Immunization, Vaccine Storage, Handling, and Safety

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This chapter discusses issues that are commonly encountered in vaccination practice. A more thorough discussion of issues common to more than one vaccine can be found in the *General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices*. These recommendations are revised every 3 to 5 years as needed; the most current edition was published in January 2011 (MMWR 2011;60 (No. RR-2):1-61). All providers who administer vaccine should have a copy of this report and be familiar with its content. It can be downloaded from the *MMWR* website or ordered in print version from the Centers for Disease Control and Prevention.

Timing and Spacing of Vaccines

The timing and spacing of vaccine doses are two of the most important issues in the appropriate use of vaccines. Specific circumstances that are commonly encountered in immunization practice are the timing of antibody-containing blood products and live vaccines (particularly measles and varicella-containing vaccines), simultaneous and nonsimultaneous administration of different vaccines, and the interval between subsequent doses of the same vaccine.

General Rule: Inactivated vaccines are generally not affected by circulating antibody to the antigen. Live attenuated vaccines may be affected by circulating antibody to the antigen.

Antibody–Vaccine Interactions

The presence of circulating antibody to a vaccine antigen may reduce or completely eliminate the immune response to the vaccine. The amount of interference produced by circulating antibody generally depends on the type of vaccine administered and the amount of antibody.

Inactivated antigens, which include recombinant vaccines, are generally not affected by circulating antibody, so they can be administered before, after, or at the same time as the antibody. Simultaneous administration of antibody (in the form of immune globulin) and vaccine is recommended for postexposure prophylaxis of certain diseases, such as hepatitis B, rabies, and tetanus.

Antibody and Measles- and Varicella-Containing* Vaccines

Product Given First	Action
Vaccine	Wait 2 weeks before giving antibody
Antibody	Wait 3 months or longer before giving vaccine (See Table, Appendix A)

*except zoster vaccine

Live Injected Vaccines

Live vaccines must replicate in order to cause an immune response. Antibody against injected live vaccine antigen may interfere with replication. If a live injectable vaccine (measles-mumps-rubella [MMR], varicella, or combination

measles-mumps-rubella-varicella [MMRV]) must be given around the time that antibody is given, the two must be separated by enough time so that the antibody does not interfere with viral replication. If the live vaccine is given first, it is necessary to wait at least 2 weeks (i.e., an incubation period) before giving the antibody. If the interval between the vaccine and antibody is less than 2 weeks, the recipient should be tested for immunity or the vaccine dose should be repeated.

If the antibody is given before a dose of MMR or varicella-containing vaccine, it is necessary to wait until the antibody has waned (degraded) before giving the vaccine to reduce the chance of interference by the antibody. The necessary interval between an antibody-containing product and MMR or varicella-containing vaccine (except zoster vaccine) depends on the concentration of antibody in the product, but is always 3 months or longer. A table listing the recommended intervals between administration of antibody products and live vaccines (MMR and varicella-containing) is included in Appendix A and in the *General Recommendations on Immunization* (2011). The interval between administration of an antibody product and MMR or varicella vaccination can be as long as 11 months. Zoster vaccine is not known to be affected by circulating antibody so it can be administered at any time before or after receipt of an antibody-containing blood product.

Yellow fever vaccine also is not known to be affected by circulating antibody. Because few North Americans are immune to yellow fever, these products do not contain significant amounts of antibody to yellow fever virus.

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 rubella vaccine. Because of the importance of rubella and varicella immunity among childbearing age women, women without evidence of immunity to rubella or varicella should receive MMR or varicella vaccine (but not MMRV) in the postpartum period. Vaccination 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 delivery and, if possible, tested 3 months later to ensure immunity to rubella and, if necessary, to measles.

Live Oral and Intranasal Vaccines

Oral typhoid vaccine is not known to be affected by the administration of immune globulin or blood products. Oral typhoid vaccine may be given simultaneously with blood products, or separated by any interval. The replication of

live attenuated influenza (LAIV) and rotavirus vaccines are not believed to be affected by antibody-containing blood products. These can be given any time before or after administration of antibody-containing blood products.

Products Containing Type-Specific or Negligible Antibody

Some blood products do not contain antibodies that interfere with vaccine replication. Palivizumab (Synagis), used for the prevention of respiratory syncytial virus (RSV) infection in infants and young children, contains antibody directed only at RSV. Washed red blood cells contain a negligible amount of antibody. These products can be given anytime before or after administration of MMR or varicella-containing vaccines.

Simultaneous and Nonsimultaneous Administration

General Rule: All vaccines can be administered at the same visit as all other vaccines.*

*exception: in children with functional or anatomic asplenia pneumococcal conjugate vaccine (PCV13) and Menactra brand meningococcal conjugate vaccines should not be administered at the same visit; separate these vaccines by at least 4 weeks

Simultaneous administration (that is, administration on the same day) of the most widely used live and inactivated vaccines does not result in decreased antibody responses or increased rates of adverse reaction. Simultaneous administration of all vaccines for which a child is eligible is very important in childhood vaccination programs because it increases the probability that a child will be fully immunized at the appropriate age. A study during a measles outbreak in the early 1990s showed that about one-third of measles cases in unvaccinated but vaccine-eligible preschool children could have been prevented if MMR had been administered at the same visit when another vaccine was given.

All indicated vaccines should be administered at the same visit. In children with functional or anatomic asplenia pneumococcal conjugate vaccine (PCV13) and Menactra brand meningococcal conjugate vaccine should not be administered at the same visit, and should be separated by at least 4 weeks. This is because children with functional or anatomic asplenia are at very high risk of pneumococcal invasive disease and Menactra is thought to interfere with the antibody response to pneumococcal conjugate vaccine. PCV13 should be administered first and then Menactra four weeks later. Individual vaccines should not be mixed

Products Containing Type-Specific or Negligible Antibody

- Palivizumab (Synagis)
  - monoclonal
  - contains only RSV antibody
- Red blood cells (RBCs), washed
  - negligible antibody content

Spacing of Vaccine Combinations Not Given Simultaneously

Combination	Minimum Interval
Two live parenteral, or live intranasal influenza vaccine	4 weeks
All other	None*

*in children with functional or anatomic asplenia pneumococcal conjugate vaccine (PCV13) and Menactra brand meningococcal conjugate vaccines should not be administered at the same visit; separate these vaccines by at least 4 weeks

Spacing of Live Vaccines Not Given Simultaneously

- If two live parenteral vaccines, or live intranasal influenza vaccine, are given less than 4 weeks apart the vaccine given second should be repeated
- Exception is yellow fever vaccine given less than 30 days after single antigen measles vaccine, single antigen mumps vaccine, single antigen rubella vaccine, or varicella vaccine.

in the same syringe unless they are licensed for mixing by the Food and Drug Administration. Only the sanofi-pasteur DTaP-IPV/Hib (Pentacel) vaccine is licensed for mixing in the same syringe. For additional guidelines, see the Vaccine Administration chapter.

Combination vaccines are generally preferred over simultaneous administration of single component vaccines. Considerations should include an assessment of the number of injections, vaccine availability, likelihood of improved coverage, likelihood of patient return, and storage and costs. Considerations should also include patient choice and the potential for adverse events. Because of the increased risk of febrile seizures following the first dose of MMRV vaccine compared to MMR and varicella vaccines, for the first dose of vaccine to prevent measles, mumps, rubella and varicella, unless the parent or caregiver expresses a preference for MMRV vaccine, separate MMR and Varicella vaccines should be administered for children 12 through 47 months of age.

Nonsimultaneous Administration of Different Vaccines

If live parenteral (injected) vaccines (MMR, MMRV, varicella, zoster, and yellow fever) and live intranasal influenza vaccine (LAIV) are not administered at the same visit, they should be separated by at least 4 weeks. This interval is intended to reduce or eliminate interference from the vaccine given first on the vaccine given later. If two live parenteral vaccines or LAIV are administered at an interval of less than 4 weeks, then the vaccine given second should be repeated in 4 weeks or confirmed to have been effective by serologic testing of the recipient (serologic testing is not recommended following LAIV, varicella, or zoster vaccines). An exception to this recommendation is yellow fever vaccine administered less than 4 weeks after single-antigen measles vaccine. A 1999 study demonstrated that yellow fever vaccine is not affected by measles vaccine given 1–27 days earlier. The effect of nonsimultaneously administered yellow fever vaccine with each of the following vaccines: mumps; varicella; zoster; LAIV; and rubella is not known. So doses of mumps, varicella, zoster, LAIV, and rubella, when administered less than 30 days prior to yellow fever vaccine, can be counted.

Live vaccines administered by the oral route (oral polio vaccine [OPV] oral typhoid, and rotavirus) are not believed to interfere with each other if not given simultaneously. These vaccines may be given at any time before or after each other. Rotavirus vaccine is not approved for children older than 32 weeks, oral typhoid is not approved for children younger than 6 years of age, and OPV is no longer available in the United States, so these vaccines are not likely to be given to the same child.

Parenteral live vaccines (MMR, MMRV, varicella, zoster, and yellow fever) and LAIV are not believed to have an effect on live vaccines given by the oral route (OPV, oral typhoid, and rotavirus). Live oral vaccines may be given at any time before or after live parenteral vaccines or LAIV.

All other combinations of two inactivated vaccines, or live and inactivated vaccines, may be given at any time before or after each other. In children with functional or anatomic asplenia PCV13 and Menactra brand meningococcal conjugate vaccine should not be administered at the same visit.

Interval Between Doses of the Same Vaccine

Immunizations are recommended for members of the youngest age group at risk for a disease for whom efficacy and safety of a vaccine have been demonstrated.

General Rule: Increasing the interval between doses of a multidose vaccine does not diminish the effectiveness of the vaccine.*Decreasing the interval between doses of a multidose vaccine may interfere with antibody response and protection.

*after the series has been completed

Most vaccines in the childhood immunization schedule require two or more doses for development of an adequate and persisting antibody response. Studies have demonstrated that recommended ages and intervals between doses of the same antigen(s) provide optimal protection or have the best evidence of efficacy. Table 1 of the *General Recommendations on Immunization* (included in Appendix A) shows the recommended and minimal ages and intervals between doses of vaccines most frequently used in the United States.

Administering doses of a multidose vaccine at shorter than the recommended intervals might be necessary when an infant or child is behind schedule and needs to be brought up-to-date quickly or when international travel is pending. In these cases, an accelerated schedule using the minimum age or minimum interval criteria can be used. Accelerated schedules should not be used routinely.

Minimum Intervals and Ages

Vaccine doses should not be administered at intervals less than the minimum intervals or earlier than the minimum age

For routine vaccination, vaccine doses should not be administered at intervals less than the recommended minimal intervals or earlier than the minimal ages. Two exceptions to this may occur. The first is for measles vaccine during a measles outbreak or before travelling abroad. Infants 6

through 11 months should receive one MMR dose, and this dose should not be counted (should be repeated at 12 months of age or older). The second exception involves administering a dose a few days earlier than the minimum interval or age, which is unlikely to have a substantially negative effect on the immune response to that dose. Although vaccinations should not be scheduled at an interval or age less than the recommended minimums, a child may have erroneously been brought to the office early, or may have come for an appointment not specifically for vaccination. In these situations, the clinician can consider administering the vaccine earlier than the minimum interval or age. If the parent/child is known to the clinician and the physician has confidence that the child will return for a visit, it is preferable to reschedule the child for vaccination closer to the recommended interval. If the parent/child is not known to the clinician or is not reliable (e.g., habitually misses appointments), it may be preferable to administer the vaccine at that visit than to reschedule a later appointment that may not be kept.

Vaccine doses administered up to 4 days before the minimum interval or age can be counted as valid. This 4-day recommendation does not apply to rabies vaccine because of the unique schedule for this vaccine. Doses administered 5 days or 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 generally be spaced after the invalid dose by an interval at least equal to the recommended minimum interval shown in Table 1 of the General Recommendations. In certain situations, local or state requirements might mandate that doses of selected vaccines be administered on or after specific ages, superseding this 4-day "grace period".

In some cases, a scheduled dose of vaccine may not be given on time. If this occurs, the dose should be given at the next visit. Not all permutations of all schedules for all vaccines have been studied. However, available data indicate that intervals between doses longer than those routinely recommended do not affect seroconversion rate or titer when the schedule is completed. Consequently, it is not necessary to restart the series or add doses of any vaccine because of an extended interval between doses. The only exception to this rule is oral typhoid vaccine in some circumstances. Some experts recommend repeating the series of oral typhoid vaccine if the four-dose series is extended to more than 3 weeks.

Violation of Minimum Intervals or Minimum Age

- ACIP recommends that vaccine doses given up to four days before the minimum interval or age be counted as valid
- Immunization programs and/or school entry requirements may not accept all doses given earlier than the minimum age or interval

Extended Interval Between Doses

- Not all permutations of all schedules for all vaccines have been studied
- Available studies of extended intervals have shown no significant difference in final titer
- It is not necessary to restart the series or add doses because of an extended interval between doses

Number of Doses

For live injected vaccines, the first dose administered at the recommended age usually provides protection. An additional dose is given to provide another opportunity for vaccine response in the small proportion of recipients who do not respond to the first dose. For instance, approximately 95% of recipients will respond to a single dose of measles vaccine. The second dose is given to ensure that nearly 100% of persons are immune (i.e., the second dose is "insurance"). Immunity following live vaccines is long-lasting, and booster doses are not necessary.

For inactivated vaccines, the first dose administered at the recommended age usually does not provide protection (hepatitis A vaccine is an exception). A protective immune response may not develop until the second or third dose. For inactivated vaccines, antibody titers may decrease (wane) below protective levels after a few years. This phenomenon is most notable for pertussis vaccine; tetanus and diphtheria vaccine immunity also wanes. For these vaccines, periodic "boosting" is required. An additional dose is given to raise antibody back to protective levels.

Not all inactivated vaccines require boosting throughout life. For example, additional doses of Hib vaccine are not required after completion of the infant primary series and 12-15 month old booster dose because Hib disease is very rare in children older than 5 years of age. Hepatitis B vaccine does not require boosting because of immunologic memory to the vaccine and the long incubation period of hepatitis B (which can produce an "autoboost").

Adverse Reactions Following Vaccination

Vaccines are intended to produce active immunity to specific antigens. An adverse reaction is an untoward effect caused by a vaccine that is extraneous to the vaccine's primary purpose of producing immunity. Adverse reactions are also called vaccine side effects. A vaccine adverse event refers to any medical event that occurs following vaccination. An adverse event could be a true adverse reaction or just a coincidental event, with further research needed to distinguish between them.

