The written history of measles is classically traced to the writings of the Persian physician Rhazes, also known as Abu Bekr, who lived during the 10th century. However, the disease was apparently recognized as early as the 7th century by such ancients as the Hebrew physician Al Yehudi. Rhazes referred to measles as hasbah, which means “eruption” in Arabic. Rubeola and morbilli are descriptive Latin words first used in the Middle Ages. The latter is a diminutive of morbus, meaning “disease”, which was reserved to refer to the bubonic plague; morbilli referred to a minor disease. Measles is probably derived from mesels, the anglicized form of misseus, which in turn is a diminutive of the Latin word miser, meaning miserable and referring to the sufferer of various eruptions or sores. The presence of nonspecific leprous sores was incorrectly identified with the disease called morbilli in Latin. Thus, mesels came to be equated with the disease and not the sufferer of ill-defined skin lesions.

Rhazes appears to have been the first to make the distinction between measles and smallpox. He considered measles to be a severe disease, “more to be dreaded than smallpox”. Although Rhazes did distinguish between the two diseases, he did not think the disease was infectious. Furthermore, although he was aware of the seasonal nature of measles, he did not think the disease was infectious.

The distinction between measles and smallpox was becoming clearer by the beginning of the 17th century, when annual bills of mortality in London in 1629 listed the two diseases separately. Thomas Sydenham clearly described the clinical characteristics of measles during this period and believed the disease to be infectious. It was, however, Francis Home, a Scottish physician who worked in Edinburgh in the mid-18th century, who truly recognized the infectious nature of the illness in his attempts to prevent it. Understanding of the epidemiology of measles was greatly enhanced by the classic investigation of a measles epidemic on the Faroe Islands in 1846 by the young Danish physician Peter Panum. He not only confirmed that measles was contagious but also defined the 14-day interval between exposure and appearance of exanthem, recognized the higher mortality at the extremes of age, and observed that infection provided lifelong immunity.

In 1911, using infected material from acute cases, Goldberger and Anderson transmitted human measles infection to monkeys, clearly demonstrating the existence of an infectious agent or substance responsible for measles. This finding anticipated the technology to isolate and culture the measles virus. In 1954, Enders and Peebles successfully isolated the measles virus in human and monkey kidney tissue cultures. Adaptation of the virus to chicken embryos and cultivation in chicken embryo tissue culture paved the road to vaccine development and licensure in 1963.

Widespread vaccination of children in the United States and others has had a dramatic effect on the incidence of measles and its associated complications. Reductions in morbidity and mortality have been so great that global eradication has been proposed and judged feasible. This would be a fitting end to a disease once confused with smallpox, the first infectious disease eradicated from the world.
isolated from the urine as late as 4 to 7 days after rash onset.56 Viremia generally clears 2 to 3 days after rash onset in parallel with the appearance of antibody.57 Persons with measles are generally considered to be infectious 4 days before through 4 days after rash onset.

Measles virus infection causes simultaneous activation and suppression of the immune system.58–62 Measurement of cytokines released during measles suggests activation of CD8+ T cells, which are important for viral clearance, and type 2 CD4+ T cells, which provide optimal antibody production. Measles virus infection leads to a decrease of CD4+ lymphocyte counts that begins before the onset of rash and lasts for up to 1 month.63 A study of measles patients in the Gambia found marked suppression of the production of interleukin-12, a known regulator of cellular immunity, and suggests a mechanism for the immune suppression associated with measles infection.64 Recovery from infection is associated with the production of serum and secretory antibodies65–67 as well as the establishment of cellular immunity.68,69,70 Although subclinical infection with boosting of antibody may occur with subsequent exposure,65,66 immunity after natural infection is believed to be lifelong.69

