3. Timing and Spacing of Immunobiologics

Updates

Major changes to the best practice guidance for timing and spacing of immunobiologics include 1) guidance for simultaneous vaccination in the context of a risk for febrile seizures and 2) clarification of the use of the grace period between doses of MMRV.

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 generally recommended for members of the youngest age group at risk for experiencing the disease for which vaccine efficacy and safety have been demonstrated.

Vaccines can be divided into two general categories: live or non-live. Most live vaccines used in the United States are "live attenuated", meaning that the microbe in the vaccine is alive but has been weakened (attenuated) through serial passage in cultures, or produced through genetic technology. One live vaccine licensed for use in the United States (oral adenovirus vaccine) is not attenuated. Live vaccines must replicate in order to induce an immune response. Several factors can interfere with replication, and these are a driving factor in the principles of timing and spacing of live vaccine. These principles will be discussed later in this chapter. Non-live vaccines can include whole or fractional vaccines produced by inactivating (killing) the microbe; or fractional vaccines such as recombinant vaccines, produced through genetic technologies. Also included under the category of non-live vaccines are toxoids, which generate an antibody response to toxins produced by a microbe rather than to the microbe itself. Several recently developed non-live vaccines do not contain antigen but employ RNA or DNA to instruct the recipient's own cellular mechanism to generate antigenic material. Some vaccines described as "live attenuated" (e.g., Jynneos Smallpox/Monkeypox vaccine) do not replicate and for the purposes of timing and spacing recommendations behave like non-live vaccines.

Certain vaccines available outside the U.S. might be categorized differently as to vaccine type (e.g., live attenuated JE vaccine and live oral polio vaccine) (Table 3-1).

Tetanus and diphtheria toxoids require booster doses to maintain protective antibody concentrations (1). 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 duration of protection. Conjugation with a protein carrier improves the effectiveness of polysaccharide vaccines by inducing T-lymphocyte–dependent immunologic function (2). Many vaccines that stimulate both cell-mediated immunity and neutralizing antibodies (e.g., live, attenuated virus vaccines) can usually induce prolonged immunity, even if antibody titers decline over time (3). 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 vaccines are protected after a single dose. However, because a limited proportion (5%-20%) 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 (4).

Of those who do not respond to the first dose of the measles component of MMR or varicella vaccine, 97%-99% respond to a second dose (5,6).

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 www.cdc.gov/vaccines/schedules/hcp/index.html.

Spacing of Multiple Doses of the Same Antigen

Vaccination providers should adhere to recommended vaccination schedules (Table 3-2). Administration at recommended ages and in accordance with recommended intervals between doses of multidose antigens provides 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 (*7*). The accelerated or minimum intervals and ages for scheduling catch-up vaccinations are available at www.cdc.gov/vaccines/schedules/hcp/index.html. Vaccine doses should not be administered at intervals less than these minimum intervals or at an age that is younger than the minimum age.*[(a)]

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 3-2). 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 than the minimum interval or age is unlikely to have a substantially negative effect on the immune response to that dose. Known as the "grace period", vaccine doses administered ≤4 days before the minimum interval or age are considered valid; however, local or state mandates might supersede this 4-day guideline (7).(b) (Day 1 is the day before the day that marks the minimum age or minimum interval for a vaccine.) The scenario most applicable to the grace period is a visit to a provider several days prior to the date indicated by the minimum interval, such as for a mild illness. Follow-up is unlikely soon after or even for a longer period of time following this mild illness visit; this therefore raises the question of whether vaccines be administered during the mild illness visit to avoid missed opportunities to vaccinate. Because of the unique schedule for rabies vaccine and the accelerated Twinrix schedule the 4-day guideline does not apply to this vaccine (*8, personal communication, Hepatitis A subject matter experts*). Doses of any vaccine administered ≥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 3-2). 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 ≥4 weeks after the invalid dose (in this case, the second) (7). The repeat dose is counted as the valid second dose. If the first and second doses of hepatitis A vaccine were administered less than 6 months apart, the second dose is invalid and should be repeated 6 months after the invalid second dose (7). However, if this repeat dose (the third dose) is administered anytime 6 months or more after the first dose, the series can be considered complete. If the minimum interval between the second and third dose of hepatitis B vaccine is violated, or if the minimum age of the third dose is violated, the third dose of hepatitis B vaccine is invalid. The repeat dose can be administered as early as 8 weeks after the 2nd valid dose as long as the dose is also after 24 weeks of age and 16 weeks after the 1st dose. (9)

If the first dose in a series is given ≥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 (7). If the vaccine is a live vaccine, ensuring that a minimum interval of 28 days has elapsed from the invalid dose is recommended (7). 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], tetanus toxoid) produce increased rates of local or systemic reactions in certain recipients when administered more frequently than recommended (10, 11).

Careful record keeping, maintenance 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 (12).

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 (13). 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 (14). Simultaneous administration also is critical when preparing for foreign travel in the near future 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 non-live vaccines has produced seroconversion rates and rates for adverse reactions similar to those observed when the vaccines are administered separately (12, 15-17). 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 (7). MMR and varicella vaccine can be administered simultaneously (7). Live, attenuated influenza vaccine (LAIV) does not interfere with the immune response to MMR or varicella vaccines administered at the same visit (18). 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 (19).

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 (20). Simultaneous administration of PPSV23 and inactivated influenza vaccine is recommended for all persons for whom both vaccines are indicated. Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) and inactivated influenza vaccine (IIV) can be administered simultaneously (21). Hepatitis B vaccine administered with yellow fever vaccine is as safe and immunogenic as when these vaccines are administered separately (22). Measles and yellow fever vaccines have been administered safely at the same visit and without reduction of immunogenicity of either component (23,24).

During the 2010-2011 influenza season, surveillance systems detected safety signals for febrile seizures in young children following IIV and PCV13 vaccines (25). CDC studied the health-care visit records of more than 200,000 vaccinated children ages 6 months through 59 months through the Vaccine Safety Datalink Project during the 2010-2011 influenza season. The analyses found that febrile seizures following IIV and PCV13 vaccines given to this age group were rare, but did occur at higher than expected rates. The risk for febrile seizures peaked in children age 16 months and were more common when the 2 vaccines were given during the same health-care visit. In this group, about one additional febrile seizure occurred among every 2,200 children vaccinated. After assessing benefits and risks, ACIP continues to recommend IIV and PCV13 be given concomitantly if both are recommended (25,26).

There are 2 exceptions to the recommendation that vaccines should be administered simultaneously. In persons with anatomic or functional asplenia and/or HIV infection, quadrivalent meningococcal conjugate vaccine (MCV4)-D (MenACWY-D, Menactra) and pneumococcal conjugate vaccine (PCV)13 (PCV13, Prevnar 13) should not be administered simultaneously (27). This is based on immunogenicity studies that showed reduced antibody concentrations for 3 serotypes of pneumococcus (subtypes 4, 6B, and 18C) when PCV7 was administered simultaneously with MenACWY-D. For persons with anatomic or functional asplenia and/or HIV, PCV13 should be administered first and MenACWY-D 4 weeks later.