Acute vaccine adverse reactions fall into three general categories: local, systemic, and allergic. The most common type of adverse reactions are local reactions, such as pain, swelling, and redness at the site of injection. Local reactions may occur with up to 80% of vaccine doses, depending on the type of vaccine. Local adverse reactions generally occur within a few hours of the injection and are usually mild and self-limited. On rare occasions, local reactions may be very exaggerated or severe. Some of these reactions, referred to

Vaccine Adverse Reactions

- Adverse reaction
  - extraneous effect caused by vaccine
  - side effect
- Adverse event
  - any medical event following vaccination
  - may be true adverse reaction
  - may be only coincidental
- Local adverse reactions
  - pain, swelling, redness at site of injection
  - occur within a few hours of injection
  - usually mild and self-limited
- Systemic adverse reactions
  - fever, malaise, headache
  - nonspecific
  - may be unrelated to vaccine
- Severe allergic (anaphylaxis)
  - due to vaccine or vaccine component
  - rare
  - risk minimized by screening

as Arthus reactions, are most frequently seen with diphtheria and tetanus toxoids. Arthus reactions are not allergic reactions. Arthus reactions are believed to be due to very high titers of antibody, usually caused by too many doses of toxoid.

Systemic adverse reactions are more generalized events and include fever, malaise, myalgias (muscle pain), headache, loss of appetite, and others. These symptoms are nonspecific; they may occur in vaccinated persons because of the vaccine or may be caused by something unrelated to the vaccine.

Systemic adverse reactions were relatively frequent with DTP vaccine, which contained a whole-cell pertussis component. However, comparison of the frequency of systemic adverse events among vaccine and placebo recipients shows they are less common with inactivated vaccines currently in use, including acellular pertussis vaccine.

Live Attenuated Vaccines

- Must replicate to produce immunity
- Symptoms usually mild
- Occur after an incubation period (usually 3-21 days)

Systemic adverse reactions may occur following receipt of live attenuated vaccines. Live attenuated vaccines must replicate in order to produce immunity. The adverse reactions that follow live attenuated vaccines, such as fever or rash, represent symptoms produced from viral replication and are similar to a mild form of the natural disease. Systemic adverse reactions following live vaccines are usually mild, and occur 3–21 days after the vaccine was given (i.e., after an incubation period of the vaccine virus). LAIV replicates in the mucous membranes of the nose and throat, not in the lungs. As a result, LAIV may cause upper respiratory symptoms (like a cold) but not influenza-like symptoms.

A third type of acute vaccine adverse reactions are allergic reactions. Allergic reactions may be caused by the vaccine antigen itself or some other component of the vaccine, such as cell culture material, stabilizer, preservative, or antibiotic used to inhibit bacterial growth. Severe allergic reactions (anaphylaxis) may be life-threatening. Fortunately, they are rare. The risk of an allergic reaction can be decreased by good screening prior to vaccination. All providers who administer vaccines must have an emergency protocol and supplies to treat anaphylaxis.

Reporting Vaccine Adverse Events

Providers should report any clinically significant adverse event that occurs after the administration of any vaccine licensed in the United States to the Vaccine Adverse Event Reporting System (VAERS), which includes reporting from both public and private sectors.

Providers should report a clinically significant adverse event even if they are unsure whether a vaccine caused the event. The telephone number to call for answers to questions and to obtain VAERS forms is (800) 822-7967, or visit the VAERS website at http://vaers.hhs.gov. VAERS accepts reports of adverse reactions through their online system.

Contraindications and Precautions to Vaccination

Contraindications and precautions to vaccination generally dictate circumstances when vaccines will not be given. Many contraindications and precautions are temporary, and the vaccine can be given at a later time.

A contraindication is a condition that increases the likelihood of a serious adverse reaction to a vaccine for a patient with that condition. If the vaccine were given in the presence of that condition, the resulting adverse reaction could seriously harm the recipient. For instance, administering MMR vaccine to a person with a true anaphylactic allergy to gelatin could cause serious illness or death in the recipient. In general, vaccines should not be administered when a contraindication condition is present.

A precaution is a condition in a recipient that *might increase* the chance or severity of a serious adverse reaction, or that might compromise the ability of the vaccine to produce immunity (such as administering measles vaccine to a person with passive immunity to measles from a blood transfusion). Injury could result, but the chance of this happening is less than with a contraindication. In general, vaccines are deferred when a precaution condition is present. However, situations may arise when the benefit of protection from the vaccine outweighs the risk of an adverse reaction, and a provider may decide to give the vaccine.

There are very few true contraindication and precaution conditions. Only four of these conditions are generally considered to be permanent contraindications: severe (anaphylactic) allergic reaction to a vaccine component or following a prior dose of a vaccine; encephalopathy not due to another identifiable cause occurring within 7 days of pertussis vaccination; severe combined immunodeficiency (SCID) and a history of intussusception as contraindications to rotavirus vaccine.

Conditions considered permanent precautions to further doses of pediatric DTaP are temperature of 105°F or higher within 48 hours of a dose, collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours of a dose, persistent inconsolable crying lasting 3 or more hours occurring within 48 hours of a dose, or a seizure, with

Contraindication

- A condition that increases the likelihood of a serious adverse reaction to a vaccine for a patient with that condition

Precaution

- A condition in a recipient that might increase the chance or severity of an adverse reaction, or
- Might compromise the ability of the vaccine to produce immunity

Contraindications and Precautions

Permanent contraindications to vaccination:

- Severe allergic reaction to a vaccine component or following a prior dose
- Encephalopathy not due to another identifiable cause occurring within 7 days of pertussis vaccination
- Severe combined immunodeficiency (rotavirus vaccine)
- History of intussusception (rotavirus vaccine)

Condition	Live	Inactivated
Allergy to component	C	C
Encephalopathy	---	C
Pregnancy	C	V*
Immuno-suppression	C	V
Severe illness	P	P
Recent blood product	P**	V

C=contraindication P=precaution
V=vaccinate if indicated

*except HPV. **MMR and varicella containing (except zoster vaccine) only

or without fever, occurring within 3 days of a dose. The occurrence of one of these events in a child following DTaP vaccine is not a precaution to later vaccination with the adolescent/adult formulation of pertussis vaccine (Tdap).

Two conditions are temporary precautions to vaccination: moderate or severe acute illness (all vaccines), and recent receipt of an antibody-containing blood product. The latter precaution applies only to MMR and varicella-containing (except zoster) vaccines. Two conditions are temporary contraindications to vaccination with live vaccines: pregnancy and immunosuppression.

Allergy

A severe (anaphylactic) allergic reaction following a dose of vaccine will almost always contraindicate a subsequent dose of that vaccine. Anaphylactic reactions are those that are mediated by IgE, occur within minutes or hours of receiving the vaccine, and require medical attention. Examples of symptoms and signs typical of anaphylactic reactions are generalized urticaria (hives), swelling of the mouth and throat, difficulty breathing, wheezing, hypotension, or shock. These reactions are very rare following vaccination and can be further minimized with appropriate screening.

A table listing vaccine contents is included in Appendix B. Persons may be allergic to the vaccine antigen or to a vaccine component such as animal protein, antibiotic, preservative, or stabilizer. The most common animal protein allergen is egg protein found in vaccines prepared using embryonated chicken eggs (e.g., yellow fever and influenza vaccines). Ordinarily, a person who can eat eggs or egg products can receive vaccines that contain egg; persons with histories of anaphylactic or anaphylactic-like allergy to eggs or egg proteins should be referred for further evaluation. Asking persons whether they can eat eggs without adverse effects is a reasonable way to screen for those who might be at risk from receiving yellow fever and egg-containing influenza vaccines.

Studies have shown that children who have a history of severe allergy to eggs rarely have reactions to MMR vaccine. This is probably because measles and mumps vaccine viruses are both grown in chick embryo fibroblasts, not actually in eggs. It appears that gelatin, not egg, might be the cause of allergic reactions to MMR. As a result, in 1998, the ACIP removed severe egg allergy as a contraindication to measles and mumps vaccines. Egg-allergic children may be vaccinated with MMR without prior skin testing.

Certain vaccines contain trace amounts of neomycin. Persons who have experienced an anaphylactic reaction to neomycin should not receive these vaccines. Most often,

neomycin allergy presents as contact dermatitis, a manifestation of a delayed-type (cell-mediated) immune response, rather than anaphylaxis. A history of delayed-type reactions to neomycin is not a contraindication for administration of vaccines that contain neomycin.

Latex is sap from the commercial rubber tree. Latex contains naturally occurring impurities (e.g., plant proteins and peptides), which are believed to be responsible for allergic reactions. Latex is processed to form natural rubber latex and dry natural rubber. Dry natural rubber and natural rubber latex 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 syringe plungers, 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 therefore, do not contain the impurities linked to allergic reactions.

The most common type of latex sensitivity is contact-type (type 4) allergy, usually as a result of prolonged contact with latex-containing gloves. However, injection-procedure-associated latex allergies among diabetic patients have been described. Allergic reactions (including anaphylaxis) after vaccination procedures are rare. Only one report of an allergic reaction after administration of hepatitis B vaccine in a patient with known severe allergy (anaphylaxis) to latex has been published.

If a person reports a severe (anaphylactic) allergy to latex, vaccines supplied in vials or syringes that contain natural rubber should not be administered unless the benefit of vaccination clearly outweighs the risk of an allergic reaction to the vaccine. 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 can be administered.

Pregnancy

The concern with vaccination of a pregnant woman is infection of the fetus and is theoretical. Only smallpox (vaccinia) vaccine has been shown to cause fetal injury. However, since the theoretical possibility exists, live vaccines should not be administered to women known to be pregnant.

Since inactivated vaccines cannot replicate, they cannot cause fetal infection. In general, inactivated vaccines may be administered to pregnant women for whom they are indicated. An exception is human papillomavirus vaccine,

Vaccination of Pregnant Women

- Live vaccines should not be administered to women known to be pregnant
- In general inactivated vaccines may be administered to pregnant women for whom they are indicated
- HPV vaccine should be deferred during pregnancy

Tdap Recommendations for Pregnant Women

- Healthcare personnel should implement a Tdap vaccination program for pregnant women who previously have not received Tdap
- Administer Tdap during each pregnancy, preferably between 27 and 36 weeks gestation
- If not administered during pregnancy, Tdap should be administered immediately postpartum

which should be deferred during pregnancy because of a lack of safety and efficacy data for this vaccine in pregnant women.

Pregnant women are at increased risk of complications of influenza. Any woman who will be pregnant during influenza season (generally December through March) should receive inactivated influenza vaccine. Pregnant women should not receive live attenuated influenza vaccine.

ACIP recommends that providers of prenatal care implement a Tdap immunization program for all pregnant women. Healthcare personnel should administer a dose of Tdap during each pregnancy, irrespective of the patient's prior history of receiving Tdap. To maximize the maternal antibody response and passive antibody transfer to the infant, optimal timing for Tdap administration is between 27 and 36 weeks gestation although Tdap may be given at any time during pregnancy. For women not previously vaccinated with Tdap, if Tdap is not administered during pregnancy, Tdap should be administered immediately postpartum.

Studies on the persistence of antipertussis antibodies following a dose of Tdap show antibody levels in healthy, nonpregnant adults peak during the first month after vaccination, with subsequent antibody waning after 1 year. Antibody levels in pregnant women likely would be similar. Because antibody levels wane substantially during the first year after vaccination, ACIP concluded a single dose of Tdap at one pregnancy would be insufficient to provide protection for subsequent pregnancies.

Susceptible household contacts of pregnant women should receive MMR and varicella vaccines, and may receive LAIV, zoster and rotavirus vaccines if they are otherwise eligible.

Immunosuppression

Vaccination of Immunosuppressed Persons

- Live vaccines should not be administered to severely immunosuppressed persons
- Persons with isolated B-cell deficiency may receive varicella vaccine
- Inactivated vaccines are safe to use in immunosuppressed persons but the response to the vaccine may be decreased

Live vaccines can cause severe or fatal reactions in immunosuppressed persons due to uncontrolled replication of the vaccine virus. Live vaccines should not be administered to severely immunosuppressed persons for this reason. Generally the ultimate determination of severe immunosuppression should be made by the provider treating the immunosuppressed patient. Persons with isolated B-cell deficiency may receive varicella vaccine. Inactivated vaccines cannot replicate, so they are safe to use in immunosuppressed persons. However, response to the vaccine may be decreased.

Both diseases and drugs can cause significant immunosuppression. Persons with congenital immunodeficiency, leukemia, lymphoma, or generalized malignancy should not receive live vaccines. However, MMR, varicella, rotavirus,

and LAIV vaccines may be given when an immunosuppressed person lives in the same house. Household contacts of immunosuppressed persons may receive zoster vaccine if indicated.

Certain drugs may cause immunosuppression. For instance, persons receiving cancer treatment with alkylating agents or antimetabolites, or radiation therapy should not be given live vaccines. Live vaccines can be given after chemotherapy has been discontinued for at least 3 months. Persons receiving large doses of corticosteroids should not receive live vaccines. For example, this would include persons receiving 20 milligrams or more of prednisone daily or 2 or more milligrams of prednisone per kilogram of body weight per day for 14 days or longer. See Varicella chapter for more information about administration of zoster vaccine to immunosuppressed persons.

Aerosolized steroids, such as inhalers for asthma, are not contraindications to vaccination, nor are alternate-day, rapidly tapering, and short (less than 14 days) high-dose schedules, topical formulations, and physiologic replacement schedules.

The safety and efficacy of live attenuated vaccines administered concurrently with recombinant human immune mediators and immune modulators are not known. There is evidence that use of therapeutic monoclonal antibodies, especially the anti-tumor necrosis factor (TNF) agents adalimumab, infliximab, and etanercept, may lead to reactivation of latent tuberculosis infection and tuberculosis disease and predispose to other opportunistic infections. Because these drugs vary dramatically in the scope and number of immune system targeted components, it is prudent to avoid administration of live attenuated vaccines while patients are taking these drugs. For immunization against seasonal influenza and typhoid, inactivated injectable alternatives are available.

The period of time providers should wait after discontinuation of immune modulator drugs before administering a live-virus vaccine is not specified by ACIP or other authoritative guidelines (except in the case of zoster vaccine). Consultation with the prescribing physician (and possibly a hospital pharmacist) is recommended for management of individual patients and guidance in estimating a particular patient's degree of immunosuppression. No basis exists for interpreting laboratory studies of immune parameters with vaccines' safety or efficacy. Some experts recommend waiting 1 month after discontinuing etanercept and 3 months after discontinuing the other anti-TNF agents. Lymphocyte depleting agents such as alemtuzumab and rituximab may cause prolonged immunosuppression.