Complications

The complications associated with measles infection have been the subject of much description and review.69,71,72–102 In industrialized countries, the most commonly cited complications associated with measles infection are otitis media (7%-9%), pneumonia (1%-6%), diarrhea (8%), postinfectious encephalitis (1 per 1,000–2,000 cases of measles), subacute sclerosing panencephalitis (SSPE) (1 per 100,000 cases), and death (1.0-3.0 per 1,000 cases). Complications are likely to be present if the fever has not lysed within 1 to 2 days of rash onset. The risk of serious complications and death is increased in children younger than 5 years and adults older than 20 years.5–9,50,97,100 Pneumonia, which is responsible for approximately 60% of deaths, is more common in young patients, whereas acute encephalitis occurs more frequently in adults.9,101 Pneumonia may occur as a primary viral pneumonia [H echt pneumonia] or as a bacterial superinfection, most commonly with staphylococcus, pneumococcus, or typhale (encapsulated) Haemophilus influenzae. Other described complications include thrombocytopenia, laryngotraheobronchitis, stomatitis, hepatitis, appendicitis and ileocolitis, pericarditis and pleurisy, pneumonia, and meningitis. Other complications include measles in the newborn after intrauterine exposure follows a shortened incubation period and may vary from mild to severe.51–53

Clinical variants

The typical course of measles described in the preceding section can be modified by the presence of antibody.51–53 This situation usually arises in the infant with maternal transplacental antibody or in a person given immune globulin (IG) after exposure, in an attempt to abort or attenuate the disease.57,58–60 Although some persons have subclinical infection,61 most will have a mild abbreviated illness that confers lasting immunity.160,161 A second clinical measles infection may occur, however, if immunity is incomplete.61–63 Typical or modified measles illness also may rarely follow reexposure after either natural infection64,165 or vaccination.166–174 Schaffner and colleagues166 reported a case of typical, albeit mild, measles in a
16-year-old girl who reportedly had measles 8 years earlier. She had a hemagglutination-inhibition (HI) antibody titer of 1:200 on the second day of rash and titers of 1:1,600 and 1:320 at 23 days and 6 months, respectively, after rash onset. The rapidity of antibody appearance, the high titer achieved, and the absence of immunoglobulin M (IgM) antibody in all of the specimens suggested a secondary immune response. Although reports examining immunity after infection rely on antibody determination, immunity relies heavily on T-lymphocyte memory and function.

Measles infection in the immunocompromised host (eg, persons with malignancies or human immunodeficiency virus [HIV] infection) can be prolonged, severe, and frequently fatal. Infection in these persons may occur in the absence of rash. The severity of illness is believed to be due primarily to impaired cell-mediated immunity. Two especially severe complications are an acute progressive encephalitis [measles inclusion body encephalitis] and a characteristic giant cell pneumonia (Hecht pneumonia). Measles has been found to be more severe in persons with HIV infection. In the United States, the case-fatality rate has been reported to be as high as 50% in HIV-infected children.

An atypical variant of measles occurred in some recipients of killed measles vaccine who were subsequently exposed to wild-type virus. Early studies found that patients with atypical measles lacked antibody to the measles virus fusion (F) protein and had exaggerated cellular responses to measles antigen. Affected patients had extremely high levels of measles-specific circulating antibody. Studies in monkeys have shown that this illness is caused by antigen-antibody immune complexes. The formalin-inactivated vaccine induced complement-fixing antibodies that failed to undergo antigen maturation; after exposure to measles, an anamnestic production of nonprotective, complement-fixing antibodies resulted in immune complex deposition and atypical measles. After an incubation period of 1 to 2 weeks, a prodrome consisting of high fever, headache, abdominal pain, myalgia and cough ensued. In the next 2 to 3 days, an unusual rash erupted on the extremities and spread centripetally. Whereas the exanthem could be erythematous and maculopapular, it was frequently petechial or vesicular and accompanied by edema, and was occasionally pruritic. The exanthem could be erythematosus and maculopapular, it was frequently petechial or vesicular and accompanied by edema, and was occasionally pruritic.