In patients recommended to receive both PCV13 and PPSV23, the 2 vaccines should not be administered simultaneously (28). PCV13 should be administered first. If PPSV23 has been administered first, PCV13 should be administered no earlier than 8 weeks later in children 6-18 years, and one year later in adults 19 years and older. Immunogenicity studies evaluating responses to PCV13 and PPSV23 administered in series showed a better immune response when PCV13 was administered first. An evaluation of immune response after a second pneumococcal vaccination administered 1 year after the initial study doses showed that subjects who received PPSV23 as the initial study dose had lower antibody responses after subsequent administration of PCV13 than those who had received PCV13 as the initial dose followed by a dose of PPSV23, regardless of the level of the initial response to PPSV23 (29,30).

Depending on which vaccines are administered during the first year of life, a child might receive up to 9 injections at the 12- through 15-month visit (MMR, varicella, Hib, PCV13, pediatric diphtheria and tetanus toxoids and acellular pertussis [DTaP], inactivated poliovirus [IPV], hepatitis A, hepatitis B [HepB], 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 (31) 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 PCV13 have protection against Hib, diphtheria, pertussis, tetanus, and pneumococcus, which lasts throughout infancy (2, 32). The third (PRP-OMP) or fourth (PRP-T) dose of the Hib series and the fourth doses of DTaP and PCV13 are critical in boosting antibody titer and ensuring continued protection (2, 33-35). 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 (33). 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 (36). 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. Recommended spacing of doses should be maintained (Table 3-2).

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 (29,37,38). Studies have demonstrated that parents and providers might be uncomfortable with multiple injections during single visits (39-41). Potential advantages of combination vaccines include 1) improved vaccine coverage rates (42), 2) timely vaccination coverage for children who are behind in the schedule (43, 44), 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 fever that occurs with the combination MMRV vaccine and combination DTaP-HepB-IPV vaccine (45,46); 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 pathogen coverage if the combination product covers fewer types of one particular vaccine-preventable disease-causing agent (47); 4) extra doses of certain antigens in the combination product (e.g., a provider who administers 4 doses of DTaP-HepB-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 (48).

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 3-3) (49-55). In the future, combination vaccines might include increasing numbers of components in different arrays to protect against these and other diseases. The use of a combination vaccine generally is preferred over separate injections of the equivalent component vaccines (56). Considerations should include provider assessment,(c) 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 (see Contraindications and Precautions) (45).

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 (56). 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 2 combination vaccines, (DTaP-IPV/Hib vaccine, marketed as Pentacel, and Hib-MenCY, marketed as MenHibrix) 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 (38).

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-IPV/Hib, DtaP-HepB-IPV, and future 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 (35).

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 (57). 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 (29, 38), 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. The National Pediatric Vaccine Stockpile exists to offset supply challenges (58).

Extra Doses of Vaccine Antigens

Administering extra antigens contained in a combination vaccine should be avoided in most situations (56). 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 (59,60). 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) (20, 33, 61).

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 non-live 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 (56). 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 severe local reactions (21, 34). *Examples o*f such vaccines include DtaP, DT (for children), and Td (for adolescents and adults). 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

Protein conjugates used in Hib conjugate vaccines produced in the United States include tetanus toxoid (in PRP-T) which is also used as a component of DtaP and Tdap vaccines (21). Simultaneous or sequential vaccination with Hib and these tetanus-toxoid containing vaccines is recommended when both are indicated (56). MCV4 and PCV13 both contain diphtheria-toxoid conjugates. There has been concern about simultaneous administration of vaccines containing like conjugates. One brand of MCV4, MenACWY-D (Menactra), demonstrates reduced immunogenicity of the antibody response to Streptococcal pneumonia strains when administered simultaneously with PCV13 compared with separate administration. It is recommended to space these vaccines by 28 days in a person with anatomic asplenia (47). Simultaneous or sequential vaccination of MCV4-CRM (Menveo), PCV13, and Tdap (34, 62), all of which contain diphtheria toxoid, is not associated with reduced immunogenicity or increase in local adverse events.

Nonsimultaneous Administration

There is no evidence that non-live vaccines interfere with the immune response to other non-live vaccines or to live vaccines. Any non-live vaccine can be administered either simultaneously or at any time before or after a different non-live vaccine or live vaccine (Table 3-4). The 2 exceptions, as mentioned above, are a 4-week interval between PCV13 and MenACWY-D in a person with anatomic asplenia and the separation of doses between PCV13 and PPSV23 (6-12 months recommended for non-high risk, 8 week minimum) if PCV13 is given first, 8 weeks in children 6-18 years, and 1 year minimum in adults 19 years and older if PPSV23 is given first (27).

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 (63,64). In a study conducted in 2 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 (65). Another study determined that the response to yellow fever vaccine is not affected by monovalent measles vaccine administered 1-27 days earlier (23).

The effect of nonsimultaneous administration of rubella, mumps, varicella, and yellow fever vaccines is unknown.

Two or more injectable or nasally administered live vaccines not administered on the same day should be separated by at least 4 weeks (Table 3-4), to minimize the potential risk for interference. If 2 such vaccines are separated by <4 weeks, the second vaccine administered should not be counted and the dose should be repeated at least 4 weeks later. On the day a live injectable or intranasal vaccine will be administered, providers should ensure that no live injectable or intranasal vaccine was given in the previous 28 days.

The 4-day grace period discussed earlier, which may be used to shorten the minimum interval between doses of the same vaccine, should not be applied to this 4-week interval between 2 different live vaccines (56). Confusion about this prohibition may arise when 2 live vaccines whose intervals are identical are administered simultaneously. For example, if MMR and varicella vaccines are administered on the same day, the second dose of each vaccine could come due 4 weeks later (depending on the patient's age). If either vaccine had been given alone at both time points, the 4-day grace period could be applied to the second dose. But in this situation the live vaccine rule prevents the grace period from being applied to the second dose of either vaccine, because Varicella-2, if administered earlier than 4 weeks, could potentially be affected by MMR1, and likewise MMR2 could be affected by Varicella-1. Note that this prohibition also applies if the combination MMRV is used rather than individual MMR and varicella vaccines.

The oral vaccines Ty21a typhoid vaccine and rotavirus can be administered simultaneously with or at any interval before or after other live vaccines (injectable or intranasal) if indicated (66).

Spacing of Vaccines and Antibody-Containing Products

Live Vaccines

Ty21a typhoid, yellow fever, LAIV, and rotavirus vaccines may be administered at any time before, concurrent with, or after administration of any antibody-containing preparation such as immune globulin, hyperimmune globulin, or intravenous immune globulin (IGIV) (67).