Immunosuppression

- Disease
  - congenital immunodeficiency
  - leukemia or lymphoma
  - generalized malignancy
- Chemotherapy
  - alkylating agents
  - antimetabolites
  - radiation
- Corticosteroids
  - 20 mg or more per day of prednisone*
  - 2 mg/kg or more per day of prednisone*
  - NOT aerosols, alternate-day, short courses, topical

*for 14 days or longer

Restarting immunosuppression after live viral vaccination has not been studied, but some experts would recommend at least a 1-month period.

Inactivated vaccines may be administered to immunosuppressed persons. Certain vaccines are recommended or encouraged specifically because immunosuppression is a risk factor for complications from vaccine-preventable diseases (i.e., influenza, invasive pneumococcal disease, invasive meningococcal disease, invasive *Haemophilus influenzae* type b disease, and hepatitis B). However, response to the vaccine may be poor depending on the degree of immunosuppression present. Because a relatively functional immune system is required to develop an immune response to a vaccine, an immunosuppressed person may not be protected even if the vaccine has been given. Additional recommendations for vaccination of immunosuppressed persons are detailed in the *General Recommendations on Immunization*.

HIV Infection

Persons infected with human immunodeficiency virus (HIV) may have no disease manifestations, or they may be severely immunosuppressed. In general, the same vaccination recommendations apply as with other types of immunosuppression. Live-virus vaccines are usually contraindicated in those with severe immunosuppression (defined by the treating provider) but inactivated vaccines may be administered if indicated.

Varicella can be a very severe illness in persons with HIV infection and is often associated with complications. Varicella vaccine can be considered for persons with HIV infection who are not severely immunosuppressed. Zoster vaccine should not be given to persons with AIDS or clinical manifestations of HIV infection. Persons with HIV infection should not receive LAIV; they should receive inactivated influenza vaccine (IIV). Yellow fever vaccine should be considered for persons who do not have AIDS or other symptomatic manifestations of HIV infection, who have established laboratory verification of adequate immune system function, and who cannot avoid potential exposure to yellow fever virus.

Household contacts without evidence of immunity to measles, mumps, rubella, or varicella should receive MMR and varicella vaccines, and may receive rotavirus, zoster and LAIV vaccines if otherwise eligible.

Vaccination of Hematopoietic Cell Transplant Recipients

Hematopoietic cell transplant (HCT) is the infusion of hematopoietic cells from a donor into a patient who has received chemotherapy and often radiation, both of which are usually bone marrow ablative. HCT is used to treat a variety of neoplastic diseases, hematologic disorders, immunodeficiency syndromes, congenital enzyme deficiencies, and autoimmune disorders. HCT recipients can receive either their own cells (i.e., autologous HCT) or cells from a donor other than the transplant recipient (i.e., allogeneic HCT).

Antibody titers to vaccine-preventable diseases (e.g., tetanus, poliovirus, measles, mumps, rubella, and encapsulated bacteria [i.e., *Streptococcus pneumoniae* and *Haemophilus influenzae* type b]) decline during the 1–4 years after allogeneic or autologous HCT if the recipient is not revaccinated. HCT recipients are at increased risk for certain vaccine-preventable diseases. As a result, HCT recipients should be routinely revaccinated after HCT, regardless of the source of the transplanted cells. Revaccination with inactivated vaccines should begin 6 months after HCT. Influenza vaccine also should be administered at 6 months after HCT, but can be given as early as 4 months after HCT. In this circumstance an additional dose should be given. Influenza vaccine should be given annually thereafter for the life of the recipient. Three doses of PCV13 should be given 6 months after HCT, followed by a dose of PPSV23. Revaccination to prevent pertussis should involve a primary series of DTaP followed by a Tdap booster. A dose of MCV4 should be given.

MMR and varicella vaccines should be administered 24 months after transplantation if the HCT recipient is presumed to be immunocompetent.

Household and other close contacts of HCT recipients and healthcare providers who care for HCT recipients should be appropriately vaccinated, particularly against influenza, measles, mumps, rubella, and varicella. Additional details of vaccination of HCT recipients and their contacts can be found in the ACIP statement titled *General Recommendations on Immunization*.

Vaccination of Hematopoietic Cell Transplant (HCT) Recipients

- Antibody titers to VPDs decline during the 1-4 years after allogeneic or autologous HCT if the recipient is not revaccinated
- HCT recipients are at increased risk of some VPDs, particularly pneumococcal disease
- Revaccination recommended beginning 6-12 months post-transplant
- Inactivated influenza vaccine at least 6 months following transplant and annual thereafter
- Inactivated vaccines (DTaP/Td, IPV, hepatitis B, Hib, PCV13, PPSV23) at 6 months
- MMR and varicella vaccines at 24 months if immunocompetent

Vaccination of Household Contacts of Hematopoietic Cell Transplant (HCT) Recipients

- Healthy household contacts of HCT recipients should receive MMR and varicella vaccines and annual influenza vaccination

Moderate or Severe Acute Illness

There is no evidence that a concurrent acute illness reduces vaccine efficacy or increases vaccine adverse events. The concern is that an adverse event (particularly fever) following vaccination could complicate the management of a severely ill person. If a person has a moderate or severe acute illness, vaccination with both live and inactivated vaccines should be delayed until the patient has recovered from the illness.

Invalid Contraindications to Vaccination

- Mild illness
- Antimicrobial therapy
- Disease exposure or convalescence
- Pregnant or immunosuppressed person in the household
- Breastfeeding
- Preterm birth
- Allergy to products not present in vaccine or allergy that is not anaphylactic
- Family history of adverse events
- Tuberculin skin testing
- Multiple vaccines

Invalid Contraindications to Vaccination

Some healthcare providers inappropriately consider certain conditions or circumstances to be contraindications or precautions to vaccinations. Such conditions or circumstances are known as invalid contraindications; these misperceptions result in missed opportunities to administer needed vaccines. Some of the most common invalid contraindications are mild illnesses, conditions related to pregnancy and breastfeeding, allergies that are not anaphylactic in nature, and certain aspects of the patient's family history.

Mild Illness

Children with mild acute illnesses, such as low-grade fever, upper respiratory infection (URI), colds, otitis media, and mild diarrhea, should be vaccinated on schedule. Several large studies have shown that young children with URI, otitis media, diarrhea, and/or fever respond to measles vaccine as well as those without these conditions. There is no evidence that mild diarrhea reduces the success of immunization of infants in the United States.

Low-grade fever is not a contraindication to immunization. Temperature measurement is not necessary before immunization if the infant or child does not appear ill and the parent does not say the child is currently ill. ACIP has not defined a body temperature above which vaccines should not be administered. The decision to vaccinate should be based on the overall evaluation of the person rather than an arbitrary body temperature.

Antimicrobial Therapy

Antibiotics do not have an effect on the immune response to most vaccines. The manufacturer advises that Ty21a oral typhoid vaccine should not be administered to persons receiving sulfonamides or other antibiotics; Ty21a should be administered at least 72 hours after a dose of an antibacterial drug.

No commonly used antimicrobial drug will inactivate a live-virus vaccine. However, antiviral drugs may affect vaccine replication in some circumstances. Live attenuated influenza vaccine should not be administered until 48 hours after cessation of therapy using antiviral drugs active against influenza (amantadine, rimantadine, zanamivir, oseltamivir). Antiviral drugs active against herpesviruses (acyclovir, famciclovir) should be discontinued 24 hours before administration of a varicella-containing vaccine, if possible.

Disease Exposure or Convalescence

If a person is not moderately or severely ill, he or she should be vaccinated. There is no evidence that either disease exposure or convalescence will affect the response to a vaccine or increase the likelihood of an adverse event.

Pregnant or Immunosuppressed Person in the Household

It is critical that healthy household contacts of pregnant women and immunosuppressed persons be vaccinated. Vaccination of healthy contacts reduces the chance of exposure of pregnant women and immunosuppressed persons.

Most vaccines, including live vaccines (MMR, varicella, zoster, rotavirus, LAIV, and yellow fever) can be administered to infants or children who are household contacts of pregnant or immunosuppressed persons, as well as to breastfeeding infants (where applicable). Vaccinia (smallpox) vaccine should not be administered to household contacts of a pregnant or immunosuppressed person in a nonemergency situation. Live attenuated influenza vaccine should not be administered to persons who have contact with persons who are hospitalized and require care in a protected environment (i.e., who are in isolation because of immunosuppression). LAIV may be administered to contacts of persons with lesser degrees of immunosuppression.

Transmission of measles and mumps vaccine viruses to household or other contacts has never been documented. Rubella vaccine virus has been shown to be shed in human milk, but transmission to an infant has rarely been documented. Transmission of varicella vaccine virus has been reported very rarely, and most women and older immunosuppressed persons are immune from having had chickenpox as a child. Transmission of zoster vaccine virus to household or other close contacts has not been reported.

Breastfeeding

Breastfeeding does not decrease the response to routine childhood vaccines and is not a contraindication for any vaccine except smallpox. Yellow fever vaccine should be avoided in breastfeeding women. 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. Breastfeeding also does not extend or improve the passive immunity to vaccine-preventable disease that is provided by maternal antibody except possibly for *Haemophilus influenzae* type b. Breastfed infants should be vaccinated according to recommended schedules.

Although rubella vaccine virus might be shed in human milk, infection of an infant is rare. LAIV may be administered to a woman who is breastfeeding if she is otherwise eligible; the risk of transmission of vaccine virus is unknown but is probably low.

Preterm Birth

Vaccines should be started on schedule on the basis of the child's chronological age. Preterm infants have been shown to respond adequately to vaccines used in infancy.

Studies demonstrate that decreased seroconversion rates might occur among preterm infants with very low birth weight (less than 2,000 grams) after administration of hepatitis B vaccine at birth. However, by 1 month chronological age, all preterm infants, regardless of initial birth weight or gestational age are as likely to respond as adequately as older and larger infants. All preterm infants born to hepatitis B surface antigen (HBsAg)-positive mothers and mothers with unknown HBsAg status must receive immunoprophylaxis with hepatitis B vaccine within 12 hours after birth. Hepatitis B immunoglobulin (HBIG) also must be given to these infants. If the maternal HBsAg status is unknown, and the infant weighs 2,000 grams or more, HBIG must be given within 7 days of birth. If the maternal HBsAg status is positive or the infant weighs less than 2,000 grams, HBIG must be given within 12 hours of birth. Note that if the infant weighs less than 2,000 grams, the initial hepatitis B vaccine dose should not be counted toward completion of the hepatitis B vaccine series, and three additional doses of hepatitis B vaccine should be administered beginning when the infant is 1 month of age.

Preterm infants with a birth weight of less than 2,000 grams who are born to women documented to be HBsAg-negative at the time of birth should receive the first dose of the hepatitis B vaccine series at 1 month of chronological age or at the time of hospital discharge.

Allergy to Products Not Present in Vaccine

Infants and children with nonspecific allergies, duck or feather allergy, or allergy to penicillin, children who have relatives with allergies, and children taking allergy shots can and should be immunized. No vaccine available in the United States contains duck antigen or penicillin.

Allergy That is Not Anaphylactic

Anaphylactic allergy to a vaccine component (such as egg or neomycin) is a true contraindication to vaccination. If an allergy to a vaccine component is not anaphylactic or is not severe, it is not a contraindication to that vaccine.

Family History of Adverse Events

A family history of seizures is a precaution for the use of MMRV vaccine. Immunosuppression may affect the decision for varicella vaccine. A family history of adverse reactions unrelated to immunosuppression or family history of seizures or sudden infant death syndrome (SIDS) is not a contraindication to vaccination. Varicella vaccine should not be administered to persons who have a family history of congenital or hereditary immunodeficiency in first-degree relatives (e.g., parents and siblings) unless the immunocompetence of the potential vaccine recipient has been clinically substantiated or verified by a laboratory.

Tuberculin Skin Test

Infants and children who need a tuberculin skin test (TST) can and should be immunized. All vaccines, including MMR, can be given on the same day as a TST, or any time after a TST is applied. For most vaccines, there are no TST timing restrictions.

MMR vaccine may decrease the response to a TST, potentially causing a false-negative response in someone who actually has an infection with tuberculosis. MMR can be given the same day as a TST, but if MMR has been given and 1 or more days have elapsed, in most situations a wait of at least 4 weeks is recommended before giving a routine TST. No information on the effect of varicella-containing vaccine or LAIV on a TST is available. Until such information is available, it is prudent to apply rules for spacing measles vaccine and TST to varicella-containing vaccine and LAIV.

There is a type of tuberculosis test known as an interferon-gamma release assay (IGRA). Even though this test improves upon the TST because it is less affected by previous doses of BCG vaccine and less affected by previous doses of tuberculosis diagnostic testing, it still may be affected by previous doses of other live vaccines so it is prudent to apply the same spacing rules as for TST.

Multiple Vaccines

As noted earlier in this chapter, administration at the same visit of all vaccines for which a person is eligible is critical to reaching and maintaining high vaccination coverage. Varicella vaccine should not be administered simultaneously with smallpox vaccine; and PCV13 and Menactra should not be administered simultaneously in children with functional or anatomic asplenia.

Screening Questions

- Is the child (or are you) sick today?
- Does the child have allergies to medications, food, or any vaccine?
- Has the child had a serious reaction to a vaccine in the past?
- Has the child had a seizure, brain or nerve problem?
- Has the child had a health problem with asthma, lung disease, heart disease, kidney disease, metabolic disease such as diabetes, or a blood disorder?
- Does the child have cancer, leukemia, AIDS, or any other immune system problem?
- Has the child taken cortisone, prednisone, other steroids, or anticancer drugs, or had x-ray treatments in the past 3 months?
- Has the child received a transfusion of blood or blood products, or been given a medicine called immune (gamma) globulin in the past year?
- Is the person pregnant or is there a chance she could become pregnant during the next month?
- Has the child received vaccinations in the past 4 weeks?

Screening for Contraindications and Precautions to Vaccination

The key to preventing serious adverse reactions is screening. Every person who administers vaccines should screen every patient for contraindications and precautions before giving the vaccine dose. Effective screening is not difficult or complicated and can be accomplished with just a few questions.

Is the child (or are you) sick today?

There is no evidence that acute illness reduces vaccine efficacy or increases vaccine adverse events. 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.

Does the child have allergies to medications, food, or any vaccine?

A history of anaphylactic reaction such as hives (urticaria), wheezing or difficulty breathing, or circulatory collapse or shock (not fainting) from a previous dose of vaccine or vaccine component is a contraindication for further doses. It may be more efficient to inquire about allergies in a generic way (i.e., any food or medication) rather than to inquire about specific vaccine components. Most parents will not be familiar with minor components of vaccine, but they should know if the child has had an allergic reaction to a food or medication that was severe enough to require medical attention. If a person reports anaphylaxis after eating eggs, a specific protocol should be followed that includes ascertaining the symptoms experienced. For specific information, see Influenza chapter.

Has the child had a serious reaction to a vaccine in the past?