Virology

The measles virus is a pleomorphic, nonsegmented, single-stranded, negative-sense RNA virus with a diameter of 120 to 250 nm. It is a member of the genus Morbillivirus in the family Paramyxoviridae and is closely related to the canine distemper, rinderpest, peste-des-petits-ruminants viruses, and a phocine distemper virus of seals. Recent phylogenetic analysis suggests divergence of measles virus from its closest relative, rinderpest virus, occurred around the 11th to 12th centuries. The only natural host for the measles virus is humans. In susceptible populations, measles is one of the most transmissible viruses known. The viral structure is composed of eight proteins encoded within a 16-kb genome, including replication factors [polymerase [L] and phosphoprotein [P]], structural proteins [hemagglutinin [H], fusion [F], nucleoprotein [N] and matrix [M]] and two accessory proteins of unknown function [C and V]. The F and H proteins are essential in viral pathogenesis. The F protein is involved in the viral-host cell membrane fusion and viral entry into the host cell. The measles H protein is involved in the attachment and entry of measles virus into host cells via interaction with cell surface receptors. Signaling lymphocyte activation molecule (SLAM, also called CD150) is a membrane glycoprotein expressed on activated T and B lymphocytes and antigen-presenting cells that acts as the principal cellular receptor for measles virus, accounting for its lymphotropic and immunosuppressive nature. Measles virus also infects respiratory epithelial cells via a recently identified receptor molecule (CD147/EMmprin), thereby facilitating transmission via aerosol droplets. Vaccine and laboratory-adapted strains of measles virus use ubiquitously expressed CD46 as an alternate receptor. Other molecules have also been implicated in measles virus infection, although their relevance remains to be determined.

An atypical variant of measles occurred in some recipients of killed measles vaccine who were subsequently exposed to wild-type virus. Early studies found that patients with atypical measles lacked antibody to the measles virus fusion (F) protein and had exaggerated cellular responses to measles antigen. Affected patients had extremely high levels of measles-specific circulating antibody. Studies in monkeys have shown that this illness is caused by antigen-antibody immune complexes. The formalin-inactivated vaccine induced complement-fixing antibodies that failed to undergo antigen maturation; after exposure to measles, an anamnestic production of nonprotective, complement-fixing antibodies resulted in immune complex deposition and atypical measles. After an incubation period of 1 to 2 weeks, a prodrome consisting of high fever, headache, abdominal pain, myalgia and cough ensued. In the next 2 to 3 days, an unusual rash erupted on the extremities and spread centripetally. Whereas the exanthem could be erythematous and maculopapular, it was frequently petechial or vesicular and accompanied by edema, and was occasionally pruritic.
Measles virus is inactivated rapidly in the presence of sunlight, heat, and extremes of pH. It can, however, be safely stored for long periods at −70°C (−94°F).

In cell cultures, the virus causes two distinct cytopathic effects. The first is formation of multinucleated syncytia (giant cells) containing numerous nuclei of fused cells. This corresponds to the predominant pathologic process observed in infected tissues, including skin and Koplik spots. When observed in lymphoid tissue, the giant cells are referred to as Warthin-Finkeldey cells; otherwise they are known as epithelial giant cells.

Figure 20-1 Genetic variation in wild-type measles viruses, 2012. The World Health Organization (WHO) recognizes 24 genotypes of wild-type measles virus (A, B1, B2, B3, C1, C2, D1, D2, D3, D4, D5, D6, D7, D8, D9, D10, D11, E, F, G1, G2, G3, H1, and H2). The figure shows a phylogenetic tree based on the sequences of the nucleoprotein genes of the WHO reference strains for each genotype. The horizontal scale is proportional to genetic relatedness.

Figure 20-2 Worldwide distribution of measles virus genotypes, 2010.
Pathogenesis as it relates to prevention

The sequence of events between exposure to measles virus and subsequent primary acute illness in the normal host has been extensively studied, described, and reviewed. \[\text{References}\] It is based on information from both monkeys and humans. In the standard model of measles virus pathogenesis, there is initial localized infection of the respiratory epithelium of the nasopharynx, and possibly of the conjunctiva, followed by spread to regional lymphatics. Further events then occur in a manner similar to those observed in the Fennec crested-mouse experimental model. Specifically, 2 to 3 days after exposure, there is a primary viremia with further replication of virus at the site of inoculation as well as in regional and distant reticuloendothelial tissue. Then, 5 to 7 days after exposure, there is intense secondary viremia. After 4 to 7 days' duration that leads to infection of and further replication in the skin, conjunctiva, respiratory tract, and other distant organs. The amount of virus in blood and infected tissues peaks 11 to 14 days after exposure and then falls rapidly during the next 2 to 3 days. Alternative models of measles virus pathogenesis have been proposed. Lemon and colleagues, using a nonhuman primate model, found that measles virus enters the host at the alveolar level, followed by its appearance in regional lymphoid tissue and subsequent systemic dissemination by viremia.