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 ≥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 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 (68,70). Therefore, after an antibody-containing product is received, live vaccines (other than Ty21a typhoid, yellow fever, LAIV, and rotavirus vaccines) should be delayed until the passive antibody has degraded (Table 3-5). In circumstances where there is high-risk of vaccine-preventable disease it is acceptable to administer a dose of vaccine prior to completion of this interval. If a dose of injectable live-virus vaccine (other than yellow fever) is administered after an antibody-containing product but at an interval shorter than recommended in this report, the vaccine dose should be repeated. The repeat dose should be administered at the interval indicated for the antibody-containing product, after the invalid dose of vaccine (Table 3-6). Immunogenicity and safety of dengue vaccine after administration of intravenous immunoglobulin (IGIV) and other immunoglobulin containing products has not been studied. Clinicians considering dengue vaccine for persons who recently received blood products (including IGIV) or other immunoglobulin containing products should delay pre-vaccination testing and administration of vaccine doses by 12 months.

Although passively acquired antibodies can interfere with the response to rubella vaccine, the low dose of anti-Rho(D) globulin or any other blood product administered to postpartum women have not been demonstrated to reduce the response to the RA27/3 strain rubella vaccine (71). Congenital rubella syndrome and congenital varicella are conditions with considerable morbidity and represent a true risk in future pregnancies. Because of the importance of rubella and varicella immunity among women of child-bearing age (4, 72), 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.

Any reduction in immunity caused by anti-Rho(D) globulin or other blood products is outweighed by the opportunity to generate immunity. These women should be vaccinated immediately after giving birth and, if possible, tested ≥3 months later to ensure immunity to rubella and, if appropriate, to measles (2). Measles and rubella serologies have a low false-positive rate and are therefore acceptable for use in this limited postpartum context.

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 3-5 and 3-6) unless serologic testing indicates a protective antibody response (7).

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 non-live vaccines.

Non-live Vaccines

Antibody-containing products interact less with non-live vaccines compared with live vaccines (73). Therefore, administering non-live vaccines 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 3-5). The vaccine or toxoid and antibody preparation should be administered at different sites using the standard recommended dose.

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 (74-77).

All brands of Hib conjugate, hepatitis B,[(d)] hepatitis A, rotavirus,[(e)] 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 in the primary series, the higher number of doses is recommended for series completion (e.g., doses of either rotavirus or Hib vaccine). For Hib vaccines, any monovalent or combination conjugate vaccine is acceptable for the booster dose of the series, if only one product was used for the primary series (56).

Limited data are available about the safety, immunogenicity, and efficacy of using acellular pertussis (i.e., 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 (78). 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 (56). 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 (56). For a child who needs 2 doses of influenza vaccine (IIV or LAIV), it is preferable to use the same type of vaccine for both doses. However, if the child is eligible for either IIV or LAIV, and the type of vaccine used for the first dose is not available, either vaccine can be used for the second dose (56). In a postlicensure study, meningococcal conjugate vaccines from different manufacturers were evaluated for successive doses of meningococcal conjugate vaccine. Persistence of antibodies were studied in recipients of MCV4-CRM after previous receipt of either MCV4-CRM or MenACWY-D.

The percentage of persons with protective titers were the same for all serogroups.

No data exist on the use of MenACWY-D after MCV4-CRM. Health-care providers should use every opportunity to provide a dose when indicated, regardless of the vaccine brand used for the previous dose or doses. For vaccines in general, vaccination should not be deferred because the brand used for previous doses is not available or is unknown (29, 79).

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 some exceptions (e.g. 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 (7).

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 PPSV23, providers should only accept written, dated records as evidence of vaccination; self-reported doses of influenza vaccine and PPSV23 are acceptable (61,80). The rationale for acceptance for influenza vaccine is that the time period of recall is one year or less, making it very likely that correct recall will occur. The rationale for acceptance for PPSV23 is high frequency of vaccination leads to an increased rate of local reactions due to the reactogenicity of this vaccine. 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. While serology should generally NOT be performed to ascertain evidence of immunity, 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. An exception to the prohibition on serologic testing is dengue. Laboratory testing to ascertain immunity to dengue (of which serology is one option) must be performed prior to vaccination, and only those individuals who are positive should be vaccinated.

[a] 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 (*81*).

[b] 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.

[c] Provider assessment should include number of injections, vaccine availability, likelihood of improved coverage, likelihood of patient return, and storage and cost considerations.

[d] 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 the schedule. Engerix-B (GlaxoSmithKline) is not approved by FDA for this schedule.

[e] Based on expert opinion.

TABLE 3-1 Types of Vaccines

Vaccine Category	Examples
Live	Oral adenovirus vaccine*
Live attenuated	ACAM2000 smallpox vaccine Bacille Calmette Guerin (BCG) vaccine Dengue vaccine Ebola vector vaccine Live attenuated influenza vaccine (LAIV) Live oral typhoid vaccine (Ty21a) Measles-mumps-rubella – containing (MMR, MMRV) Oral cholera vaccine Rotavirus vaccines (RV1, RV5) Varicella (Var) vaccine Yellow Fever vaccine
Non-live	Anthrax vaccine COVID-19 vaccines (Pfizer, Moderna, Novavax) *Haemophilus influenzae* type b (Hib) vaccines Hepatitis A (HepA) vaccines Hepatitis B (HepB) vaccines Human papillomavirus (HPV) vaccines Inactivated poliovirus vaccine (IPV) Inactivated typhoid vaccine (Typhim Vi) Influenza vaccines (IIV4, RIV4) Japanese Encephalitis Vaccine (JEV) Meningococcal conjugate (MenACWY) vaccine Pneumococcal conjugate vaccines (PCV13, PCV20, PCV15) Pneumococcal polysaccharide vaccine (PPSV23) Rabies vaccine Recombinant zoster vaccine (RZV) Respiratory syncytial virus vaccine (RSV) Serogroup B meningococcal (MenB) vaccines (MenB-FHbp, MenB-4C) Tetanus-toxoid, diphtheria-toxoid, or pertussis-containing vaccines (DTaP, Tdap, DT, Td, DTaP-HepB-IPV, DTaP-IPV/Hib, DTaP-IPV, DTaP-IPV-Hib-HepB)†
Non-replicating§	COVID-19 vaccine (Janssen) Jynneos smallpox/monkeypox vaccine

* Oral adenovirus vaccine is used primarily in the military for prevention of adenovirus infection. It should not be confused with Janssen COVID-19 vaccine which is used for the prevention of SARS-CoV-2 infection

† The tetanus-toxoid components of these vaccines are toxoids, not vaccines.

§ These vaccines do not replicate and therefore behave like non-live vaccines.