A history of anaphylactic reaction to a previous dose of vaccine or vaccine component is a contraindication for subsequent doses. A 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 (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 hours within 48 hours of a dose, and (d) fever of 105°F (40°C) or higher 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. Usually 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). A local reaction (redness or swelling at the site of injection) is not a contraindication to subsequent doses.

Has the child had a seizure, or brain or nerve problem?

DTaP and Tdap are contraindicated for children who have a history of encephalopathy not attributed to an identifiable cause within 7 days following DTP/DTaP. An unstable progressive neurologic problem is a precaution to the use of DTaP and Tdap. Children with stable neurologic disorders (including seizures) unrelated to vaccination may be vaccinated as usual.

A history of Guillain-Barré syndrome is a precaution for tetanus-containing and influenza vaccines.

Patients with a personal or family history of febrile or afebrile seizures have a precaution for MMRV vaccine. Simultaneous MMR and varicella vaccine administration (the single component vaccines) is not associated with an increased risk of fever or seizures and is therefore the acceptable alternative to MMRV.

Has the child had a health problem with asthma, lung disease, heart disease, kidney disease, metabolic disease such as diabetes, or a blood disorder?

Children with any of these conditions should not receive LAIV. Children with these conditions should receive inactivated influenza vaccine only.

Does the child have cancer, leukemia, AIDS, or any other immune system problem?

Live-virus vaccines (e.g., MMR, varicella, rotavirus, and the intranasal live attenuated influenza vaccine [LAIV]) are usually contraindicated in severely immunocompromised children. Persons with severe immunosuppression should not receive MMR, varicella, rotavirus, or LAIV vaccines. However, there are exceptions. For example, MMR and varicella vaccines are recommended for HIV-infected children who do not have evidence of severe immunosuppression. For details, consult the ACIP recommendations for each vaccine.

Has the child taken cortisone, prednisone, other steroids, or anticancer drugs, or had x-ray treatments in the past 3 months?

Live-virus vaccines (e.g., MMR, varicella, zoster, LAIV) should be postponed until after chemotherapy or long-term, high-dose steroid therapy has ended. Details and the length of time to postpone vaccination are described elsewhere in this chapter and in the *General Recommendations on Immunization*.

Has the child received a transfusion of blood or blood products, or been given a medicine called immune (gamma) globulin in the past year?

Certain live virus vaccines (e.g., MMR and varicella) may need to be deferred, depending on the type of blood product and the interval since the blood product was administered. Information on recommended intervals between immune globulin or blood product administration and MMR or varicella vaccination is in Appendix A and in the *General Recommendations on Immunization*.

Is the person pregnant or is there a chance she could become pregnant during the next month?

Live-virus vaccines (e.g., MMR, varicella, zoster, LAIV) are contraindicated during pregnancy because of the theoretical risk of virus transmission to the fetus. Sexually active young women who receive MMR or varicella vaccination should be instructed to practice careful contraception for 1 month following receipt of either vaccine. On theoretical grounds, inactivated poliovirus vaccine should not be given during pregnancy; however, it may be given if the risk of exposure is imminent (e.g., travel to endemic-disease areas) and immediate protection is needed.

Has the child received vaccinations in the past 4 weeks?

If the child was given either live attenuated influenza vaccine or an injectable live-virus vaccine (e.g., MMR. varicella, yellow fever) in the past 4 weeks, he or she should wait 28 days before receiving another live vaccine. Inactivated vaccines may be given at the same time or at any time before or after a live vaccine.

Every person should be screened for contraindications and precautions before vaccination. Standardized screening forms for both children and adults have been developed by the Immunization Action Coalition and are available at http://www.immunize.org.

Selected References

American Academy of Pediatrics. Active and passive immunization. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases*. 29th edition. Elk Grove Village, IL: American Academy of Pediatrics; 2012.

Atkinson WL, Kroger AT, Pickering LK. General immunization practices. In: Plotkin SA, Orentsein WA, Offit PA. eds. *Vaccines*. 5th ed., China: Saunders; 2008.

CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2011;60(No. RR-2):1–61.

Dietz VJ, Stevenson J, Zell ER, et al. Potential impact on vaccination coverage levels by administering vaccines simultaneously and reducing dropout rates. *Arch Pediatr Adolesc Med* 1994;148:943–9.

James JM, Burks AW, Roberson RK, Sampson HA. Safe administration of the measles vaccine to children allergic to eggs. *N Engl J Med* 1995;332:1262–9.

King GE, Hadler SC. Simultaneous administration of childhood vaccines: an important public health policy that is safe and efficacious. *Pediatr Infect Dis J* 1994;13:394–407.

Plotkin SA. Vaccines, vaccination and vaccinology. *J. Infect Dis* 2003;187:1349–59.

Tomblyn M, Chiller T, Einsele H, et. al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. *Biol Blood Marrow Transplant* 2009;15:1143-1238.

Wood, RA, Berger M, Dreskin M, et. al. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. *Pediatrics* 2008;122 (No. 3) e771-7.

This chapter provides an overview of best practice guidance for storage and handling. CDC's *Vaccine Storage and Handling Toolkit*, http://www.cdc.gov/vaccines/recs/storage/toolkit/storage-handling-toolkit.pdf, contains comprehensive information on best practices and recommendations. Manufacturers' product information and package inserts include the most current information about the storage and handling of specific vaccines. Refer to CDC's *Storage and Handling* webpage for links to these and other resources, http://www.cdc.gov/vaccines/recs/storage/default.htm. Participants in the Vaccines for Children (VFC) program or those who have any vaccines purchased with public funds should consult their state or local immunization program for specifics because some program requirements may differ from the information contained in the *Vaccine Storage and Handling* Toolkit.

Vaccine Storage and Handling

There are few immunization issues more important than the appropriate storage and handling of vaccines. Vaccine-preventable disease rates have decreased in part because of proper storage and handling of vaccines. Exposure of vaccines to temperatures outside the recommended ranges can decrease their potency and reduce the effectiveness and protection they provide. Storage and handling errors can cost thousands of dollars in wasted vaccine and revaccination. Errors can also result in the loss of patient confidence when repeat doses are required. It is better to not vaccinate than to administer a dose of vaccine that has been mishandled. Vaccine management, including proper storage and handling procedures, is the basis on which good immunization practices are built.

Vaccines must be stored properly from the time they are manufactured until they are administered. Assuring vaccine quality and maintaining the cold chain is a shared responsibility among manufacturers, distributors, public health staff, and health-care providers. A proper cold chain is a temperature-controlled supply chain that includes all equipment and procedures used in the transport and storage and handling of vaccines from the time of manufacture to administration of the vaccine. By following a few simple steps and implementing best storage and handling practices, providers can ensure that patients will get the full benefit of vaccines they receive.

Storage and Handling Plans

Every facility should have detailed written protocols for routine and emergency vaccine storage and handling and they should be updated annually. These policies and procedures should be available in writing as a reference for all staff members and easily accessible.

Vaccine Storage and Handling

- Vaccine-preventable disease rates decreased in part because of proper storage and handling
- Storage and handling errors
  - decrease potency and reduce effectiveness and protection
  - cost thousands of dollars in wasted vaccine and revaccination
  - loss of patient confidence
- It is better to not vaccinate than to administer a dose of vaccine that has been mishandled

Cold Chain (a temperature-controlled supply chain)

- Vaccines must be stored properly from the time they are manufactured until they are administered
- Shared responsibility among manufacturers, distributors, public health staff, and healthcare providers

Vaccine Storage and Handling Plans

- Develop and maintain written ROUTINE plan for:
  - ordering and accepting vaccine deliveries
  - storing and handling vaccines
  - managing inventory
  - managing potentially compromised vaccines
- Develop and maintain written EMERGENCY vaccine retrieval and storage plan
  - back-up storage location with appropriate storage units, temperature monitoring capability, and back-up generator that can maintain power to the vaccine storage units
  - adequate supply of packing materials and portable refrigerators and freezers or qualified containers and packouts, or refrigerated truck

Staff Training and Education

- Assign responsibilities to a primary vaccine coordinator
- Designate at least one alternate (back-up) vaccine coordinator

A routine storage and handling plan provides guidelines for daily activities, such as:

- Ordering and accepting vaccine deliveries
- Storing and handling vaccines
- Managing inventory
- Managing potentially compromised vaccines

Every facility should also have an emergency vaccine retrieval and storage plan. The plan should identify a back-up location where the vaccines can be stored. Considerations when choosing this site include appropriate storage units, temperature monitoring capability, and a back-up generator that can maintain power to the vaccine storage units. Potential back-up locations might include a local hospital, pharmacy, long-term care facility, or the Red Cross.

There should be an adequate supply of packing materials and portable refrigerators and freezers or qualified containers and packouts on hand to accommodate the facility's largest annual vaccine inventory (e.g., flu season). A refrigerated truck may be needed to move large inventories of vaccine.

Power outages or natural disasters are not the only events that can compromise vaccine. Forgotten vials of vaccine left out on the counter or doses of vaccine stored at improper temperatures due to a storage unit failure are other examples of how vaccines can be potentially compromised. Protocols after an event will vary depending on individual state or agency policies. Contact the local or state health department immunization program (hereafter referred to as "immunization program"), vaccine manufacturer(s), or both for appropriate actions or guidelines that should be followed for all potentially compromised vaccines. Do not discard vaccines unless directed to by the immunization program and/or the manufacturer.

Staff Training and Education

Assign a primary vaccine coordinator who is responsible for ensuring that vaccines are stored and handled correctly at each facility. Designate at least one alternate (back-up) vaccine coordinator who can perform these responsibilities in the absence of the primary coordinator. These responsibilities include, but are not limited to, the following tasks:

- Ordering vaccines
- Overseeing proper receipt and storage of vaccine deliveries
- Organizing vaccines within the storage unit(s)

- Temperature monitoring of the storage unit(s) (i.e., current temperature at least 2 times each workday).
- Recording temperature readings on a log
- Daily physical inspection of the storage unit(s)
- Rotating stock so that vaccines closest to their expiration dates will be used first
- Monitoring expiration dates and ensuring that expired vaccines and diluents are removed from the storage unit(s) and not administered to patients
- Responding to potential temperature excursions
- Overseeing proper vaccine transport
- Maintaining all appropriate vaccine storage and handling documentation, including temperature-excursion responses
- Maintaining storage equipment and maintenance records
- Maintaining proper documentation for the VFC program in participating facilities
- Ensuring that designated staff is adequately trained

A physician partner or member of management should be directly involved with the clinical staff that is responsible for vaccine storage and handling. Management staff should have a clear understanding of the vaccine replacement costs and clinical implications of mismanaged vaccines.

All personnel who handle or administer vaccines should be familiar with the storage and handling policies and procedures for their facility. This includes not only those who administer vaccines, but also anyone who delivers or accepts vaccine shipments and anyone who has access to the unit(s) where vaccines are stored. Vaccine storage and handling training should be provided to all new personnel who handle or administer vaccines, including temporary staff. Continuing education for staff is essential when new vaccines are stocked and when there are any changes to the storage and handling guidelines for a particular vaccine. CDC has a free web-based storage and handling module as part of the online training tool, "*You Call the Shots*," at http://www.cdc.gov/vaccines/ed/youcalltheshots.htm. Continuing education credit for a variety of healthcare professionals and a certificate of completion are available. Many immunization programs and professional organizations also offer vaccine storage and handling training programs.

Training and Education

- Staff who
  - handle or administer vaccines
  - deliver or accept vaccine shipments
  - have access to vaccine storage unit(s)
- Provide training and continuing education when
  - new or temporary staff are oriented
  - new vaccines are stocked
  - changes to storage and handling guidelines occur

Vaccine Deliveries

- Notify vaccine coordinator or alternate (back-up) coordinator when delivery arrives
- Avoid having people accept deliveries who may not understand the importance of storage at appropriate temperatures upon arrival
- Examine vaccine deliveries
  - container
  - contents
  - shipping temperature monitors/indicators
- If there are concerns, label vaccines "Do NOT Use," store under appropriate conditions, separate from other vaccines
- Consult immunization program, distributor, and/or vaccine manufacturer for guidance

Receiving and Unpacking Vaccine Deliveries

Proper vaccine storage and handling is important from the moment the vaccine arrives at the facility. All office staff should be trained to notify the vaccine coordinator or the alternate (back-up) coordinator when a vaccine delivery has arrived. This is extremely important for receptionists or other front desk staff since they may be the first to know that vaccines have been delivered. Avoid having other people accept deliveries who may not understand the importance of storage at appropriate temperatures. The vaccine coordinator should request delivery during office hours and update vaccine orders to reflect any period of time the office will be closed, such as holidays or scheduled vacation time.

Examine deliveries right away and store vaccines at the proper temperatures immediately upon arrival. Examine the shipping container and its contents for any evidence of damage during shipment. Cross check the contents with the packing slip to be sure they match. Check heat and cold temperature monitors/indicators if either are included in the shipping container following instructions on the monitors for reading and reporting. If a monitor indicates a possible temperature excursion during shipping, the monitor reading should be documented for future reference. Report the reading to the distributor within the required timeframe if VFC vaccines or other vaccines purchased with public funds are involved. Vaccines sent directly by the manufacturer are in specially designed boxes and may not contain heat or cold temperature monitors.

Allowable shipping time varies among distributors and manufacturers and is dependent on the type of container and packout. Determine if shipping time was within allowable limits noted on shipping insert or container. If the shipping time was more than the allowable limit or there are any discrepancies with the packing slip or concerns about the contents, immediately notify the primary vaccine coordinator (or the alternate [back-up] coordinator). If neither is available, notify a supervisor immediately. Label the vaccines "Do NOT Use" and store the vaccines under appropriate conditions separate from other vaccines. Then, according to your facility's procedures, contact your immunization program, the distributor, and/or vaccine manufacturer(s) for guidance.

Record the contents of each container on an inventory log (stock record). This log should include the name of each vaccine, the number of doses for each vaccine received, the date it was received, the condition of the vaccines upon arrival, the names of the vaccine manufacturers, the lot numbers, the expiration dates for each vaccine, and any action taken regarding questionable vaccines.

Vaccine Storage and Temperature Monitoring Equipment

These items should be selected carefully, used properly, maintained regularly (including professionally serviced when needed), and monitored consistently to ensure the recommended temperatures are maintained. This chapter provides only general guidelines for equipment. Providers should consult their immunization program, particularly providers of VFC vaccines or other vaccines purchased with public funds, for any specific storage equipment requirements.

Keep a logbook for each piece of vaccine storage equipment. The serial number of each piece of equipment, the date each piece of equipment was installed, the dates of any routine maintenance tasks (such as cleaning), the dates of any repairs or service, and the contact information of the service provider should be recorded. A logbook is also an ideal place to keep the instructions that came with the equipment.