The pathogenesis of measles infection indicates that prevention through immunization could be accomplished by inhibiting replication at the initial site of infection or by inhibiting the viremia that occurs during the incubation period. The first approach requires the presence of local secretory IgA antibody or transudated IgG; the second approach requires circulating antibody, either actively or passively acquired, to neutralize the virus. Although infection can be prevented solely after administration of antibody, induction of cellular immunity would also seem to be desirable. Children with primary agammaglobulinemia do not have more severe measles infections than do children with normal immune systems, and both develop long-lasting immunity after infection. These observations indicate that the cell-mediated immune system alone is capable of preventing measles.

On reexposure, it is uncertain whether prevention of the primary viremia is necessary or even feasible, but it is obvious that the secondary viremia should be prevented. In fact, an initial limited replication and the circulation of a small amount of viral antigen may be necessary to restimulate the immune system and to elicit an anamnestic antibody response.

Diagnosis

Measles should be suspected in children who present with an acute erythematous rash and fever, preceded by a 2- to 4-day prodrome of cough, coryza, conjunctivitis, and photophobia. Recent experience suggests that clinical measles may be difficult to distinguish from other causes of febrile rash illness, particularly in areas where the incidence of measles has been low. Clinical features that support the diagnosis of measles include the presence of Koplik spots, the characteristic 2 to 4 days of intensifying prodromal symptoms, the progression of the rash from the head to the trunk and out to the extremities, and the lysis of fever shortly after the appearance of the rash. Health care providers working in measles-endemic areas may be more familiar with these clinical findings than are health care providers working in areas with a low incidence of measles. A clinical case definition for epidemiologic purposes is the presence of rash lasting 3 or more days; a fever (temperature of 38.4°C [101°F] or higher, if measured; and cough, conjunctivitis, or coryza. Its use for clinical diagnosis is limited, particularly because of the criterion requiring at least 3 days of rash before the diagnosis is made. In some parts of the world, a less specific clinical definition not requiring 3 days' duration of rash is being used for epidemiologic purposes. Laboratory tests are necessary to confirm the diagnosis, especially when measles is rare. Other illnesses, such as rubella, dengue, parvovirus B19, human herpesvirus type 6, and measles vaccine reactions, can meet these clinical definitions.

In the United States, it is recommended that clinicians obtain a blood or other suitable specimen for laboratory confirmation from all patients suspected of having measles.

Although virus isolation, direct cytologic examination of clinical material, or demonstration of virus antigen can be used to diagnose measles, detection of measles-specific IgM antibody from a single blood specimen is the most commonly used method. An increase in measles antibodies between acute and convalescent serum specimens is also diagnostic but requires the collection of two blood specimens. RT-PCR can be used to identify measles virus RNA in urine, blood, oral fluid, and nasopharyngeal mucus. Because measles is an RNA virus, RNA must be reverse transcribed to DNA before PCR analysis, resulting in a much reduced sensitivity for diagnosing measles compared with diagnosing DNA viruses.

In primary acute infection, detectable antibodies generally appear in the serum within the first few days of rash onset, peak within about 4 weeks, and subsequently decline somewhat but persist for life (Figure 20-3). \[\text{Figure}\] Both IgG and IgM antibodies are initially produced, followed by the appearance of regional lymph node tissue. Further events then occur in a manner similar to those observed in the Fennec crested-mouse experimental model.

Figure 20-3 Schematic of the immune response in acute measles infection. EIA, enzyme immunoassay; HI, hemagglutination; NT, neutralization; CF, complement fixation; IgM, immunoglobulin M.
reference laboratories and research work. Fluorescence tests are available, also referred to as enzyme immunoassays (EIAs), and also referred to as enzyme-linked immunosorbent assays (ELISAs). Currently EIAs tests for measles IgG are the most widely used because they are generally sensitive and convenient. Good correlation has been shown between HI and Nt antibody in many studies, as well as between EIA and other serologic methods for the diagnosis of acute measles. The EIA for measles IgG is based on significant changes in optical density values and cannot be translated directly to antibody concentrations or titers. Currently, the recommended laboratory method for the confirmation of clinically diagnosed measles is a serum-based IgM EIA collected at the time the patient is first seen for medical care. A single specimen is adequate to detect the presence of IgM antibody. A number of commercial kits using an indirect EIA method (with removal of the patient's IgG antibody before testing for IgM) or an antibody capture EIA technique (without removal of IgG) are now available and have shown to have similar sensitivity (83%-92%) and specificity (87%-100%). However, if measles prevalence is low (eg, 1%), a modest reduction in the specificity of the assay from 99% to 95% will decrease the positive predictive value of the assay from 48% to 15% (ie, only 15% of EIA-positive clinical cases will be true measles). Patients with parvovirus B19 or rubella infections may have false-positive reactions (rate of about 4%) when tested with measles IgM EIAs.