TABLE 3-2. Recommended and minimum ages and intervals between vaccine doses[a],[b],[c],[d]

Known as the "grace period", vaccine doses administered ≤4 days before the minimum interval or age are considered valid; however, local or state mandates might supersede this 4-day guideline

"3 calendar months" (or fewer) can be converted into weeks per the formula "1 month = 4 weeks"

Vaccine and dose number	Recommended age for this dose	Minimum age for this dose	Recommended interval to next dose	Minimum interval to next dose
DEN4CYD-1	9—16 years	9 years	6 months	5 months after age at 1st dose
DEN4CYD-2	9—16 years	9 years + 5 months	6 months	5 months after age at second dose
DEN4CYD-3	9—16 years	9 years +10 months	—	—
DTaP-1[e]	2 months	6 weeks	8 weeks	4 weeks
DTaP-2	4 months	10 weeks	8 weeks	4 weeks
DTaP-3	6 months	14 weeks	6-12 months[f]	6 months[f]
DTaP-4	15-18 months	15 months[f]	3 years	6 months
DTaP-5[g]	4-6 years	4 years	—	—
HepA-1[e]	12-23 months	12 months	6-18 months	6 months
HepA-2	≥18 months	18 months	—	—
HepB-1[h]	Birth	Birth	4 weeks-4 months	4 weeks
HepB-2	1-2 months	4 weeks	8 weeks-17 months	8 weeks
HepB-3[i]	6-18 months	24 weeks	—	—
Hib-1[j]	2 months	6 weeks	8 weeks	4 weeks
Hib-2	4 months	10 weeks	8 weeks	4 weeks
Hib-3[k]	6 months	14 weeks	6-9 months	8 weeks
Hib-4	12-15 months	12 months	—	—
HPV Two Dose Series[l]				

HPV-1	11-12 years	9 years	6 months	5 months
HPV-2	11-12 years (+6 months)	9 years + 5 months[m]	—	—
HPV Three Dose Series				
HPV-1[n]	11-12 years	9 years	1-2 months	4 weeks
HPV-2	11-12 years (+1-2 months)	9 years (+4 weeks)	4 months	12 weeks[n]
HPV-3[n]	11-12 years (+6 months)	9 years (+5 months)	—	—
Influenza, inactivated[o]	≥6 months	6 months[p]	4 weeks	4 weeks
IPV-1[e]	2 months	6 weeks	8 weeks	4 weeks
IPV-2	4 months	10 weeks	8 weeks-14 months	4 weeks
IPV-3	6-18 months	14 weeks	3-5 years	6 months
IPV-4[q]	4-6 years	4 years	—	—
LAIV[o]	2-49 years[r]	2 years	4 weeks	4 weeks
MenACWY-1[s]	11-12 years	2 months[t]	4-5 years	8 weeks
MenACWY-2	16 years	11 years (+8 weeks)[u]	—	—
MenB-1	Healthy adolescents: 16-23 years	16 years	Bexsero: 4 weeks Trumenba: 6 months[c]	Bexsero: 4 weeks Trumenba: 6 months[c]
	Persons at increased risk: ≥10 years	10 years	Bexsero: 4 weeks Trumenba: 1-2 months[c]	Bexsero: 4 weeks Trumenba: 1 month
MenB-2	Healthy adolescents: 16-23 years (+1 month)	16 years (+1 month)	—	—
	Persons at increased risk: ≥10 years (+1 month)	10 years (+1 month)	Bexsero: — Trumenba: 4-5 months[c]	Bexsero: — Trumenba: 4 months[c]

MenB-3[v]	Persons at increased risk: ≥ 10 years (+ 6 months[c])	10 years (+ 6 months[c])	—	—
MMR-1[w]	12-15 months	12 months	3-5 years	4 weeks
MMR-2[w]	4-6 years	13 months	—	—
PCV13-1[j, x]	2 months	6 weeks	8 weeks	4 weeks
PCV13-2	4 months	10 weeks	8 weeks	4 weeks
PCV13-3	6 months	14 weeks	6 months	8 weeks
PCV13-4	12-15 months	12 months	—	—
PCV15	See footnote x below			
PCV20	See footnote x below			
PPSV-1	—	2 years	5 years	5 years
PPSV-2[y]	—	7 years	—	—
Rotavirus-1[z]	2 months	6 weeks	8 weeks	4 weeks
Rotavirus-2	4 months	10 weeks	8 weeks	4 weeks
Rotavirus-3[z]	6 months	14 weeks	—	—
Td	11-12 years	7 years	10 years	5 years
Tdap[aa]	≥11 years	7 years	—	—
Varicella-1[w]	12-15 months	12 months	3-5 years	12 weeks[bb]
Varicella-2[w]	4-6 years	15 months[cc]	—	—
RZV - 1	≥50 years	50 years[dd]	2-6 months	4 weeks
RZV - 2	≥50 years (+ 2-6 months)	50 years	—	—

Abbreviations: DEN4CYD = dengue vaccine; 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; MenACWY = quadrivalent meningococcal conjugate vaccine; MenB = serogroup B meningococcal vaccine; MenB-4C = Bexsero; MenB-FHbp = Trumenba; MMR = measles, mumps, and rubella; MMRV
= measles, mumps, rubella, and varicella; MPSV4 = quadrivalent meningococcal polysaccharide vaccine; PCV13 = pneumococcal conjugate vaccine; PPSV23= pneumococcal polysaccharide vaccine; PRP-OMP = polyribosylribitol phosphate-meningococcal outer membrane protein conjugate; RZV = recombinant zoster vaccine; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

(a) 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.

(b) Information on travel vaccines, including typhoid, Japanese encephalitis, and yellow fever, is available at https://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://emergency.cdc.gov/bioterrorism/ .

(c) "Months" refers to calendar months.

(d) Within a number range, a hyphen (-) should be read as "through."

(e) Combination vaccines containing the hepatitis B component are available (see Table 3-3). These vaccines should not be administered to infants aged <6 weeks because of the other vaccine components (i.e., Hib, DTaP, HepA, and IPV).

(f) The minimum recommended age for DTaP-4 is 15 months, with a recommended 6 months from DTaP-3 (the recommended interval between DTaP-3 and DTaP-4 is 6 months). However, DTaP4 need not be repeated if given on or after 12 months of age and at least 4 months after DTaP-3. The 4-day grace period can be applied when validating past doses and can be applied to the minimum age of 12 months and the minimum interval of 4 months between DTaP-3 and DTaP-4. The 4-day grace period can be used when planning doses ahead of time, but should be applied to the minimum age of 15 months and the minimum interval between DTaP-3 and DTaP-4 of 6 months.

(g) If a fourth dose of DTaP is given on or after the fourth birthday, a fifth dose is not needed if the interval between the third dose and fourth dose is at least 6 months.

(h) Adjuvanted Hepatitis B vaccine (HepB-CgG) can be administered to adults 18 years old and older on a two dose schedule, the first and second dose separated by 4 weeks.

(i) 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.

(j) For Hib and PCV13, children receiving the first dose of vaccine at age ≥7 months require fewer doses to complete the series.

(k) 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. The final dose has a minimum age of 12 months.