Freezers and Refrigerators

Using proper vaccine storage units can help prevent costly vaccine losses and the inadvertent administration of compromised vaccines. CDC recommends stand-alone units, meaning self-contained units that either freeze or refrigerate, and are suitable for vaccine storage. These units can vary in size, from compact, counter-top or under-the-counter style to large, pharmaceutical grade units. Studies demonstrated that stand-alone units maintain the required temperatures better than combination units, particularly the freezer section of household, combination units.

If existing equipment is a household, combination refrigerator/freezer, CDC recommends using only the refrigerator compartment for refrigerated vaccines. Use a separate stand-alone freezer to store frozen vaccines. Research found that freezers in household combination units cannot hold proper storage temperatures for frozen vaccines particularly during defrost cycles. This applies to both temporary and long-term storage.

Any freezer or refrigerator used for vaccine storage must be able to maintain the required temperature range throughout the year. The unit should be dedicated to the storage of biologics and must be large enough to hold inventory a provider might have at the busiest point in the year without crowding (including flu vaccine). There should also be enough room to store water bottles in the refrigerator and frozen water bottles in the freezer to stabilize the temperatures and help maintain temperature longer in a power outage.

Freezers and Refrigerators

- Stand-alone units that only freeze or refrigerate
  - can vary in size from compact, counter-top or under-the-counter to large, pharmaceutical grade
  - maintain required temperatures better than combination units, particularly the freezer section of these units
- If existing equipment is a household, combination refrigerator/freezer
  - only use refrigerator for vaccine storage
  - use a stand-alone freezer for frozen vaccines
  - applies to both temporary and long-term storage
- Able to maintain required temperature range throughout year
- Dedicated to storage of biologics
- Large enough to hold year's largest vaccine inventory without crowding (including flu vaccine)
- If stand-alone freezer is manual defrost, must defrost regularly and have another storage unit that maintains appropriate temperatures for temporary storage during defrosting
- Frost-free or automatic defrost cycle may be preferred

Storage Unit Placement

- Promote good air circulation around storage unit
  - place in well-ventilated room
  - allow for space on all sides and top
  - allow at least 4 inches between storage unit and a wall
  - do not block motor cover
  - ensure unit stands level with at least 1 to 2 inches between bottom of unit and floor

Dormitory-style Refrigerator

- Small combination freezer/refrigerator unit with one external door and an evaporator plate (cooling coil), which is usually located inside an icemaker compartment (freezer) within the refrigerator
- NOT recommended for vaccine storage under any circumstances, even temporarily
- Prohibited for storage of VFC vaccines or other vaccines purchased with public funds
- NOT recommended for vaccine storage under any circumstances, even temporarily

If your stand-alone freezer is manual defrost, you must defrost regularly and have another storage unit that maintains appropriate temperatures for temporary storage of the vaccine while defrosting. A frost-free unit with an automatic defrost cycle may be preferred if regular manual defrosting cannot be assured.

Good air circulation around a vaccine storage unit is essential for proper cooling functions. A storage unit should be in a well-ventilated room with space around the sides and top and at least 4 inches between the unit and a wall. Nothing should block the cover of the motor compartment and the unit should be level and stand firmly with at least 1 to 2 inches between the bottom of the unit and the floor.

CDC does not recommend storage of any vaccine in a dormitory-style or bar-style, combined refrigerator/freezer unit under any circumstances, even temporarily. A dormitory-style refrigerator is defined as a small combination freezer/refrigerator unit with one exterior door and an evaporator plate (cooling coil), which is usually located inside an icemaker compartment within the refrigerator. These units have exhibited severe temperature control and stability issues throughout the entire storage area. Dormitory-or bar-style units pose a significant risk of freezing vaccines, even when used for temporary storage. The use of this type of unit is prohibited for storage of VFC vaccines or other vaccines purchased with public funds.

Temperature Monitoring Devices

Temperature Monitoring is a critical part of good storage and handling practice. CDC recommends using only a calibrated digital data logger with a current and valid certificate of calibration testing (also known as a Report of Calibration). This certificate informs the user of a temperature monitoring device's level of accuracy compared to a recognized standard. Calibrated temperature monitoring devices are required for providers who receive VFC vaccines or other vaccines purchased with public funds.

All temperature monitoring devices, through normal use, drift over time, which affects their accuracy. Because of this, temperature monitoring devices should undergo periodic calibration testing. Testing should be performed every 1 to 2 years from the last testing date or according to the manufacturer's suggested timeline. CDC recommends that testing meets standards defined in the *Vaccine Storage and Handling Toolkit*. If calibration testing indicates that your temperature monitoring device is no longer accurate, it should be replaced. Immunization programs are often excellent resources for information on temperature monitoring devices.

Several types of temperature monitoring devices are available. CDC recommends digital data loggers with the following characteristics: a digital display easily readable from outside the unit; a detachable probe in a buffered material, which more closely reflects vaccine temperatures rather than air temperature in the unit; an alarm for out-of-range temperatures; current and minimum and maximum temprature accuracy within +/-1°F (+/-.5°C); a low battery indicator; memory that stores at least 4000 readings; and user programmable logging interval. CDC recommends a back-up digital data logger for each vaccine storage unit. Staff should be trained and understand how to set up, read and analyze temperature data provided by the data logger.

Temperature monitoring device placement within the unit is just as important as device selection. Place the buffered probe with the vaccines. This should be in the middle, center of the storage unit away from walls, ceiling, cooling vents, door, floor, and back of the unit. Prior to storing vaccines in a unit, allow the unit temperature to stabilize for a week before placing vaccines in the unit. CDC recommends using a digital data logger to monitor the temperature in the storage unit prior to storage of vaccines.

Temperature Monitoring

Regular temperature monitoring is key to proper cold chain management. Store frozen vaccines (Varicella, MMRV, and Zoster) in a freezer between -58°F and +5°F (-50°C and -15°C). Store all other routinely recommended vaccines in a refrigerator between 35°F and 46°F (2°C and 8°C). The desired average refrigerator vaccine storage temperature is 40°F (5°C). Exposure to temperatures outside these ranges may result in reduced vaccine potency and increased risk of vaccine-preventable diseases.

CDC recommends reviewing and recording temperatures in both the freezer and refrigerator units at least 2 times each workday, in the morning and before leaving at the end of the workday.

This best practice recommendation applies to all vaccine storage units, regardless of whether or not there is a temperature alarm, or a digital data logger that continuously records temperatures in the unit. These readings will provide a better indication of any problems with the storage unit's function.

Reviewing and recording temperatures also provides an opportunity to visually inspect the storage unit, reorganize the vaccines when necessary (e.g., moving vaccine away

Temperature Monitoring Devices

- Use only calibrated temperature monitoring devices with a certificate of calibration testing (Report of Calibration) from an accredited laboratory
  - required for providers who receive VFC vaccines or vaccines purchased with public funds
- Calibration testing every 1 to 2 years from last calibration testing date or according to the manufacturer's suggested timeline

Digital Data Logger Characteristics

- Digital temperature display outside storage unit
- Detachable probe in a buffered material
- Alarm
- Current and minimum and maximum temperatures
- Accuracy within +/-1°F (+/-.5°C)
- Low battery indicator
- Measures current and daily minimum and maximum temperatures in the unit
- Memory for storing at least 4,000 readings
- Uses programmable logging interval

Recommended Temperatures

- Freezer
  - between -58°F and +5°F (between -50°C and -15°C)
- Refrigerator
  - between 35°F and 46°F (between 2°C and 8°C)
  - average: 40°F (5°C)

Temperature Monitoring

- Review and record temperatures in both freezer and refrigerator units 2 times each day, once in the morning and once before leaving at the end of the workday
- Post temperature log on the door of each storage unit
- If using a continuous temperature monitor, download temperature data and review weekly
- Keep temperature logs (hard copies and downloaded data) 3 years or according to individual state record retention requirements

Temperature Excursion

- If stored vaccines have been exposed to temperatures outside recommended ranges
  - store the vaccines properly
  - separate from other vaccine supplies
  - mark "Do NOT Use"
  - contact immunization program, vaccine manufacturer(s), or both for guidance

from walls or cold air vents), identify vaccines and diluents with short expiration dates, remove any expired vaccines and diluents, and provide a timely response to temperature excursions.

Post a temperature log on each storage unit door or nearby in a readily accessible and visible location. In addition, if using a device that enables download of temperature data, review and store data at least once every week and reset the device before returning to storage unit monitoring.

CDC recommends maintaining an ongoing file of temperature data, including hard copies and downloaded data for at least 3 years or according to individual state record retention requirements. As the storage unit ages, recurring temperature variances or problems can be tracked and documented. This data can be important when evaluating the need for a new storage unit or if there is a potential need to recall and revaccinate patients because of improperly stored vaccine.

Twice daily temperature monitoring may not be accomplished when a provider's office is closed. A digital data logger that stores data and/or can be accessed remotely can provide information on storage temperatures while the office is closed and help assure that timely corrective action can be taken if temperatures go out of range. Providers should determine how they are to be notified in the event of an emergency (e.g., a power outage) during hours when the facility is not open.

Equally important to temperature monitoring is taking timely corrective action when there is a temperature excursion. If it is discovered that stored vaccines have been exposed to temperatures outside the recommended ranges, these vaccines should remain properly stored, but separated from other vaccine supplies and marked "Do NOT Use" until guidance can be obtained. Protocols after an event will vary depending on individual state or agency policies. Contact your immunization program, vaccine manufacturer(s), or both for guidance.

Vaccine and Diluent Placement and Labeling

Vaccines should be stored in the center of the unit as this is the area where appropriate temperatures are typically most stable. A storage unit should be big enough so that vaccines can be placed in the part of the unit best able to maintain the constant, required temperature away from the walls, coils, cooling vents, ceiling, door, floor and back of the unit. Vaccines and diluents should be kept in their original packaging with the lids on until ready for administration and stacked in rows with vaccine and diluent of the same

type. Trays or uncovered containers/bins that allow for air circulation can be used to organize the vaccines and diluents within the storage unit. Do not store vaccines in unit doors or in deli, vegetable, or fruit crisper drawers. Avoid storing vaccines on the refrigerator top shelf. If the top shelf must be used, place water bottles close to the vent and only store vaccines not sensitive to coldest temperatures (e.g., MMR).

Some diluents must be refrigerated and others may be stored in the refrigerator or at room temperature. Always follow the manufacturer's guidance in the product information/package inserts. If possible, store diluent next to the corresponding vaccine. Some of these diluents may contain vaccine antigen. Never store diluents in the freezer.

There should be space between the vaccine and diluent stacks or containers. This will help to avoid confusion between products, provide for air circulation around and through stacks for even cooling, and protect vaccines from unnecessary light exposure. Not only live attenuated vaccines, but also some inactivated vaccines must be protected from light. Information on light sensitivity can be found in the manufacturer's product information/package insert.

Each vaccine and diluent stack or container should be clearly labeled. This can be accomplished by attaching labels directly to the shelves on which vaccines and diluents are stored or by placing labels on the containers. Store pediatric and adult vaccines on different shelves. Use color coded labels that include the vaccine type, as well as age and gender indications, if applicable. Having each vaccine and diluent stack or container labeled helps decrease the chance that someone will inadvertently administer the wrong vaccine or use the wrong diluent to reconstitute a vaccine. Vaccines that sound or look alike should not be stored next to each other, e.g., DTaP and Tdap. VFC vaccines and other vaccines purchased with public funds should be identified and stored separately from vaccines purchased with private funds.

Vaccine and Diluent Placement and Labeling

- Store vaccines away from walls, coils, cooling vents, top shelf, ceiling, door, floor, and back of unit
- Keep vaccines and diluents in original packaging with lids on to protect from light
- Stack in rows with same type of vaccine and diluent
- Use uncovered storage containers to organize vaccines and diluents
- Do not store vaccines in storage unit doors, on the top shelf, on the floor, or in deli, vegetable or fruit crisper drawers
- Store pediatric and adult vaccines on different shelves
- Use labels with vaccine type, age, and gender indications or color coding
- Do not store sound-alike and look-alike vaccines next to each other
- VFC vaccines and other vaccines purchased with public funds should be identified and stored separately from vaccines purchased with private funds

Vaccine Storage Troubleshooting

To maintain the proper temperature ranges, the freezer and refrigerator units must be in good working condition and they must have power at all times. There are several things that can be done to prevent problems.

Plug storage units directly into wall outlets. Do not use power outlets with built-in circuit switches (they have little red reset buttons), outlets that can be activated by a wall switch, or multi-outlet power strips. These can be tripped or switched off, resulting in loss of electricity to the storage

Diluent Storage

- Store diluent as directed in manufacturer's product information
- Store refrigerated diluent with corresponding vaccine (these diluents may contain vaccine antigen)
- Never store diluents in the freezer
- Label diluent to avoid inadvertent use of the wrong diluent when reconstituting a vaccine

unit. Plug only one storage unit into an outlet. This will help to prevent a safety switch from being triggered to turn off power and reduce the risk of overloading the outlet which could be a fire hazard.

Use plug guards or safety-lock plugs to prevent someone from inadvertently unplugging the unit. A temperature alarm system that will alert staff to after-hour temperature excursions, particularly if large vaccine inventories are maintained, may be helpful in assuring a timely response to storage problems. Label circuit breakers to alert custodians and electricians not to unplug vaccine storage units or turn off the power. This can be done by posting a warning sign near the electrical outlet, on storage units, and at the circuit breaker box. Warning signs should include emergency contact information.

Place containers of water, labeled "Do NOT Drink," in the refrigerator to help stabilize the temperature in the unit. Place water bottles where vaccines are not stored, such as the door, top shelf, and on the floor of the storage unit. The same principle applies to the freezer. Store frozen water bottles in the freezer and the freezer door. Be careful that the water bottles do not weigh down doors so much that the seals are compromised and the doors do not close properly. These measures will help keep the temperature stable with frequent opening and closing of the storage unit.

In addition to temperature monitoring, a physical inspection of storage units should be performed daily. An inspection should include the following:

- Are the vaccines placed properly in the unit?
- Are the vaccines in their original packaging?
- Are vaccines being stored away from the walls, coils, cooling vents, ceiling, and floor and not in the doors?

During a workday it is easy for vaccines to be shifted into an area of the storage unit where the temperature may not be appropriate or stable, such as against a wall, under a cold air vent, or in the door. CDC recommends that vaccines be kept in storage units dedicated only to vaccines. If other biologic specimens, such as blood or urine, must be stored in the same unit as vaccines, specimens should be stored on a lower shelf. This is to ensure that if a specimen leaks, the vaccines will not be contaminated. Food and beverages should not be stored in a vaccine storage unit because frequent opening of the unit can lead to temperature instability.