Correct interpretation of serologic data depends on proper timing of specimens relative to rash onset. This is especially important in interpreting negative IgM results. For example, in one study, the sensitivity of an antibody capture IgM assay was approximately 80% within the first 72 hours after rash onset and rose to 100% between 3 and 14 days after rash onset. Sensitivity of the assay within the first 3 days of rash onset is thought to be similar for other commercially available kits. If the validity of the initial measles IgM test is in doubt, a second convalescent specimen should be taken and tested for IgM and for a rise in IgG titer compared with the initial specimen. In some cases, interpretation may be difficult and requires precise information regarding dates of rash onset, prior measles vaccination, and specimen collection.

Two approaches provide alternatives to venipuncture for collection of diagnostic specimens: oral fluid and blood spots on filter paper. In the United Kingdom, a commercial IgM EIA-based assay has been developed and is routinely used to test oral fluid specimens for measles, with a reported sensitivity of 94%, specificity of 91%, and positive predictive value of 99% compared with serum. Use of oral fluid samples has appeal because the technique is noninvasive, can be used for rubella and mumps testing, does not require processing in the field, or a cold chain for transport to the laboratory, and can be used to test for not only measles IgM and IgG but also the measles virus genome for molecular characterization. Although still considered an invasive technique, fingertip blood collection from infants can be used for rubella and mumps testing, does not require processing in the field, can be shipped without a cold chain, and can be used to test for not only measles IgM and IgG but also the measles virus genome.

In addition, the eluted serum can be tested by using commercially available EIAs with minimal loss of sensitivity or specificity.

**Treatment**

A number of preparations, such as interferon, thymic humoral factor, thymostimulin, levamisole, ribavirin, and IG, have been used to treat measles. None of these is commonly used to treat uncomplicated measles, although limited studies with ribavirin have shown reduced duration of illness. Ribavirin and interferon may be effective in treating severe measles in immunocompromised persons. High doses of vitamin A have been shown to decrease mortality and morbidity in young children hospitalized with measles in developing countries.

The WHO currently recommends vitamin A for children with acute measles. Treatment with vitamin A is once daily for 2 days at 200,000 IU for children ages 12 months or older, 100,000 IU for infants 6 to 11 months of age, and 50,000 IU for infants younger than 6 months. In the United States as well as in developing countries, children with measles have been found to have low levels of serum retinol, and those with more severe illness have lower levels.

The American Academy of Pediatrics (AAP) recommends using two doses of vitamin A (200,000 IU) on consecutive days, which has been shown to be associated with a reduction in the risk of mortality in children younger than two years (relative risk [RR], 0.18; 95% CI, 0.03-0.61) and the risk of pneumonia-specific mortality (RR, 0.33; 95% CI, 0.08-0.92). There was no evidence that vitamin A in a single dose was associated with a reduced risk of mortality among children with measles. In addition, vitamin A therapy should be administered to children with measles who are immunosuppressed, who have clinical evidence of vitamin A deficiency, or who have recently immigrated from areas with a high mortality rate from measles. Antibiotics, in the absence of pneumonia, sepsis, or other signs of a secondary bacterial complication, are generally not recommended. However, a recent clinical trial in Guinea-Bissau found that case-patients who received prophylactic antibiotics (co-trimoxazole) had less pneumonia and conjunctivitis and higher weight gain, suggesting a beneficial role of prophylactic antibiotics in the treatment of measles.

Various chemotherapeutic agents have also been used in patients with SSPE in an attempt to treat or at least alter the clinical course of the disease. Of these, inosiplex (Isoprinosine) and interferon have been the most extensively studied, despite anecdotal evidence of their effectiveness, controlled trials are lacking.