(l) A two-dose schedule of HPV vaccine is recommended for most persons beginning the series between 9 through 14 years of age. See HPV vaccine-specific recommendations for details.
www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6549a5.pdf

(m) If a patient is eligible for a 2-dose HPV series, and the second dose is given less than four weeks after the first dose, it is an invalid dose. Administer another dose 6-12 months after the first dose. If the second dose is given less than five months after the first dose, but more than four weeks after the first dose, the next dose should be administered at least 12 weeks after the second dose, and at least 6-12 months after the first dose. The 4-day grace period may be used. If the third dose was administered before December 16, 2016, and was administered 12 weeks after the 2nd dose, and 16 weeks after the first dose, it is a valid dose. The 4-day grace period may be used. If the third dose was administered on or after December 16, 2016, and was administered 12 weeks after the 2nd dose and 5 months after the first dose, it is a valid dose. The 4-day grace period may be used.

(n) The minimum age for HPV-3 is based on the baseline minimum age for the first dose (i.e., 9 years) and the minimum interval of 5 months between the first and third dose. If the third dose was administered before December 16, 2016, and was administered 12 weeks after the 2nd dose, and 16 weeks after the first dose, it is a valid dose. The 4-day grace period may be used. If the third dose was administered on or after December 16, 2016, and was administered.

(o) One dose of influenza vaccine per season is recommended for most persons. To determine which children younger than 9 years should receive 2 doses in a single season, please see influenza vaccine-specific recommendations (*82*). If a dose of LAIV is administered to a child 6 months to 2 years of age in error, the dose does not need to be repeated.

(p) The minimum age for inactivated influenza vaccine varies by vaccine manufacturer. See package insert for vaccine-specific minimum ages.

(q) A fourth dose is not needed if the third dose was administered at ≥4 years and at least 6 months after the previous dose.

(r) If a dose of LAIV is administered to someone 6 months to 2 years of age, the dose does NOT need to be repeated. If someone is still indicated for dose 2 of the prime-boost, and younger than 2 years of age, the second dose should be IIV.

(s) Revaccination with meningococcal vaccine is recommended for previously vaccinated persons who remain at high risk for meningococcal disease (*47*).

(t) MenACWY-D (Menactra) can be given as young as 9 months for high-risk persons. MenACWY-CRM (Menveo) can be given as young as 2 months for high-risk persons. Hib-MenCY can be given as young as 6 weeks for high-risk persons. Hib-MenCY is given as a 4-dose series at 2 months, 4 months, 6 months and 12-18 months. MenACWY-TT (MenQuadfi) can be given as young as 2 years for high-risk persons.

(u) For routine non-high risk adolescent vaccination, the minimum age for the booster dose is 16 years.

(v) This dose is not necessary if Bexsero is correctly administered, or if Trumenba is correctly administered to healthy adolescents.

(w) Combination MMRV vaccine can be used for children aged 12 months-12 years. See text for details.

(x) Infants and children can optionally receive PCV15 instead of PCV13. High-risk adults 19 years through 64 years who are known to have not received any pneumococcal vaccine or whose PCV13 history is unknown should receive either PCV20 or PCV15. Adults 65 years old and older who are known to have not received any pneumococcal vaccine or whose PCV13 history is unknown should receive either PCV20 or PCV15. If PCV15 is administered and if PPSV23 naïve, a dose of PPSV23 should be administered a year later. On the basis of shared clinical decision-making, adults 65 years old and older who have received a complete series of pneumococcal vaccine can receive a dose of PCV20 at least five years after the most recent dose. For adults who have started the recommended pneumococcal vaccine series with PCV13 but have not received all recommended doses, look at ACIP Vaccine Recommendations and Schedules for details.

(y) A second dose of PPSV23 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 (*61*).

(z) 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. If 2 doses of Rotarix (GlaxoSmithKline) are administered as age appropriate, a third dose is not necessary.

(aa) Only 1 dose of Tdap is recommended. Subsequent doses should be given as Td or Tdap. 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.

(bb) A special grace period of 2 months, based on expert opinion, can be applied to the minimum interval of 3 months, when evaluating records retrospectively, which results in an acceptable minimum interval of 4 weeks. An additional 4 days should not be added on to this grace period.

(cc) A special grace period of 2 months, based on expert opinion, can be applied to the minimum age of 15 months when evaluating records retrospectively, which results in an acceptable minimum age of 13 months. An additional 4 days should not be added on to this grace period.

(dd) If a 1st dose of recombinant zoster vaccine is administered to someone 18 – 49 years of age, the dose does not need to be repeated. A 4 day grace period can be added to the absolute minimum age of 18 years when evaluating records retrospectively.

TABLE 3-3. FDA-licensed combination vaccines[a]

Vaccine[b]	Trade name (year licensed)	Age range	Routinely recommended ages
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
Hib-MenCY	MenHibrix (2012)	6 weeks-18 months	Four-dose schedule at 2, 4, 6, and 12-15 months of age[c]
DTaP-IPV	Quadracel (2015)	4-6 years	Fifth dose of DTaP and fourth or fifth dose of IPV
DTaP-IPV-Hib-HepB	Vaxelis (2018)	6 weeks – 4 years	Three-dose series at 2, 4, and 6 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: (*82*).

[a] 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.

[b] In descriptions of combination vaccines, dash (-) indicates products in which the active components are supplied in their final (combined) form by the manufacturer; slash (/) indicates products in which active components must be mixed by the user.

[c] Hib-MenCY can be used for routine dosing of Hib vaccine but is recommended only for meningococcal vaccination in persons at high-risk of meningococcal disease.

TABLE 3-4. Guidelines for spacing of live and non-live antigens	
Antigen combination	**Recommended minimum interval between doses**
Two or more non-live [a],[b],[c]	May be administered simultaneously or at any interval between doses
Non-live and live [d]	May be administered simultaneously or at any interval between doses
Two or more live injectable [d]	28 days minimum interval, if not administered simultaneously

Source: (*83*).

[a] 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.

[b] In persons with functional or anatomic asplenia, MCV-D and PCV13 should not be administered simultaneously and should be spaced by 4 weeks. Likewise for persons with immunosuppressive high-risk conditions indicated for PCV13 and PPSV23, PCV13 should be administered first, and PPSV23 should be administered no earlier than 8 weeks later. For persons 65 years old or older indicated for PCV13 and PPSV23, PCV13 should be administered first and PPSV23 should be administered 6-12 months later. For persons with high-risk conditions indicated for PCV15 and PPSV23, the interval between PCV15 and PPSV23 should be one year, for those with immunosuppressive high-risk conditions the interval may be shortened to 8 weeks.

[c] For providers who wish to use Menactra in patients indicated for DTaP, the two vaccines should be administered simultaneously. If they cannot be administered simultaneously, administer Menactra first, and then administer DTaP 6 months later.

[d] The live oral vaccines Ty21a typhoid vaccine and rotavirus vaccine may be administered simultaneously with or at any interval before or after non-live or live injectable vaccines.

