seek medical care for your child. Your child will need this important document for the rest of his or her life to enter day care or school, for employment, or for international travel.



# Information for Health Professionals about the Screening Questionnaire for Child & Teen Immunization

Are you interested in knowing why we included a certain question on the Screening Questionnaire? If so, read the information below. If you want to find out even more, consult the references listed at the bottom of this page.

## 1. Is the child sick today? [all vaccines]

There is no evidence that acute illness reduces vaccine efficacy or increases vaccine adverse events (1, 2). However, as a precaution with moderate or severe acute illness, all vaccines should be delayed until the illness has improved. Mild illnesses (such as otitis media, upper respiratory infections, and diarrhea) are NOT contraindications to vaccination. Do not withhold vaccination if a person is taking antibiotics.

## 2. Does the child have allergies to medications, food, a vaccine component, or latex? [all vaccines]

History of anaphylactic reaction such as hives (urticaria), wheezing or difficulty breathing, or circulatory collapse or shock (not fainting) to a vaccine component or latex is a contraindication to some vaccines. For example, if a person experiences anaphylaxis after eating eggs, do not administer influenza vaccine, or if a person has anaphylaxis after eating gelatin, do not administer measles-mumps-rubella (MMR), MMR+varicella (MMRV), or varicella (VAR) vaccine. A local reaction is not a contraindication. For a table of vaccines supplied in vials or syringes that contain latex, go to [www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf](http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf). For an extensive table of vaccine components, see reference 3.

## 3. Has the child had a serious reaction to a vaccine in the past? [all vaccines]

History of anaphylactic reaction (see question 2) to a previous dose of vaccine or vaccine component is a contraindication for subsequent doses (1). History of encephalopathy within 7 days following DTP/DTaP is a contraindication for further doses of pertussis-containing vaccine. Precautions to DTaP (not Tdap) include the following: (a) seizure within 3 days of a dose, (b) pale or limp episode or collapse within 48 hours of a dose, (c) continuous crying for 3 or more hours within 48 hours of a dose, and (d) fever of 105°F (40°C) within 48 hours of a previous dose. There are other adverse events that might have occurred following vaccination that constitute contraindications or precautions to future doses. Under normal circumstances, vaccines are deferred when a precaution is present. However, situations may arise when the benefit outweighs the risk (e.g., during a community pertussis outbreak).

## 4. Has the child had a health problem with lung, heart, kidney, or metabolic disease (e.g., diabetes), asthma, or a blood disorder? Is he/she on long-term aspirin therapy? [LAIV]

Children with any of the health conditions listed above should not be given the intranasal, live attenuated influenza vaccine (LAIV). These children should be vaccinated with the injectable influenza vaccine.

## 5. If the child to be vaccinated is between the ages of 2 and 4 years, has a healthcare provider told you that the child had wheezing or asthma in the past 12 months? [LAIV]

Children who have had a wheezing episode within the past 12 months should not be given the live attenuated influenza vaccine. Instead, these children should be given the inactivated influenza vaccine.

## 6. Has the child, a sibling, or a parent had a seizure; has the child had brain or other nervous system problem? [DTaP, Td, Tdap, TIV, LAIV, MMRV]

DTaP and Tdap are contraindicated in children who have a history of encephalopathy within 7 days following DTP/DTaP. An unstable progressive neurologic problem is a precaution to the use of DTaP and Tdap, and a progressive neurologic disorder in a teen is a precaution to the use of Td. For children with stable neurologic disorders (including seizures) unrelated to vaccination, or for children with a family history of seizures, vaccinate as usual (*exception*: children with a personal or family [i.e., parent or sibling] history of seizures generally should not be vaccinated with MMRV; they should receive separate MMR and VAR vaccines). A history of Guillain-Barré syndrome (GBS) is a consideration with the following: 1) Td/Tdap: if GBS has occurred within 6 weeks of a tetanus-containing vaccine and decision is made to continue vaccination, give age-appropriate Tdap instead of Td if no history of prior Tdap; 2) Influenza vaccine (TIV or LAIV): if GBS has occurred within 6 weeks of a prior influenza vaccination, vaccinate with TIV if at high risk for severe influenza complications.