While it is important to take measures to prevent problems, equally important is taking immediate corrective action when a problem does exist, for example, when the storage

unit temperature falls outside the recommended range. Staff should know who to contact in case of a malfunction or disaster.

If you experience a power outage, immediately begin to implement your emergency plan. Depending on room temperature, storage temperatures may be maintained for only a very short period of time. If there is an extended period of time before the situation can be corrected and there are no other storage units available on site, move the vaccines to the back-up storage facility using the guidelines in the emergency plan.

Vaccine and Diluent Inventory Control

Conduct a vaccine inventory monthly to ensure adequate supplies to meet demand. Include vaccine diluents in the inventory. Determining factors for the amount of vaccine and diluent ordered include: projected demand, storage capacity, and current vaccine supply. Avoid overstocking vaccine supplies, which could lead to vaccine wastage or having outdated vaccine on hand.

Check vaccine and diluent expiration dates a minimum of weekly. Rotate stock so that vaccines and diluents with the soonest expiration dates are used first to avoid waste from expiration. If the date on the label has a specific month, day, and year, the vaccine can be used through the end of that day. If the expiration date on the label is a month and year, the vaccine can be used through the last day of that month. A multidose vial of vaccine that has been stored and handled properly and is normal in appearance can be used through the expiration date printed on the vial unless otherwise stated in the manufacturer's product information. Some vaccines should be used within a certain time frame after the first time a needle is inserted (e.g., multidose vials), after the vaccine is reconstituted (e.g., vaccines requiring reconstitution), or if the manufacturer deems it is necessary to shorten the expiration date. This time frame is called the "beyond use date" or BUD. The BUD is the date or time after which the vaccine should not be used. It may not be the same as the expiration date printed on the vial by the manufacturer. The BUD varies among vaccines and can be found in the package insert. Check the package insert to determine if the vaccine has a BUD, and for the correct time frame (e.g., days, hours) the vaccine can be stored once the vial has been entered or has been reconstituted. Calculate the BUD using the time interval found in the vaccine's package insert. Label the vaccine with the correct beyond use date/time and your initials. Refer to the CDC's *Vaccine Inventory Management* for specific vaccine product information, including the beyond use dates at http://www.cdc.gov/vaccines/recs/storage/toolkit/storage-handling-

Preventive Measures

- Plug unit directly into wall; do NOT use multi-outlet power strip
- Do NOT use power outlets with built-in circuit switchers
- Do NOT use power outlets that can be activated by a wall switch
- Plug only one unit into an outlet
- Use a plug guard or safety-lock plug
- Install a temperature alarm
- Label circuit breakers and electrical outlets
- Post warning signs that include emergency contact information
- Use water bottles in refrigerator and frozen water bottles in freezer to maintain temperature
- Perform daily inspection of storage unit(s)
- If other biologics must be stored in the same unit, store them BELOW the vaccines to avoid contamination
- Never store food and beverages in the same unit with vaccines
- Take immediate corrective action when there is a problem

Vaccine and Diluent Inventory Control

- Conduct a monthly vaccine and diluent inventory
- Order vaccine based on
  - projected demand
  - storage capacity
  - current supply
- Avoid overstocking

Expiration Dates

- Monitor vaccine and diluent expiration dates at minimum, weekly
- Rotate stock so that vaccine and diluent with soonest expiration dates are used first
- If normal in appearance and stored and handled properly, product can be used
  - through end of day indicated if expiration date is mm/dd/yyyy (e.g., 12/15/2015 – use through 12/15/2015)
  - through end of month indicated if expiration date is mm/yyyy (e.g., 12/2015 – use through 12/31/2015)
- Multidose vials
  - can be used through expiration date on vial unless otherwise stated in manufacturer's product information
- Reconstituted vaccine
  - expiration date/time might change once opened or reconstituted. This is referred to as the Beyond Use Date (BUD) and is provided in the manufacturer's product information
- Note any change in expiration date/time on vial
- Never use expired vaccine or diluent

toolkit.pdf. Note on a vial any change from the original expiration date/time printed on it, along with your initials. Never use expired vaccine or diluent and immediately remove them from the storage unit.

Emergency or Off-Site/ Satellite Facility Transport

General guidance regarding transport is provided here and in CDC's *Vaccine Storage and Handling Toolkit*. Providers should also contact vaccine manufacturers and/or their immunization program for guidance. Some immunization programs may have vaccine packing and transport practices and procedures for maintaining the cold chain in the field that are specific to their area.

Vaccine manufacturers do not generally recommend or provide guidance for transport of vaccines and CDC discourages regular transport. If possible, have vaccines delivered directly to the off-site/satellite facility. Each transport increases the risk that vaccines will be exposed to inappropriate storage conditions.

Plan for emergencies by ensuring that you have proper equipment to maintain the cold chain during transport. CDC recommends that if emergency transport of vaccines is necessary, it should be done using a qualified container and pack-out or portable refrigerator/freezer. Vaccine manufacturers do not recommend re-use of shipping containers and packing material for routine transport.

If vaccines must be transported to an off-site/satellite facility, the amount of vaccines transported should be limited to the amount needed for that workday, including transport and work time (maximum 8 hours). CDC recommends using a digital data logger with a current and valid certificate of calibration testing. CDC does not recommend cold chain monitors (CCMs) since they do not provide adequate data on excursions that may occur during transport.

The facility's standard operating procedure (SOP) should specify that:

- Vaccines are attended at all times during transport to maintain the cold chain
- Vaccines are not placed in the vehicle trunk
- Vaccines are delivered directly to the facility
- Vaccines are promptly unpacked and placed in appropriate storage units on arrival

A digital data logger with a current and valid certificate of calibration testing is placed with the vaccines during transport.

Diluents should be transported with their corresponding vaccines to ensure that there are always equal numbers of vaccine and diluent for reconstitution. Follow manufacturer guidance for specific temperature requirements. Diluents that contain antigen (e.g., DTaP-IPV diluent used with Hib lyophilized vaccine) should be transported with their corresponding vaccines at refrigerator temperature. NEVER transport any diluents at freezer temperature. Refer to CDC's *Vaccine Storage and Handling Toolkit*, or your immunization program for guidance on vaccine and diluent transport.

Transporting Varicella-Containing Vaccines to Off-Site/Satellite Facilities

The vaccine manufacturer does not recommend transporting varicella-containing vaccines to off-site/satellite facilities. Varicella-containing vaccines are fragile. If these vaccines must be transported to an off-site/satellite facility, CDC recommends transport with a portable freezer unit that maintains the temperature between -58°F and +5°F (-50°C and -15°C). Portable freezers may be available for rent in some places. If varicella-containing vaccines must be transported and a portable freezer unit is not available, do not use dry ice.

Varicella-containing vaccines may also be transported at refrigerator temperature between 35°F and 46°F, (2°C and 8°C) for up to 72 continuous hours prior to reconstitution using the guidelines in CDC's *Vaccine Storage and Handling Toolkit*.

Having a patient pick up a dose of vaccine (e.g., zoster vaccine) at a pharmacy and transporting it in a bag to a clinic for administration is not an acceptable transport method for zoster vaccine or any other vaccine.

Monitoring Temperatures at Off-Site/ Satellite Facility

Vaccines should be placed in an appropriate storage unit(s) at the recommended temperature range(s) immediately upon arrival at the alternate facility. CDC recommends placing a digital data logger in the storage unit(s) with the vaccines. Read and document temperatures 2 times during the workday. CDC does not recommend keeping vaccines in a transport container unless it is a portable refrigerator or freezer unit. If vaccines must be kept in transport containers during an off-site clinic:

Transport to Off-Site/ Satellite Facilities

- Not recommended by vaccine manufacturers
- If possible, have vaccines delivered directly to the off-site/satellite facility
- Plan for emergencies by ensuring you have proper equipment to maintain cold chain during transport
- If transport is necessary, use a qualified container and pack-out or portable refrigerator/freezer
- Vaccine manufacturers do not recommend re-use of shipping containers and packing material for routine transport

Transport of Varicella-containing Vaccines to Off-Site/ Satellite Facilities

- The manufacturer does not recommend transporting varicella-containing vaccines to off-site facilities
- If vaccine must be transported, use a portable freezer that maintains the temperature between -58°F and +5°F (-50°C and -15°C)
- Do NOT use dry ice
- Varicella-containing vaccines may be also transported at refrigerator temperature between 35°F and 46°F (2°C and 8°C), for up to 72 continuous hours prior to reconstitution
- Must use the guideline in CDC's *Vaccine Storage and Handling Toolkit*
- Patient transport of vaccine (e.g. zoster) from pharmacy to a clinic for administration is not an acceptable transport method for any vaccine

- Container(s) should remain closed as much as possible.
- Calibrated temperature monitoring device(s) (preferably with a buffered probe) should be placed as close as possible to vaccines.
- The temperature(s) inside the containers(s) should be read and documented at least hourly.
- Only the amount of vaccine needed at one time (no more than 1 multidose vial or 10 doses) should be removed for preparation and administration by each vaccinator.

Vaccine Preparation

Most vaccines are supplied in single-dose vials or manufacturer-filled syringes. These preparations do not contain a bacteriostatic (preservative) agent. Once a single-dose vial is opened, meaning that the protective cap has been removed, it should be discarded at the end of the workday if not used. The same is true for an activated manufacturer-filled syringe. Removing the needle cap or attaching a needle activates a manufacturer-filled syringe and breaks the sterile seal. Multidose vials contain a bacteriostatic (preservative) agent. Once opened, a multidose vial may be used through the expiration date unless contaminated or the manufacturer's product information specifies a different timeframe (BUD).

CDC recommends that providers draw up vaccine only at the time of administration and not predraw vaccines. Filling a syringe before it is needed increases the risk for administration errors. Once in the syringe, vaccines are difficult to tell apart. Other problems associated with this practice are wasted vaccine, the risk of inappropriate temperature conditions, resulting in potentially reduced vaccine potency, and possible bacterial contamination in vaccines that do not contain a preservative, such as single-dose vials.

Syringes other than those filled by the manufacturer should be used only for immediate administration and not for vaccine storage. If for some reason, like a large flu clinic, more than one dose of a particular vaccine must be predrawn, draw up only a few syringes at one time (no more than 10 doses or the contents of a single multidose vial). In accordance with best practice standards, these syringes should be administered by the person who filled them.

As an alternative to predrawing vaccine, CDC recommends using manufacturer-filled syringes for large immunization events, such as community influenza clinics. These syringes are designed for both storage and administration.

Vaccine Preparation

- Once the protective cap is removed, vaccine in single-dose vial should be used or discarded at end of workday
- Once manufacturer-filled syringe is activated (remove needle cap or attach needle) sterile seal is broken and should be used or discarded at end of workday
- Do not predraw vaccine
  - increases risk for administration errors
  - wasted vaccine
  - possible bacterial growth in vaccines that do not contain a preservative
  - administration syringes not designed for storage
- Consider using manufacturer-filled syringes for large immunization events because they are designed for both storage and administration

Vaccine Disposal

Unused vaccine and diluent doses may be returnable under certain circumstances. Contact the vaccine supplier, which may be the immunization program or the vaccine manufacturer, for specific policies regarding the disposition of returnable vaccine, unopened vials, expired vials, unused doses, and potentially compromised vaccine due to inappropriate storage conditions.

In general, most empty vaccine vials are not considered hazardous or pharmaceutical waste and do not require disposal in a biomedical waste container. However, requirements for medical waste disposal are regulated by state environmental agencies so you should contact your immunization program or state environmental agency to ensure that your disposal procedures are in compliance with state and federal regulations.

Vaccine Disposal

- Consult immunization program or vaccine manufacturer regarding returnable vaccines
- Refer to CDC's *Vaccine Storage and Handling Toolkit* for comprehensive storage and handling guidance.

Acknowledgement

The editors thank Donna Weaver, Patricia Beckenhaupt, and JoEllen Wolicki, National Center for Immunization and Respiratory Diseases, CDC, for their contribution to this chapter.

Selected References

Centers for Disease Control and Prevention (CDC). General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2011;60(no. RR-2): 23-27. http://www.cdc.gov/vaccines/pubs/ACIP-list.htm

CDC. Recommendations and Guidelines: Storage and Handling: http://www.cdc.gov/vaccines/recs/storage/default.htm

Food and Drug Administration (FDA): http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093830.htm

Manufacturers' Product Information: http://www.immunize.org/packageinserts/

National Institute of Standards and Technology (NIST). Thermal Analysis of Refrigeration Systems Used for Vaccine Storage, 2009, Household, Dormitory-Style Refrigerators and Data Loggers. http://www.nist.gov/manuscript-publication-search.cfm?pub_id=904574

Immunization Action Coalition Storage and Handling Handouts: http://www.immunize.org/clinic/storage-handling.asp

Vaccine safety is a prime concern for the public, manufacturers, immunization providers, and recipients of vaccines. This chapter describes how vaccines licensed for use in the United States are monitored for safety, and presents general information about the provider's role in immunization safety. Further information about contraindications and precautions for individual vaccines, such as pregnancy and immunosuppression, and about potential adverse events associated with the vaccine is contained in the chapter on General Recommendations on Immunization, and in the chapters on specific vaccines.

Importance of Vaccine Safety

- Decreases in disease risks and increased attention on vaccine risks
- Public confidence in vaccine safety is critical
  - higher standard of safety is expected of vaccines
  - vaccinees generally healthy (vs. ill for drugs)
  - lower risk tolerance = need to search for rare reactions
  - vaccination universally recommended and mandated

The Importance of Vaccine Safety Programs

Vaccination is among the most significant public health success stories of all time. However, like any pharmaceutical product, no vaccine is completely safe or completely effective. While almost all known vaccine adverse events are minor and self-limited, some vaccines have been associated with very rare but serious health effects. The following key considerations underscore the need for an active and ongoing vaccine safety program.

Decreases in Disease Risks

Today, vaccine-preventable diseases are at or near record lows. Many people no longer see reminders of the severity and potential life-threatening complications of these diseases. Recent outbreaks of vaccine–preventable diseases show that even vaccinated people are at risk for disease if there is not adequate vaccine coverage in the population. Parents and providers in the United States may be more likely to know someone who has experienced an adverse event following immunization than they are to know someone who has experienced a vaccine-preventable disease. The success of vaccination has led to increased public attention on potential health risks associated with vaccines.