TABLE 3-5. Guidelines for administering antibody-containing products[a] and vaccines			
Type of administration	**Products administered**		**Recommended minimum interval between doses**
Simultaneous (during the same clinic day)	Antibody-containing products and non-live 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.[b] 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 3-6)
Nonsimultaneous	**Administered first**	**Administered second**	
	Antibody-containing products	Non-live antigen	No interval necessary
	Non-live antigen	Antibody-containing products	No interval necessary
	Antibody-containing products	measles, mumps, rubella vaccine, varicella vaccine, and combined measles, mumps, rubella, varicella vaccine antigens	Dose related[b],[c]

	MMR vaccine, varicella vaccine, and combined measles, mumps, rubella, varicella vaccine antigens	Antibody-containing products	2 weeks[b]

[a] Blood products containing substantial amounts of immune globulin include intramuscular, subcutaneous, 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.

[b] Yellow fever vaccine; rotavirus vaccine; oral Ty21a typhoid vaccine; and live, attenuated influenza 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.

[c] 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 3-6).

TABLE 3-6. 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[a]**	**Recommended interval before measles- or live varicella-containing vaccine[b] administration (months)[c]**
Blood transfusion		
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%)[d]	10 mL/kg (60 mg IgG/kg) IV	6
Whole blood (hematocrit 35%-50%)[d]	10 mL/kg (80-100 mg IgG/kg) IV	6
Plasma/platelet products	10 mL/kg (160 mg IgG/kg) IV	7
Botulinum Immune Globulin Intravenous (Human)	1.0 mL/kg (50 mg IgG/kg) IV	6
Cytomegalovirus IGIV	150 mg/kg maximum	6
Hepatitis A IG		
Contact prophylaxis	0.1 mL/kg (16.5 mg IgG/kg) IM	6[e]
International travel, <1 month stay	0.1 mL/kg (16.5 mg IgG/kg) IM	6[e]
International travel, ≥1 month stay	0.2 mL/kg (33 mg IgG/kg) IM	6[e]
Hepatitis B IG	0.06 mL/kg (10 mg IgG/kg) IM	3
IGIV		
Replacement therapy for immune deficiencies[f]	300-400 mg/kg IV[e]	8

Immune thrombocytopenic purpura treatment	400 mg/kg IV	8
Postexposure varicella prophylaxis	400 mg/kg IV	8
Postexposure measles prophylaxis for immunocompromised contacts	400 mg/kg IV	8
Immune thrombocytopenic purpura treatment	1000 mg/kg IV	10
Kawasaki disease	2 g/kg IV	11
Measles prophylaxis IG		
Standard (i.e., nonimmunocompromised) contact	0.50 mL/kg (80 mg IgG/kg) IM	6
Monoclonal antibody to respiratory syncytial virus F protein (e.g., Synagis [MedImmune])(g)	15 mg/kg IM	None
Rabies IG	20 IU/kg (22 mg IgG/kg) IM	4
Tetanus IG	250 units (10 mg IgG/kg) IM	3
Varicella IG	125 units/10 kg (60-200 mg IgG/kg) IM, maximum 625 units	5

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.

(a) 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. Sources: Mason W, Takahashi M, Schneider T. Persisting passively acquired measles antibody following gamma globulin therapy for Kawasaki disease and response to live virus vaccination [Abstract 311]. Presented at the 32 meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy, Los Angeles, California, October, 1992, AND Siber GR, Werner BG, Halsey NA, et al. Interference of immune globulin with measles and rubella immunization. *J Pediatr*. 1993;122(2):204-211. DOI: 10.1016/S0022-3476(06)80114-9, AND Mason WH, Schneider TL, Takahashi M. Duration of passively acquired measles antibody and response to live virus vaccination allowing gamma globulintherapy for Kawasaki syndrome. *Prog Pediatr Cardiol*. 1992;1(1):82. DOI: 10.1016/S1058-9813(06)80067-6. The extrapolation is performed by counting months from 80 mg down to (1-3 mg) (e.g. 80 >>> 40 >> >20 >> >10 >>> 5>>>2.5….equal to FIVE intervals) and adding a grace month, so 80 mg values take a "6 month" interval)

(b) Does not include recombinant zoster vaccine, since this vaccine is non-live.

(c) The interval between blood/passive antibody products and testing for history of dengue infection (which is mandatory prior to administration of dengue vaccine) should be 12 months

(d) Assumes a serum IgG concentration of 16 mg/mL.

(e) The reason the interval is 6 months (and not 4 months) is that the quantity of 16.5 IgG/kg does not reflect the upper ceiling of the quantity of measles IgG in the product.

(f) Measles vaccination is recommended for children with mild or moderate immunosuppression from HIV infection, and varicella vaccination may be considered for children with mild or moderate immunosuppression from HIV infection, but both are contraindicated for persons with severe immunosuppression from HIV or any other immunosuppressive disorder.

(g) Contains antibody only to respiratory syncytial virus.

REFERENCES

1. CDC. Diphtheria, tetanus, and pertussis: recommendations for vaccine use and other preventive measures. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Recomm Rep*. 1991;40(RR-10):1-28.
2. CDC. *Haemophilus b* conjugate vaccines for prevention of *Haemophilus influenzae* type b disease among infants and children two months of age and older. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Recomm Rep*. 1991;40(RR-1):1-7.
3. Plotkin SA. Immunologic correlates of protection induced by vaccination. *Pediatr Infect Dis J*. 2001;20(1):63-75. DOI: 10.1097/00006454-200101000-00013
4. Watson JC, Hadler SC, Dykewicz CA, Reef S, Phillips L. 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 Recomm Rep*. 1998;47(RR-8):1-57.
5. Watson JC, Pearson JA, Markowitz LE, et al. An evaluation of measles revaccination among school-entry-aged children. *Pediatrics*. 1996;97(5):613-618.
6. Marin M, Guris D, Chaves SS, Schmid S, Seward JF. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56(RR-4):1-40.
7. Atkinson WL, Pickering LK, Schwartz B, Weniger BG, Iskander JK, Watson JC. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR Recomm Rep*. 2002;51(RR-2):1-35.
8. Manning SE, Rupprecht CE, Fishbein D, et al. Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2008;57(RR-3):1-28.
9. https://www.cdc.gov/vaccines/programs/iis/cdsi.html
10. Levine L, Edsall G. Tetanus toxoid: what determines reaction proneness? *J Infect Dis*. 1981;144(4):376. DOI: 10.1093/infdis/144.4.376