## 7. Does the child have cancer, leukemia, AIDS, or any other immune system problem? [LAIV, MMR, MMRV, RV, VAR]

Live virus vaccines (e.g., MMR, MMRV, varicella, rotavirus, and the intranasal live, attenuated influenza vaccine [LAIV]) are usually contraindicated in immunocompromised children. However, there are exceptions. For example, MMR is recommended for asymptomatic HIV-infected children who do not have evidence of severe immunosuppression. Likewise, varicella vaccine should be considered for HIV-infected children with age-specific CD4+ T-lymphocyte percentage at 15% or greater and may be considered for children age 8 years and older with CD4+ T-lymphocyte counts of greater than or equal to 200 cells/ $\mu$ L. Immunosuppressed children should not receive LAIV. Infants who have been diagnosed with severe combined immunodeficiency (SCID) should not be given a live virus vaccine, including rotavirus (RV) vaccine. For details, consult the ACIP recommendations (4, 5, 6).

## 8. In the past 3 months, has the child taken cortisone, prednisone, other steroids, or anticancer drugs, or had radiation treatments? [LAIV, MMR, MMRV, VAR]

Live virus vaccines (e.g., MMR, MMRV, varicella, LAIV) should be postponed until after chemotherapy or long-term high-dose steroid therapy has ended. For details and length of time to postpone, consult the ACIP statement (1). To find specific vaccination schedules for stem cell transplant (bone marrow transplant) patients, see reference 7. LAIV can be given only to healthy non-pregnant individuals age 2–49 years.

## 9. In the past year, has the child received a transfusion of blood or blood products, or been given immune (gamma) globulin or an antiviral drug? [LAIV, MMR, MMRV, VAR]

Certain live virus vaccines (e.g., LAIV, MMR, MMRV, varicella) may need to be deferred, depending on several variables. Consult the most current ACIP recommendations or the current *Red Book* for the most current information on intervals between antiviral drugs, immune globulin or blood product administration and live virus vaccines (1, 2).

## 10. Is the child/teen pregnant or is there a chance she could become pregnant during the next month? [LAIV, MMR, MMRV, VAR]

Live virus vaccines (e.g., MMR, MMRV, varicella, LAIV) are contraindicated one month before and during pregnancy because of the theoretical risk of virus transmission to the fetus (1, 6). Sexually active young women who receive a live virus vaccine should be instructed to practice careful contraception for one month following receipt of the vaccine (5, 8). On theoretical grounds, inactivated poliovirus vaccine should not be given during pregnancy; however, it may be given if risk of disease is imminent (e.g., travel to endemic areas) and immediate protection is needed. Use of Td or Tdap is not contraindicated in pregnancy. At the provider's discretion, either vaccine may be administered during the 2nd or 3rd trimester (9).

## 11. Has the child received vaccinations in the past 4 weeks? [LAIV, MMR, MMRV, VAR, yellow fever]

If the child was given either live, attenuated influenza vaccine (LAIV) or an injectable live virus vaccine (e.g., MMR, MMRV, varicella, yellow fever) in the past 4 weeks, they should wait 28 days before receiving another vaccination of this type. Inactivated vaccines may be given at the same time or at any spacing interval.