**Epidemiology**

**General epidemiology**

In the absence of an immunization program, measles is a ubiquitous, highly contagious, seasonal disease affecting nearly every person in a given population by adolescence. An important exception is island populations, which can remain free of infection for variable periods and then, after reintroduction of the virus, experience epidemic disease that involves all age groups not affected by the last wave of infection. Of these, inosiplex (Isoprinosine) and interferon have been the most extensively studied, despite anecdotal evidence of their effectiveness, controlled trials are lacking.

Measles is transmitted primarily from person to person by aerosolized droplet nuclei. The period of maximal contagion occurs during the prodrome. Secondary attack rates in susceptible household and institutional contacts are high and can be on the order of 90% or greater. Because virus is excreted before and after the appearance of rash, the onset of exanthem in secondary household cases occurs an average of 14 to 15 days (range of 7-21 days) after that in the index case. Almost all primary infections (except those in elderly persons, immune persons, or neonates) are thought to be clinically overt. Asymptomatic transmission from exposed immune persons has not been demonstrated. Although susceptible monkeys may become infected with measles, there is no significant animal reservoir.

Before the introduction of vaccines in most developed countries, school-age children had the highest risk of infection and accounted for the largest proportion of cases. However, in dense urban areas, transmission among preschoolers took on greater importance.
occur, they were relatively rare compared with the situation in developing countries. In the United States before the introduction of vaccine in 1963, major epidemics occurred approximately every 2 to 3 years. Each year, disease peaked in late winter and early spring. The highest occurrence of disease was in children 5 to 9 years of age, who accounted for more than 50% of reported cases (Table 20-1). More than 95% of cases had occurred by age 15 years. The highest risk of death was in children younger than 1 year and in adults.

The measles virus is so contagious that it can be expected to circulate wherever a relatively large number of susceptible persons congregate, even in the face of a low population susceptibility rate. This explains the outbreaks that were typical among military recruits before the institution of routine measles vaccination. Outbreaks among high-school and college students, most of whom have been vaccinated, demonstrate the virus’s capability to seek out the small number of remaining susceptible persons.

Before widespread vaccination, in many developing countries, the average age at infection was much lower than that observed in developed countries. In some areas of Africa, more than 50% of 2-year-old and 100% of 4-year-old children may be expected to have had measles. Poor nutrition and rapid loss of maternal antibody may explain why a greater proportion of these infants are susceptible at an earlier age than are those in developed areas, and infection, in turn, results from the early age at which infants are exposed to the community at large. Young age at infection contributes to the high risk of serious complications and death. Also, malnutrition, especially vitamin A deficiency, may be an important factor leading to the marked severity of measles in the developing world because of defects in cellular (and possibly humoral) immunity. However, there is some evidence that crowding, which leads to a potential increased dose of transmitted virus, may be a more significant determinant of the severity of infection than is protein-calorie malnutrition.

### Significance as a public health problem

Although remarkable control of measles has been achieved in some areas of the world, in 2000, measles was still the leading cause of vaccine-preventable deaths in children and the fifth leading cause of all deaths among children less than 5 years of age. Measles is also responsible for much diarrhea, respiratory disease, blindness, and convulsions. Measles is a major cause of death in the early age at which infants are exposed to the community, in turn, results from the early age at which infants are exposed to the community at large. Young age at infection contributes to the high risk of serious complications and death. Also, malnutrition, especially vitamin A deficiency, may be an important factor leading to the marked severity of measles in the developing world because of defects in cellular (and possibly humoral) immunity. However, there is some evidence that crowding, which leads to a potential increased dose of transmitted virus, may be a more significant determinant of the severity of infection than is protein-calorie malnutrition.

### Table 20-1 Age Distribution and Mean Annual Incidence of Reported Measles Cases by Age Group

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*Data represent prevaccine years and are from four reporting areas: New York City, District of Columbia, Illinois, and Massachusetts.
†Data from the entire United States.