11. Edsall G, Elliott MW, Peebles TC, Eldred MC. Excessive use of tetanus toxoid boosters. *JAMA*. 1967;202(1):111-113. DOI: 10.1001/jama.1967.03130140075009
12. King GE, Hadler SC. Simultaneous administration of childhood vaccines: an important public health policy that is safe and efficacious. *Pediatr Infect Dis J*. 1994;13(5):394-407.
13. National Vaccine Advisory Committee. Standards for child and adolescent immunization practices. *Pediatrics*. 2003;112(4):958-963.
14. Hutchins SS, Escolan J, Markowitz LE, et al. Measles outbreak among unvaccinated preschool-aged children: opportunities missed by health care providers to administer measles vaccine. *Pediatrics*. 1989;83(3):369-374.
15. Deforest A, Long SS, Lischner HW, et al. Simultaneous administration of measles-mumps-rubella vaccine with booster doses of diphtheria-tetanus-pertussis and poliovirus vaccines. *Pediatrics*. 1988;81(2):237-246.
16. Dashefsky B, Wald E, Guerra N, Byers C. Safety, tolerability, and immunogenicity of concurrent administration of *Haemophilus influenzae* type b conjugate vaccine (meningococcal protein conjugate) with either measles-mumps-rubella vaccine or diphtheria-tetanus-pertussis and oral poliovirus vaccines in 14- to 23-month-old infants. *Pediatrics*. 1990;85(4 Pt 2):682-689.
17. Giammanco G, Li Volti S, Mauro L, et al. Immune response to simultaneous administration of a recombinant DNA hepatitis B vaccine and multiple compulsory vaccines in infancy. *Vaccine*. 1991;9(10):747-750. DOI: 10.1016/0264-410X(91)90291-D
18. Grohskopf LA, Sokolow LZ, Olsen SJ, Bresee JS, Broder KR, Karron RA. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices, United States, 2015-16 influenza season. *MMWR Morb Mortal Wkly Rep*. 2015;64(30):818-825.
19. CDC. Typhoid immunization: recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Recomm Rep*. 1990;39(RR-10):1-5.
20. DeStefano F, Goodman RA, Noble GR, McClary GD, Smith S, Broome CV. Simultaneous administration of influenza and pneumococcal vaccines. *JAMA*. 1982;247(18):2551-2554. DOI: 10.1001/jama.1982.03320430055032

21. Kretsinger K, Broder KR, Cortese MM, et al. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. *MMWR Recomm Rep*. 2006;55(RR-17):1-37.
22. Yvonnet B, Coursaget P, Deubel V, Diop-Mar I, Digoutte JP, Chiron JP. Simultaneous administration of hepatitis B and yellow fever vaccines. *J Med Virol*. 1986;19(4):307-311. DOI: 10.1002/jmv.1890190403
23. Stefano I, Sato HK, Pannuti CS, et al. Recent immunization against measles does not interfere with the sero-response to yellow fever vaccine. *Vaccine*. 1999;17(9-10):1042-1046. DOI: 10.1016/S0264-410X(98)00320-X
24. Staples JE, Gershman M, Fischer M. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59(RR-7):1-27.
25. Leroy Z, Broder K, Menschik D, Shimabukuro T, Martin D. Febrile seizures after 2010-2011 influenza vaccine in young children, United States: a vaccine safety signal from the vaccine adverse event reporting system. *Vaccine*. 2012;30(11):2020-2023. DOI: 10.1016/j.vaccine.2011.12.042
26. Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. *Vaccine*. 2012;30(11):2024-2031. DOI: 10.1016/j.vaccine.2012.01.027
27. CDC. Recommendation of the Advisory Committee on Immunization Practices (ACIP) for use of quadrivalent meningococcal conjugate vaccine (MenACWY-D) among children aged 9 through 23 months at increased risk for invasive meningococcal disease. *MMWR Morb Mortal Wkly Rep*. 2011;60(40):1391-1392.
28. CDC. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising

conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2012;61(40):816-819.

29. CDC. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6-18 years with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2013;62(25):521-524.
30. Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >/=65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2014;63(37):822-825.
31. CDC. Recommended immunization schedules for persons aged 0 through 18 years—United States, 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60(5):1-4.
32. Shinefield HR, Black S, Ray P, et al. Safety and immunogenicity of heptavalent pneumococcal CRM197 conjugate vaccine in infants and toddlers. *Pediatr Infect Dis J*. 1999;18(9):757-763. DOI: 10.1097/00006454-199909000-00004
33. CDC. Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1997;46(RR-7):1-25.
34. Broder KR, Cortese MM, Iskander JK, et al. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-3):1-34.
35. Nuorti JP, Whitney CG. Prevention of pneumococcal disease among infants and children - use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine - recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59(RR-11):1-18.
36. Mast EE, Margolis HS, Fiore AE, et al. 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 1: immunization of infants, children, and adolescents. *MMWR Recomm Rep*. 2005;54(RR-16):1-31.

37. Committee on Infectious Diseases. Recommended childhood and adolescent immunization schedules—United States, 2010. *Pediatrics*. 2010;125(1):195-196. DOI: 10.1542/peds.2009-3194
38. CDC. Recommended adult immunization schedule—United States, 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60(4):1-4.
39. Woodin KA, Rodewald LE, Humiston SG, Carges MS, Schaffer SJ, Szilagyi PG. Physician and parent opinions. Are children becoming pincushions from immunizations? *Arch Pediatr Adolesc Med*. 1995;149(8):845-849. DOI: 10.1001/archpedi.1995.02170210019003
40. Kuppermann M, Nease RF, Jr., Ackerson LM, Black SB, Shinefield HR, Lieu TA. Parents' preferences for outcomes associated with childhood vaccinations. *Pediatr Infect Dis J*. 2000;19(2):129-133. DOI: 10.1097/00006454-200002000-00010
41. Meyerhoff A, Jacobs RJ, Greenberg DP, Yagoda B, Castles CG. Clinician satisfaction with vaccination visits and the role of multiple injections, results from the COVISE Study (Combination Vaccines Impact on Satisfaction and Epidemiology). *Clin Pediatr (Phila)*. 2004;43(1):87-93.
42. Marshall GS, Happe LE, Lunacsek OE, et al. Use of combination vaccines is associated with improved coverage rates. *Pediatr Infect Dis J*. 2007;26(6):496- 500. DOI: 10.1097/INF.0b013e31805d7f17
43. Kalies H, Grote V, Verstraeten T, Hessel L, Schmitt HJ, von Kries R. The use of combination vaccines has improved timeliness of vaccination in children. *Pediatr Infect Dis J*. 2006;25(6):507-512. DOI: 10.1097/01.inf.0000222413.47344.23
44. Happe LE, Lunacsek OE, Kruzikas DT, Marshall GS. Impact of a pentavalent combination vaccine on immunization timeliness in a state Medicaid population. *Pediatr Infect Dis J*. 2009;28(2):98-101. DOI: 10.1097/INF.0b013e318187d047

45. Marin M, Broder KR, Temte JL, Snider DE, Seward JF. Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59(RR-3):1-12.

46. Thompson LA, Irigoyen M, Matiz LA, LaRussa PS, Chen S, Chimkin F. The impact of DTaP-IPV-HB vaccine on use of health services for young infants. *Pediatr Infect Dis J*. 2006;25(9):826-831. DOI: 10.1097/01.inf.0000232635.81312.06

47. Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020. Recommendations and Reports / September 25, 2020 / 69(9);1-41.