### References:

1. CDC. General recommendations on immunization, at [www.cdc.gov/vaccines/pubs/acip-list.htm](http://www.cdc.gov/vaccines/pubs/acip-list.htm).
2. AAP. *Red Book: Report of the Committee on Infectious Diseases* at [www.aapredbook.org](http://www.aapredbook.org).
3. Table of Vaccine Components: [www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/exipient-table-2.pdf](http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/exipient-table-2.pdf).
4. CDC. Measles, mumps, and rubella—vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps. *MMWR* 1998; 47 (RR-8).
5. CDC. Prevention of varicella: Recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2007; 56 (RR-4).
6. CDC. Prevention and Control of Influenza—Recommendations of ACIP at [www.cdc.gov/flu/professionals/vaccination/](http://www.cdc.gov/flu/professionals/vaccination/).
7. CDC. Excerpt from Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients, *MMWR* 2000; 49 (RR-10), [www.cdc.gov/vaccines/pubs/down-loads/b\\_hstc-recs.pdf](http://www.cdc.gov/vaccines/pubs/down-loads/b_hstc-recs.pdf).
8. CDC. Notice to readers: Revised ACIP recommendation for avoiding pregnancy after receiving a rubella-containing vaccine. *MMWR* 2001; 50 (49).
9. CDC. Prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants: Recommendations of the ACIP. *MMWR* 2008; 57 (RR-4).



**VACCINE ADVERSE EVENT REPORTING SYSTEM**

24 Hour Toll-Free Information 1-800-822-7967  
P.O. Box 1100, Rockville, MD 20849-1100

**PATIENT IDENTITY KEPT CONFIDENTIAL**

*For CDC/FDA Use Only*

VAERS Number \_\_\_\_\_

Date Received \_\_\_\_\_

Patient Name: _____ Last                      First                      M.I. Address _____ _____ _____ City                      State                      Zip Telephone no. (____) _____	Vaccine administered by (Name): _____ Responsible Physician _____ Facility Name/Address _____ _____ _____ City                      State                      Zip Telephone no. (____) _____	Form completed by (Name): _____ Relation <input type="checkbox"/> Vaccine Provider <input type="checkbox"/> Patient/Parent to Patient <input type="checkbox"/> Manufacturer <input type="checkbox"/> Other Address (if different from patient or provider) _____ _____ _____ City                      State                      Zip Telephone no. (____) _____
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1. State	2. County where administered	3. Date of birth ____/____/____ mm dd yy	4. Patient age	5. Sex <input type="checkbox"/> M <input type="checkbox"/> F	6. Date form completed ____/____/____ mm dd yy
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7. Describe adverse events(s) (symptoms, signs, time course) and treatment, if any	8. Check all appropriate: <input type="checkbox"/> Patient died (date ____/____/____) <input type="checkbox"/> Life threatening illness <input type="checkbox"/> Required emergency room/doctor visit <input type="checkbox"/> Required hospitalization (____days) <input type="checkbox"/> Resulted in prolongation of hospitalization <input type="checkbox"/> Resulted in permanent disability <input type="checkbox"/> None of the above
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9. Patient recovered <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> UNKNOWN	10. Date of vaccination ____/____/____ mm dd yy Time _____ AM PM	11. Adverse event onset ____/____/____ mm dd yy Time _____ AM PM
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13. Enter all vaccines given on date listed in no. 10					
Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous Doses	
a. _____	_____	_____	_____	_____	
b. _____	_____	_____	_____	_____	
c. _____	_____	_____	_____	_____	
d. _____	_____	_____	_____	_____	

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10						
Vaccine (type)	Manufacturer	Lot number	Route/Site	No. Previous doses	Date given	
a. _____	_____	_____	_____	_____	_____	
b. _____	_____	_____	_____	_____	_____	

15. Vaccinated at: <input type="checkbox"/> Private doctor's office/hospital <input type="checkbox"/> Public health clinic/hospital <input type="checkbox"/> Military clinic/hospital <input type="checkbox"/> Other/unknown	16. Vaccine purchased with: <input type="checkbox"/> Private funds <input type="checkbox"/> Public funds <input type="checkbox"/> Military funds <input type="checkbox"/> Other/unknown	17. Other medications
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18. Illness at time of vaccination (specify)	19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify)
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20. Have you reported this adverse event previously? <input type="checkbox"/> No <input type="checkbox"/> To health department <input type="checkbox"/> To doctor <input type="checkbox"/> To manufacturer	<b>Only for children 5 and under</b>	
	22. Birth weight _____ lb. _____ oz.	23. No. of brothers and sisters