Disease	Pre-vaccine Era*	2006§	% decrease
Diphtheria	175,885	0	100
Measles	503,282	55	99.9
Mumps	152,209	6,584	95.7
Pertussis	147,271	15,632	89.4
Polio (paralytic)	16,316	0	100
Rubella	47,745	11	99.9
Congenital Rubella Syndrome	823	1	99.9
Tetanus	1,314	41	99.9
H. influenzae type b and unknown (<5 yrs)	20,000†	208	99.9
Total	1,064,854	22,532	97.9
Vaccine Adverse Events	N/A	15,484	N/A

*Baseline 20th century annual morbidity
§Source: MMWR 2007;56(33):851-64
†Estimated because no national reporting existed in the pre-vaccine era

Public Confidence

Maintaining public confidence in immunizations is critical for preventing a decline in vaccination rates that can result in outbreaks of disease. While the majority of parents understand the benefits of immunization and have their children vaccinated, some have concerns about the safety of vaccines. Public concerns about the safety of whole-cell pertussis vaccine in the 1980s resulted in decreased vaccine coverage and the return of epidemic disease in Japan, Sweden, United Kingdom, and several other countries. Around the same time in the United States, similar concerns led to increases both in the number of lawsuits against manufacturers and the price of vaccines, and to a decrease in the number of manufacturers willing to produce vaccines. This led to the National Childhood Vaccine Injury Act which is discussed in this chapter. Despite high national vaccination coverage rates, there are areas of low coverage that allow outbreaks of vaccine-preventable diseases to occur, many due to concerns about vaccine safety leading parents to refuse or delay their children's immunizations. For example, during 2008, more measles cases were reported than in any year since 1997. More than 90% of those infected had not been vaccinated, or their vaccination status was unknown. In California during January 1-June 30, 2010, 1,337 pertussis cases were reported to the California Department of Public Health, a 418% increase from the 258 cases reported during the same period in 2009. Providing accurate and timely vaccine safety information to healthcare providers, parents, and the general population has a positive effect on vaccine uptake and is a high priority for CDC. Close monitoring and timely assessment of suspected vaccine adverse events can distinguish true vaccine reactions from coincidental unrelated events and help to maintain public confidence in immunizations.

A higher standard of safety is generally expected of vaccines than of other medical interventions because in contrast to most pharmaceutical products, which are administered to ill persons for curative purposes, vaccines are generally given to healthy persons to prevent disease. Public tolerance of adverse reactions related to products given to healthy persons, especially healthy infants and children, is substantially lower than for reactions to products administered to persons who are already sick. This lower tolerance of risk for vaccines translates into a need to investigate the possible causes of very rare adverse events following vaccinations.

Adding to public concern about vaccines is the fact that immunization is mandated by many state and local school entry requirements. Because of this widespread use, safety problems with vaccines can have a potential impact on large numbers of persons. The importance of ensuring the safety of a relatively universal human-directed "exposure"

like immunizations is the basis for strict regulatory control of vaccines in the United States by the Food and Drug Administration (FDA).

Sound Immunization Recommendations and Policy

Public health recommendations for vaccine programs and practices represent a dynamic balancing of risks and benefits. Vaccine safety monitoring is necessary to accurately weigh this balance and adjust vaccination policy. This was done in the United States with smallpox and oral polio vaccines as these diseases neared global eradication. Complications associated with each vaccine exceeded the risks of the diseases, leading to discontinuation of routine smallpox vaccination in the United States (prior to global eradication) and a shift to a safer inactivated polio vaccine. Sound immunization policies and recommendations affecting the health of the nation depend upon the ongoing monitoring of vaccines and continuous assessment of immunization benefits and risks.

Importance of Vaccine Safety

- Ongoing safety monitoring needed for the development of sound policies and recommendations

Adverse Events Following Immunization and Assessment of Causality

Adverse events following immunization can be classified by frequency (common, rare), extent (local, systemic), severity (hospitalization, disability, death), causality, and preventability (intrinsic to vaccine, faulty production, faulty administration). Adverse events following immunizations may be coincidental events or the vaccine may have increased the risk of the adverse event. Some adverse events following immunization may be due to the vaccine preparation itself and the individual response of the vaccinee, and would not have occurred without vaccination. Examples of such events are vaccine-associated paralytic poliomyelitis after oral polio vaccine, or vaccine-strain measles viral infection in an immunodeficient recipient. Other health events may be precipitated by an immunization, such as a vaccine-associated fever precipitating a febrile seizure. Vaccine administration errors may lead to adverse events as well, for example, when administration of a vaccine too high in an adult's arm causes deltoid bursitis. However, many adverse events following immunization are coincidental; they are temporally related to immunization, but occurring by chance without a causal relationship.

To assess causality of an adverse event following immunization, much information is generally needed. A good reference for causality determination is available at www.ncbi.nlm.nih.gov/pubmed/22507656. An adverse health event can be causally attributed to vaccine more readily if: 1) the health problem occurs during a plausible time period

following vaccination; 2) the adverse event corresponds to those previously associated with a particular vaccine; 3) the event conforms to a specific clinical syndrome whose association with vaccination has strong biologic plausibility (e.g., anaphylaxis) or occurs following the natural disease; 4) a laboratory result confirms the association (e.g., isolation of vaccine strain varicella virus from skin lesions of a patient with rash); 5) the event recurs on re-administration of the vaccine ("positive rechallenge"); 6) a controlled clinical trial or epidemiologic study shows greater risk of a specific adverse event among vaccinated vs. unvaccinated (control) groups; or 7) a finding linking an adverse event to vaccine has been confirmed by other studies.

Assessing and Monitoring Safety of Vaccines

Prelicensure

Prelicensure Vaccine Safety Studies

- Laboratory
- Animals
- Humans

Prelicensure Human Studies

- Phases I, II, III trials
- Common reactions are identified
- Vaccines are tested in thousands of persons before being licensed and allowed on the market

Vaccines, like other pharmaceutical products, undergo extensive safety and efficacy evaluations in the laboratory, in animals, and in sequentially phased human clinical trials prior to licensure. Phase I human clinical trials usually involve anywhere from 20 to 100 volunteers and focus on detecting serious side effects. Phase II trials generally enroll hundreds of volunteers. These trials might take a few months, or last up to three years. Phase II trials determine the best dose and number of doses for effectiveness and safety. Next, the vaccine moves into Phase III trials, which may last several years. A few hundred to several thousand volunteers may be involved. Some volunteers receive another already-licensed vaccine, allowing researchers to compare one vaccine with another for adverse health effects—anything from a sore arm to a serious reaction. If the vaccine is shown to be safe and effective in Phase III, the manufacturer applies for a license from the FDA. The FDA licenses the vaccine itself (the "product license") and licenses the manufacturing plant where the vaccine will be made (the "establishment license"). During the application, the FDA reviews the clinical trial results, product labeling, the manufacturing plant itself, and the manufacturing protocols.

Fundamental to preventing safety problems is the assurance that any vaccines for public use are made using Good Manufacturing Practices and undergo lot testing for purity and potency. Manufacturers must submit samples of each vaccine lot and results of their own tests for potency and purity to the FDA before releasing them for public use. FDA licensure occurs after a vaccine has met rigorous standards of efficacy and safety, and when its potential benefits in preventing disease clearly outweigh any risks. Phase III trials may be powered sufficiently to identify certain potential adverse reactions prior to licensure. For example, in the pentavalent rotavirus vaccine trials, 70,000 infants received

either vaccine or placebo, so this permitted evaluation of safety with respect to intussusception. However, while rates of common vaccine reactions, such as injection-site reactions and fever, can be estimated before licensure, the comparatively small number of patients enrolled in these trials generally limits detection of rare side effects or side effects that may occur many months after the vaccine is given. Even the largest prelicensure trials (more than 10,000 persons) are inadequate to assess the vaccine's potential to induce rare side effects. Therefore, it is essential to continue to monitor vaccine-associated adverse events once the vaccine has been licensed and recommended for public use.

National Childhood Vaccine Injury Act (NCVIA) of 1986
During the mid-1970s, there were vaccine safety-related lawsuits filed on behalf of those presumably injured by the whole-cell pertussis component of diphtheria-tetanus-pertussis (DTP) vaccine. Legal decisions were reached and damages awarded despite the lack of scientific evidence to support vaccine injury claims. As a result of vaccine manufacturers being held liable, prices soared and many manufacturers halted vaccine production. A vaccine shortage resulted, and public health officials became concerned about the return of epidemic disease. To respond to these concerns, Congress passed the National Childhood Vaccine Injury Act (NCVIA) in 1986. Among the requirements of the NCVIA were the establishment of the Vaccine Adverse Event Reporting System (VAERS) to collect reports of vaccine adverse events, and the National Vaccine Injury Compensation Program to compensate individuals who experience certain health events following immunization. Postlicensure vaccine safety monitoring is now a multifaceted activity which helps address these concerns as well.

Postlicensure Vaccine Safety Monitoring

Postlicensure evaluation of vaccine safety is critical because rare reactions, delayed reactions, or reactions among subpopulations may not be detected before vaccines are licensed. Several monitoring systems are used in the US to detect and study adverse events that occur after immunizations. In addition to Phase IV trials required of manufacturers, the CDC and FDA use two main systems to monitor the safety of vaccines in use: VAERS and the Vaccine Safety Datalink (VSD). The objectives of postlicensure surveillance are to:

- identify rare adverse reactions after immunization not detected during prelicensure studies;
- monitor increases in known adverse health events after immunization;

Postlicensure Vaccine Safety Systems

- Vaccine Adverse Event Reporting System (VAERS)
- Vaccine Safety Datalink (VSD)

Postlicensure Surveillance

- Identify rare reactions
- Monitor increases in known adverse health events
- Identify risk factors for reactions
- Identify vaccine lots with unusual rates or types of event
- Identify signals

Vaccine Adverse Event Reporting System (VAERS)

- National spontaneous surveillance system
- Jointly administered by CDC and FDA
- Receives about 30,000 reports per year
- Detects
  - new or rare events
  - increases in rates of known side effects
  - patient risk factors
- Additional studies required to confirm VAERS signals
- Not all reports of adverse events are causally related to vaccine

- identify risk factors or preexisting conditions that may be associated with a higher incidence of adverse reactions;
- identify whether there are particular vaccine lots with unusually high rates or certain types of events; and
- identify "signals," possible adverse reactions that may warrant further study to establish the association of an adverse event with vaccination, or affect current immunization recommendations.

The Vaccine Adverse Event Reporting System (VAERS)

The National Childhood Vaccine Injury Act (NCVIA) of 1986 mandated that healthcare providers who administer vaccines and vaccine manufacturers report adverse health events following vaccinations. This act led to the creation of the Vaccine Adverse Event Reporting System (VAERS) in 1990. VAERS is a national spontaneous surveillance system, jointly administered by CDC and FDA, which accepts reports of adverse events after US-licensed vaccinations from health professionals, vaccine manufacturers, and the public. Reports are submitted via the Internet, mail, and fax. All reports are coded using the Medical Dictionary for Regulatory Activities (MedDRA) (http://www.meddramsso.com/) and entered into the VAERS database. VAERS receives about 30,000 US reports per year. Though this may seem like a large number, it is relatively small considering that millions of doses of vaccines are given to adults and children in the US each year.

Healthcare providers are required to report certain adverse health events following specific vaccinations to VAERS (see http://vaers.hhs.gov/resources/VAERS_Table_of_Reportable_Events_Following_Vaccination.pdf) and are encouraged to report any clinically significant adverse event after vaccination even if the reporter is not certain that the incident is vaccine-related. Vaccine manufacturers are required to report all adverse health events that come to their attention (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=600.80). In 2012, US VAERS reports were received from healthcare providers (41%), manufacturers (29%), unknown or other reporters (17 %), and patients or parents (14%).

VAERS collects information about the patient, the vaccination(s) given, the adverse event, and the person reporting the event. Serious adverse event reports as defined in the Federal Register are those involving reported hospitalization or prolongation of hospitalization (if vaccine is given in hospital), death, life threatening illness, or permanent disability. Attempts are made to obtain additional medical information for all reports classified as serious. For these

reports, letters to obtain information about recovery status are also sent to the reporters. All patient-identifying information submitted to VAERS, directly or as part of follow-up activities, is protected by strict confidentiality requirements.

Despite limitations inherent to spontaneous reporting systems, VAERS has been able to fulfill its primary purpose of detecting new or rare vaccine adverse events, increases in rates of known side effects, and patient risk factors for particular types of adverse events. Additional studies are required to confirm possible safety signals detected by VAERS because not all reported adverse events are causally related to vaccine. See the section in this chapter titled "Reporting Adverse Events Following Immunization to VAERS" for information on submitting reports. In addition, VAERS often provides early safety data after a vaccine is licensed or during a public health emergency.

VAERS data with personal identifiers removed are available at http://vaers.hhs.gov/index or at http://wonder.cdc.gov/vaers.html.

Vaccine Safety Datalink (VSD)

In 1990, CDC established the Vaccine Safety Datalink to address gaps in the scientific knowledge of rare and serious adverse events following immunizations. This project involves partnerships with large health plans to monitor vaccine safety. A complete list of VSD partners can be found at http://www.cdc.gov/vaccinesafety/Activities/VSD.html. Each participating organization utilizes its electronic health records and immunization registries to contribute to a large linked database. Available information includes data on vaccination (vaccine type, date of vaccination, concurrent vaccinations), health conditions, medical encounters (outpatient visits, inpatient visits, urgent care visits), birth data, and census data.

The VSD allows for planned immunization safety studies, as well as timely investigations of hypotheses that arise from review of medical literature, reports to VAERS, changes in immunization schedules, or the introduction of new vaccines. The Rapid Cycle Analyses (RCA) conducted by the VSD enable CDC and its co-investigators to monitor adverse events following vaccination in near real time, so the public can be informed quickly of possible risks. VSD data come from participating health plans that serve more than 9 million people annually, representing nearly 3% of the United States population, and records for more than 150 million vaccinations, enabling the VSD to study possible rare adverse events after immunization. Data files used in VSD studies remain at each participating site; specific data

Vaccine Safety Datalink (VSD)

- Involves partnerships with large health plans
- Links vaccination and health records
- Allows for planned immunization safety studies
- Allows for investigations of hypotheses that arise from review of medical literature, reports to VAERS, changes in immunization schedules, or the introduction of new vaccines

are pulled together for each analysis and do not contain personal identifiers. Further information about VSD is available at http://www.cdc.gov/vaccinesafety/Activities/VSD.html.