48. Weniger BG, Chen RT, Jacobson SH, et al. Addressing the challenges to immunization practice with an economic algorithm for vaccine selection. *Vaccine*. 1998;16(19):1885-1897. DOI: 10.1016/S0264-410X(98)00170-4

49. Liang J, Wallace G, Mootrey G. Licensure of a diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine and guidance for use as a booster dose. *MMWR Morb Mortal Wkly Report* 2015;64: 948-9.

50. CDC. FDA approval of a Haemophilus b Conjugate Vaccine combined by reconstitution with an acellular pertussis vaccine. *MMWR Morb Mortal Wkly Rep*. 1996;45(45):993-995.

51. CDC. FDA approval for a combined hepatitis A and B vaccine. *MMWR Morb Mortal Wkly Rep*. 2001;50(37):806-807.

52. CDC. FDA licensure of diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant), and poliovirus vaccine combined, (PEDIARIX) for use in infants. *MMWR Morb Mortal Wkly Rep*. 2003;52(10):203-204.

53. CDC. Licensure of a combined live attenuated measles, mumps, rubella, and varicella vaccine. *MMWR Morb Mortal Wkly Rep*. 2005;54(47):1212-1214.

54. CDC. Licensure of a diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine and guidance for use as a booster dose. *MMWR Morb Mortal Wkly Rep*. 2008;57(39):1078-1079.

55. CDC. Licensure of a diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, and haemophilus B conjugate vaccine and guidance for use in infants and children. *MMWR Morb Mortal Wkly Rep*. 2008;57(39):1079-1080.

56. Kroger AT, Sumaya CV, Pickering LK, Atkinson WL. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011:1-60.

57. Plotkin SA. Vaccines: correlates of vaccine-induced immunity. *Clin Infect Dis*. 2008;47(3):401-409. DOI: 10.1086/589862

58. Lane KS, Chu SY, Santoli JM. The United States pediatric vaccine stockpile program. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2006;42 Suppl 3:S125-129. DOI: 10.1086/499591

59. Midthun K, Horne AD, Goldenthal KL. Clinical safety evaluation of combination vaccines. *Dev Biol Stand*. 1998;95:245-249.

60. Pichichero ME, Blatter MM, Reisinger KS, et al. Impact of a birth dose of hepatitis B vaccine on the reactogenicity and immunogenicity of diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-*Haemophilus influenzae* type b combination vaccination. *Pediatr Infect Dis J*. 2002;21(9):854- 859. DOI: 10.1097/01.inf.0000027669.37444.24

61. CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1997;46(RR-8):1-24.

62. Bilukha OO, Rosenstein N. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2005;54(RR-7):1-21.

63. Petralli JK, Merigan TC, Wilbur JR. Action of endogenous interferon against vaccinia infection in children. *Lancet*. 1965;2(7409):401-405. DOI: 10.1016/S0140-6736(65)90755-5

64. Petralli JK, Merigan TC, Wilbur JR. Circulating interferon after measles vaccination. *N Engl J Med*. 1965;273:198-201. DOI: 10.1056/nejm196507222730405

65. Verstraeten T, Jumaan AO, Mullooly JP, et al. A retrospective cohort study of the association of varicella vaccine failure with asthma, steroid use, age at vaccination, and measles-mumps-rubella vaccination. *Pediatrics*. 2003;112(2):e98-103. DOI: 10.1542/peds.112.2.e98

66. CDC. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1994;43(RR-1):1-38.

67. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008;57(RR-5):1-30; quiz CE32-34.

68. Siber GR, Werner BG, Halsey NA, et al. Interference of immune globulin with measles and rubella immunization. *J Pediatr*. 1993;122(2):204-211. DOI: 10.1016/S0022-3476(06)80114-9

69. Mason WH, Schneider TL, Takahashi M. Duration of passively acquired measles antibody and response to live virus vaccination allowing gamma globulin therapy for Kawasaki syndrome. *Prog Pediatr Cardiol*. 1992;1(1):82. DOI: 10.1016/S1058-9813(06)80067-6

70. Kaplan JE, Nelson DB, Schonberger LB, et al. The effect of immune globulin on the response to trivalent oral poliovirus and yellow fever vaccinations. *Bull World Health Organ*. 1984;62(4):585-590.

71. Black NA, Parsons A, Kurtz JB, McWhinney N, Lacey A, Mayon-White RT. Post-partum rubella immunisation: a controlled trial of two vaccines. *Lancet*. 1983;2(8357):990-992. DOI: 10.1016/S0140-6736(83)90979-0

72. CDC. Control and prevention of rubella: evaluation and management of suspected outbreaks, rubella in pregnant women, and surveillance for congenital rubella syndrome. *MMWR Recomm Rep*. 2001;50(RR-12):1-23.

73. Siber GR, Snydman DR. Use of immune globulin in the prevention and treatment of infections. In: Remington J, Swartz M, eds. *Current clinical topics in infectious diseases*. Vol 12. Malden, MA: Blackwell Science; 1992.

74. Greenberg DP, Lieberman JM, Marcy SM, et al. Enhanced antibody responses in infants given different sequences of heterogeneous *Haemophilus influenzae* type b conjugate vaccines. *J Pediatr*. 1995;126(2):206-211. DOI: 10.1016/S0022-3476(95)70546-5

75. Anderson EL, Decker MD, Englund JA, et al. Interchangeability of conjugated *Haemophilus influenzae* type b vaccines in infants. *JAMA*. 1995;273(11):849-853. DOI: 10.1001/jama.1995.03520350031024
76. Piazza M, Abrescia N, Picciotto L, et al. [Demonstration of the interchangeability of 2 types of recombinant anti-hepatitis-B vaccine]. *Boll Soc Ital Biol Sper*. 1993;69(4):273-280.
77. Bryan JP, Henry CH, Hoffman AG, et al. Randomized, cross-over, controlled comparison of two inactivated hepatitis A vaccines. *Vaccine*. 2000;19(7-8):743-750. DOI: 10.1016/S0264-410X(00)00301-7
78. Greenberg DP, Pickering LK, Senders SD, et al. Interchangeability of 2 diphtheria-tetanus-acellular pertussis vaccines in infancy. *Pediatrics*. 2002;109(4):666-672. DOI: 10.1542/peds.109.4.666
79. CDC. Use of diphtheria toxoid-tetanus toxoid-acellular pertussis vaccine as a five-dose series. Supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2000;49(RR-13):1-8.
80. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep*. 2010;59(RR-8):1-62.
81. McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2013;62(RR-4):1-34.
82. Grohskopf LA, Alyanak E, Broder KR. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2020−21 Influenza Season. MMWR Recomm Rep 2020;69(No. RR-8):1-26.
83. American Academy of Pediatrics. Active Immunization. In: Pickering L, Baker C, Kimberlin D, Long S, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatric; 2012.