21. Adverse event following prior vaccination (check all applicable, specify)	<b>Only for reports submitted by manufacturer/immunization project</b>	
<input type="checkbox"/> In patient <input type="checkbox"/> In brother or sister	Adverse Event _____ Onset Age _____ Type Vaccine _____ Dose no. in series _____	24. Mfr./imm. proj. report no.
	26. 15 day report? <input type="checkbox"/> Yes <input type="checkbox"/> No	25. Date received by mfr./imm.proj.
		27. Report type <input type="checkbox"/> Initial <input type="checkbox"/> Follow-Up

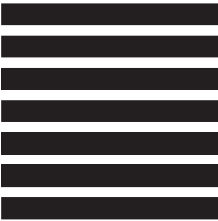
Health care providers and manufacturers are required by law (42 USC 300aa-25) to report reactions to vaccines listed in the Table of Reportable Events Following Immunization. Reports for reactions to other vaccines are voluntary except when required as a condition of immunization grant awards.



NO POSTAGE  
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OR APO/FPO

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**VAERS**  
P.O. Box 1100  
Rockville MD 20849-1100



**DIRECTIONS FOR COMPLETING FORM**

(Additional pages may be attached if more space is needed.)

**GENERAL**

- Use a separate form for each patient. Complete the form to the best of your abilities. Items 3, 4, 7, 8, 10, 11, and 13 are considered essential and should be completed whenever possible. Parents/Guardians may need to consult the facility where the vaccine was administered for some of the information (such as manufacturer, lot number or laboratory data.)
- Refer to the Reportable Events Table (RET) for events mandated for reporting by law. Reporting for other serious events felt to be related but not on the RET is encouraged.
- Health care providers other than the vaccine administrator (VA) treating a patient for a suspected adverse event should notify the VA and provide the information about the adverse event to allow the VA to complete the form to meet the VA's legal responsibility.
- These data will be used to increase understanding of adverse events following vaccination and will become part of CDC Privacy Act System 09-20-0136, "Epidemiologic Studies and Surveillance of Disease Problems". Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.
- Postage will be paid by addressee. Forms may be photocopied (must be front & back on same sheet).

**SPECIFIC INSTRUCTIONS**

Form Completed By: To be used by parents/guardians, vaccine manufacturers/distributors, vaccine administrators, and/or the person completing the form on behalf of the patient or the health professional who administered the vaccine.

- Item 7: Describe the suspected adverse event. Such things as temperature, local and general signs and symptoms, time course, duration of symptoms, diagnosis, treatment and recovery should be noted.
- Item 9: Check "YES" if the patient's health condition is the same as it was prior to the vaccine, "NO" if the patient has not returned to the pre-vaccination state of health, or "UNKNOWN" if the patient's condition is not known.
- Item 10: Give dates and times as specifically as you can remember. If you do not know the exact time, please
- and 11: indicate "AM" or "PM" when possible if this information is known. If more than one adverse event, give the onset date and time for the most serious event.
- Item 12: Include "negative" or "normal" results of any relevant tests performed as well as abnormal findings.
- Item 13: List ONLY those vaccines given on the day listed in Item 10.
- Item 14: List any other vaccines that the patient received within 4 weeks prior to the date listed in Item 10.
- Item 16: This section refers to how the person who gave the vaccine purchased it, not to the patient's insurance.
- Item 17: List any prescription or non-prescription medications the patient was taking when the vaccine(s) was given.
- Item 18: List any short term illnesses the patient had on the date the vaccine(s) was given (i.e., cold, flu, ear infection).
- Item 19: List any pre-existing physician-diagnosed allergies, birth defects, medical conditions (including developmental and/or neurologic disorders) for the patient.
- Item 21: List any suspected adverse events the patient, or the patient's brothers or sisters, may have had to previous vaccinations. If more than one brother or sister, or if the patient has reacted to more than one prior vaccine, use additional pages to explain completely. For the onset age of a patient, provide the age in months if less than two years old.
- Item 26: This space is for manufacturers' use only.