Clinical Immunization Safety Assessment (CISA) Project

Clinical Immunization Safety Assessment (CISA) Project

- Improve understanding of vaccine safety issues at individual level
- Review individual cases
- Develop strategies to assess individuals
- Conduct studies to identify risk factors

The CDC supports the Clinical Immunization Safety Assessment (CISA) Project to improve the understanding of adverse events following immunization (AEFI) at the individual-patient level. The CISA Project's goals are to: (1) serve as a vaccine safety resource for consultation on clinical vaccine safety issues, including individual case reviews, and assist with immunization decision-making; (2) assist CDC in developing strategies to assess individuals who may be at increased risk for AEFI; and (3) conduct studies to identify risk factors and preventive strategies for AEFI, particularly in special populations. CISA experts provide advice that has led to a broader understanding of vaccine safety issues and informs clinical or public health practices. A healthcare provider who needs expert opinion on a vaccine safety question about a specific patient can contact CDC at CISAeval@cdc.gov to request a CISA evaluation. Individual case evaluations may lead to development of protocols or guidelines for healthcare providers to help them make the right assessments and manage similar situations. CISA has also contributed to Advisory Committee on Immunization Practices (ACIP) recommendations. Established in 2001, the CISA Project currently consists of seven academic centers of excellence with vaccine safety expertise working in partnership with CDC. A list of these centers, and additional information about the CISA Project, can be found at http://www.cdc.gov/vaccinesafety/Activities/cisa.html.

Vaccine Injury Compensation

Vaccine Injury Compensation Program (VICP)

- Established by National Childhood Vaccine Injury Act (1986)
- "No fault" program
- Covers all routinely recommended childhood vaccines
- Vaccine Injury Table

A main impact of the National Childhood Vaccine Injury Act (NCVIA) of 1986 was the initiation of the National Vaccine Injury Compensation Program (VICP). This program, administered by the Health Resources and Services Administration (HRSA), compensates individuals who experience certain health events following immunization on a "no fault" basis. "No fault" means that persons filing claims are not required to prove negligence on the part of either the healthcare provider or manufacturer to receive compensation. The program covers all routinely recommended childhood vaccines, although adults who receive a covered vaccine may also file a claim. Claims may be based on a Vaccine Injury Table (available at http://www.hrsa.gov/vaccinecompensation/vaccinetable.html), which lists conditions associated with each vaccine and provides a rebuttable presumption of causation, or by proving by preponderant evidence that the vaccine caused an injury not on the Table.

This Table was developed initially by Congress and has been modified by the Secretary of the Department of Health and Human Services (DHHS) to better reflect current science regarding which serious adverse events are reasonably certain to be caused by vaccines. The Table was created to provide swift compensation to those possibly injured by vaccines. As more information becomes available from research on vaccine side effects, the Table will continue to be amended.

VICP has provided compensation to individuals injured by rare vaccine-related adverse events and provided liability protection for vaccine manufacturers and administrators. Further information about the VICP is available at http://www.hrsa.gov/vaccinecompensation/vaccinetable.html.

During the 2009 H1N1 influenza pandemic, the government implemented a new compensation program called Countermeasures Injury Compensation Program (CICP). This program provides compensation for certain individuals who are seriously injured by countermeasures as specified in a declaration by the Secretary of DHHS. Both security (bioterrorism) and pandemic countermeasures are covered. The CICP currently covers serious adverse events caused by pandemic influenza vaccines, including the 2009 monovalent H1N1 influenza vaccine that was widely distributed in the 2009 influenza season and any pandemic influenza vaccines in clinical trials such as H5, H7, H9, etc. The CICP also currently covers serious adverse events caused by anthrax, smallpox, and botulism vaccines, including those used by the Department of Defense. Covered countermeasures within the CICP are not limited to vaccines and may include certain medications or devices used to diagnose, prevent, or treat the covered condition (currently pandemic influenza, smallpox, anthrax, botulism, and acute radiation syndrome). People have one year from receipt of the countermeasure to file with the CICP. More information can be found at http://www.hrsa.gov/countermeasurescomp.

The Immunization Provider's Role

Even though federal regulations require vaccines to undergo years of testing before they can be licensed, and vaccines are monitored continually for safety and effectiveness, immunization providers still play a key role in helping to ensure the safety and efficacy of vaccines. They do this through proper vaccine storage and administration, timing and spacing of vaccine doses, observation of contraindications and precautions, management of vaccine adverse reactions, reporting of adverse events following immunization to VAERS, and educating patients and parents about vaccine benefits and risks. Each of these steps is described

The Provider's Role

- Immunization providers can help to ensure the safety and efficacy of vaccines through proper:
  - vaccine storage and administration
  - timing and spacing of vaccine doses
  - observation of contraindications and precautions
  - management of adverse reactions
  - reporting to VAERS
  - benefit and risk communication

only briefly here. Further information is available elsewhere in this book or in resource materials from CDC or other organizations.

Vaccine Storage and Administration

To achieve the best possible results from vaccines, immunization providers should carefully follow the recommendations found in each vaccine's package insert for storage, handling, and administration. Other steps to help ensure vaccine safety include: 1) inspecting vaccines upon delivery and monitoring refrigerator and freezer temperatures to ensure maintenance of the cold chain; 2) rotating vaccine stock so the oldest vaccines are used first; 3) never administering a vaccine later than the expiration date; 4) administering vaccines within the prescribed time periods following reconstitution; 5) waiting to draw vaccines into syringes until immediately prior to administration; 6) never mixing vaccines in the same syringe unless they are specifically approved for mixing by the FDA; and 7) recording vaccine and administration information, including lot numbers and injection sites, in the patient's record. If errors in vaccine storage and administration occur, corrective action should be taken immediately to prevent them from happening again and public health authorities should be notified. More information on vaccine storage and handling is available in the "Vaccine Storage and Handling" chapter and CDC's "Vaccine Storage and Handling Toolkit", available on the CDC Vaccines and Immunizations website at http://www.cdc.gov/vaccines/recs/storage/toolkit/.

Timing and Spacing

Timing and spacing of vaccine doses are two of the most important issues in the appropriate use of vaccines. To ensure optimal results from each immunization, providers should follow the recommended immunization schedules for children, adolescents, and adults. Decreasing the timing intervals between doses of the same vaccine may interfere with the vaccine's antibody response. For more specific information on timing and spacing of vaccines, see Chapter 2, "General Recommendations on Immunization." A table showing recommended minimum ages and intervals between vaccine doses is contained in Appendix A.

Providers should also remember the following:

- Administering all needed vaccines during the same visit is important because it increases the likelihood that children will be fully immunized as recommended. Studies have shown that vaccines are as effective when administered simultaneously as they are individually and carry no greater risk for adverse reactions.

- Some vaccines, such as pediatric diphtheria and tetanus, may cause local reactions when given too frequently. Good recordkeeping, maintaining careful patient histories, and adherence to recommended schedules can decrease the chances that patients receive extra doses of vaccines.

Contraindications and Precautions

Certain vaccines should not be given, or should be given only under controlled circumstances, to certain patients. A contraindication is a condition that increases the likelihood of a serious adverse reaction to a vaccine for a recipient with that condition. In general, a vaccine should not be administered when a contraindication is present. A precaution is a condition that might increase the likelihood or severity of an adverse reaction in a recipient, or compromise the ability of the vaccine to produce immunity. Vaccination is generally deferred when a precaution is present. Situations may arise when the benefits of vaccination outweigh the risk of a side effect, and the provider may decide to vaccinate the patient. Many contraindications and precautions are temporary and the vaccine may be given at a later time. More information about contraindications can be found in the Advisory Committee on Immunization Practices (ACIP) statements for individual vaccines. Recommendations for immunizing persons who are immunocompromised can be found in Appendix A. Information on allergic reactions to vaccines can be found in the American Academy of Pediatrics *Red Book*.

Screening for contraindications and precautions is important for preventing serious adverse outcomes after vaccination. Every provider who administers vaccines should screen every patient before giving a vaccine dose. Sample screening questionnaires can be found in Chapter 2, "General Recommendations on Immunization." Many conditions are often inappropriately regarded as contraindications to vaccination. In most cases, the following are not considered contraindications:

- Minor acute illness (e.g., diarrhea and minor upper respiratory tract illnesses, including otitis media) with or without low-grade fever
- Mild to moderate local reactions and/or low-grade or moderate fever following a prior dose of the vaccine
- Current antimicrobial therapy
- Recent exposure to infectious disease
- Convalescent phase of illness
- Pregnant or immunosuppressed person in the household

Contraindication

A condition that increases the likelihood of a serious adverse reaction to a vaccine for a recipient with that condition

Precaution

A condition in a recipient that might:

- Increase the chance or severity of an adverse reaction, or
- Compromise the ability of the vaccine to produce immunity

Invalid Contraindications to Vaccination

- Minor acute illness
- Mild/moderate local reaction or fever following a prior dose
- Antimicrobial therapy
- Disease exposure or convalescence
- Pregnancy or immunosuppression in the household
- Preterm birth
- Breastfeeding
- Allergies to products not in vaccine

- Preterm birth
- Breastfeeding
- Allergies to products not in vaccine

Managing Adverse Reactions after Immunization

Providers should use their best clinical judgment regarding specific management of adverse events after immunization. Allergic reactions to vaccines are estimated to occur after vaccination of children and adolescents at a rate of one for every 1.5 million doses of vaccine. All providers who administer vaccines should have procedures in place and be prepared for emergency care of a person who experiences an anaphylactic reaction. Epinephrine and equipment for maintaining an airway should be available for immediate use. All vaccine providers should be familiar with the office emergency plan and should be certified in cardiopulmonary resuscitation.

Reporting Adverse Events Following Immunization to VAERS

Healthcare providers are required by the National Childhood Vaccine Injury Act of 1986 to report certain adverse events to VAERS and are encouraged to report any adverse event even if they are not sure a vaccine was the cause. A table listing reportable events is available at http://vaers.hhs.gov/reportable.htm. Reporting can be done in one of three ways:

1. Online through a secure website: https://vaers.hhs.gov/esub/step1.
2. If a reporter is unable to report by Internet, they may fax a completed VAERS form* to 877-721-0366.
3. Mail a completed VAERS form* to:

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

*A one-page VAERS form can be downloaded from http://vaers.hhs.gov/resources/vaers_form.pdf or can be requested by telephone at 800-822-7967 or by fax at 877-721-0366.

When providers report suspected vaccine reactions to VAERS, they provide valuable information that is needed for the ongoing evaluation of vaccine safety. CDC and FDA use VAERS information to ensure the safest strategies of vaccine use and to further reduce the rare risks associated with vaccines.

Benefit and Risk Communication

Parents, guardians, legal representatives, and adolescent and adult patients should be informed of the benefits and risks of vaccines in understandable language. Opportunity for questions should be provided before each vaccination. Discussion of the benefits and risks of vaccination is sound medical practice and is required by law.

The National Childhood Vaccine Injury Act 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 before each dose of vaccine. Copies of VISs are available from state health authorities responsible for immunization, or they can be obtained from CDC's website at http://www.cdc.gov/vaccines/pubs/vis/default.htm or from the Immunization Action Coalition at http://www.immunize.org. Translations of VISs into languages other than English are available from certain state immunization programs and from the Immunization Action Coalition website. Further information about VISs and their use is contained in Appendix C.

Healthcare providers should anticipate questions that parents or patients may have regarding the need for or safety of vaccination. Some individuals may refuse certain vaccines, or even reject all vaccinations. Some might have religious or personal objections to vaccinations. Having a basic understanding of how patients view vaccine risk and developing effective approaches to dealing with vaccine safety concerns when they arise are imperative for vaccination providers. Healthcare providers can accomplish this by assessing patients' specific concerns and information needs, providing them with accurate information, and referring them to credible sources for more information. CDC's website contains extensive and up-to-date information on vaccines and tools for discussing vaccines with patients (see http://www.cdc.gov/vaccines/hcp/patient-ed/conversations/index.html for provider resources).

When a parent or patient initiates discussion regarding a vaccine concern, the healthcare provider should discuss the specific concern and provide factual information, using language that is appropriate. Effective, empathetic vaccine risk communication is essential in responding to misinformation and concerns. The Vaccine Information Statements provide an outline for discussing vaccine benefits and risk. Other vaccine safety informational resources are available at http://www.cdc.gov/vaccinesafety/.

For patients who question or refuse vaccination, identifying common ground and discussing measures for deferring vaccinations is a more effective public health strategy for

Benefit and Risk Communication

- Opportunities for questions should be provided before each vaccination
- Vaccine Information Statements (VISs)
  - must be provided before each dose of vaccine
  - public and private providers
  - available in multiple languages

providers than excluding these patients from their practice. Healthcare providers can reinforce key points regarding each vaccine, including safety, and emphasize risks encountered by unimmunized children. Parents should be informed about state laws pertaining to school or child care entry, which might require that unimmunized children stay home from school during outbreaks. Documentation of these discussions in the patient's record, including the refusal to receive certain vaccines (i.e., informed refusal), might reduce any potential liability if a vaccine-preventable disease occurs in the unimmunized patient.

Acknowlegement

The editors thank Dr. Cindy M. Weinbaum of the Division of Healthcare Quality Promotion, CDC, for her update and critical review of this chapter.

Selected References

American Academy of Pediatrics. Vaccine Safety and Reporting of Adverse Events. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012:41-53.

Berger B, Omer S. Could the United States experience rubella outbreaks as a result of vaccine refusal and disease importation? *Human Vaccines*. 6(12):1016.

Bohlke K, Davis RL, Marcy SM, et al. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003;112(4):815–20.

CDC. Suspension of Rotavirus Vaccine after Reports of Intussusception—United States, 1999. *MMWR* 2004;53(34):786-789.

CDC. Syncope after vaccination—United States, January 2005–July 2007 *MMWR* 2008;57(17);457-460.

CDC. General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2011;60(No. RR-2):1–60.

CDC. Current Trends National Childhood Vaccine Injury Act: Requirements for permanent vaccination records and for reporting of selected events after vaccination. *MMWR* 1988;37(13):197–200.

CDC. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)—United States 1991-2001. *MMWR* 2003; 52(No.SS-1):1–24.

Chen RT, Hibbs B. Vaccine safety: current and future challenges. *Pediatr Ann* 1998;27(7):445–55.

Chen RT, Glasser J, Rhodes P, et al. The Vaccine Safety Datalink (VSD) Project: A new tool for improving vaccine safety monitoring in the United States. *Pediatrics* 1997; 99(6):765–73.

Chen RT, Rastogi SC, Mullen JR, et al. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994;12(6): 542–50.

Iskander JK, Miller ER, Chen RT. The role of the Vaccine Adverse Event Reporting System (VAERS) in monitoring vaccine safety. *Pediatric Annals* 2004;33(9): 599-606.

Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W, Sutherland A, Izurieta HS, Ball R, Miller N, Braun MM, Markowitz LE, Iskander J. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA* 2009 Aug 19;302(7):750-7.

Varricchio F, Iskander J, Destefano F, Ball R, Pless R, Braun MM, Chen RT. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J* 2004 Apr 23 (4): 287-294.

Vellozzi C, Broder KR, Haber P, Guh A, Nguyen M, Cano M, Lewis P, McNeil MM, Bryant M, Singleton J, Martin D, DeStefano F. Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009-January 31, 2010. *Vaccine* 2010 Oct 21;28(45):7248-55.

VAERS website available at www.vaers.hhs.gov.