Passive immunity to measles can be acquired through physiologic transfer of maternal measles antibodies from mother to child or by administration of measles antibodies from convalescent donors to persons at risk of infection. Maternal antibodies provide time-limited protection against measles during the first months of life when infection can be most devastating. Women who have antibodies to measles, from measles infection or vaccination, transfer antibodies to their children during pregnancy via the placenta and after delivery by breastfeeding. Among newborns, the duration of protection by transplacental measles antibody varies from some being unprotected (ie, their mother lacked immunity) to others being protected for up to 15 months of age. The factors that affect the duration of transplacental measles antibodies among infants and the effect of these antibodies on response to measles vaccination are presented in the section “Maternal antibody and age at vaccination”. Measles-specific antibodies, including secretory IgA, are excreted in the breast milk of immune mothers and have been shown to neutralize measles virus in vitro. Many of the key factors related to breast milk antibodies against measles are not well determined. In two studies in Africa in the 1980s, one showed a significant reduction in the measles mortality rate of hospitalized children who were breastfed compared with those who had been weaned, while the other study showed no protective effect of breastfeeding.

Administration of measles antibodies as immune globulin provides short-term protection from measles for susceptible persons. Preexposure prophylaxis against measles and other diseases is provided to persons with primary humoral immune deficiency diseases (PIDD) via frequent administration of immune globulin given intravenously (IGIV) or subcutaneously (IGSC). Postexposure prophylaxis with immune globulin given intramuscularly (IGIM) is recommended for persons exposed to measles or at high risk of exposure for whom vaccine is either contraindicated or was not given within 3 days of exposure [see “Postexposure prophylaxis” and “Use of immune globulin”].

In 1926, Zininger summarized early efforts to prevent measles by injection of whole blood, serum, or plasma from donors who had a previous measles infection. A significant reduction in the measles attack rate among persons who received convalescent blood products after exposure to measles was shown, and convalescent blood products were widely used as postexposure prophylaxis in the 1920s and 1930s. In the 1940s, Janeway...
demonstrated that administration of IG within 6 days after intimate exposure prevented measles in about three of four persons, with mild measles occurring in the fourth.158

Immunoglobulin products are prepared from plasma pools derived from thousands of donors. Measles disease results in higher antibody titers than does vaccination. Therefore, donor populations with predominantly vaccine-induced measles immunity yield lower measles antibody titers in IG preparations. A study in Japan showed lower measles antibody titers in IGIM may result in a reduced level of postexposure protection including those with low measles antibody titers.163

In the United States, the Food and Drug Administration (FDA) requires that all IG preparations contain a measles-neutralizing antibody level that demonstrates adequate potency when compared with the US standard.164 In 2007, the FDA Blood Products Advisory Committee reduced the potency requirements for IGIM, IGIV, and IGSC lots to be 0.60 of the standard lot titer for both IGIM and IGSC, which are given in much higher volumes than IGIM. The new potency requirement for IGIV and IGSC lots is calculated to provide a protective measles antibody titer given the recommended minimum doses, and dose frequency.165 The potency requirement for IGIM remains 0.60 of the standard lot titer.

**Active immunization**

**Vaccine strains**

**Origin and development**

After the isolation and propagation of measles virus in tissue culture by Enders and Peebles in 1954, vaccine development, testing, and licensure quickly followed.11–21 The Edmonston strain, named after the youth from whom the virus was isolated, was used for many of the vaccines developed worldwide (Figure 20-4).166–168 To make the now-famous Edmonston B vaccine, Enders and colleagues169,170 further passaged the Edmonston strain to 35°C to 6°C (95°F to 96.8°F) 24 times in primary kidney cells and 28 times in primary human amnion cells, adapted it to chicken embryos (6 passages), and then passed it in chicken embryo cells. This attenuated Edmonston B vaccine was licensed in the United States in March 1963 along with another Edmonston B virus strain that had been adapted to primary dog kidney cells.164–166 Although the administration of the Edmonston B vaccine was associated with a high rate of fever (temperature of 39.4°C [103°F] or higher in 20% to 40% of vaccinees) and rash (approximately 50%), the recipients remained remarkably well. However, simultaneous administration of a small dose of IG with the vaccine (eventually set at 0.02 mL/kg) reduced the occurrence of high fever and rash by approximately 50% (Figure 20-4).166,369–372,384,385,387–392 Approximately 18.9 million doses of Edmonston B vaccine were administered in the United States between 1963 and 1975 (Table 20-2 and Figure 20-6).

### Killed vaccine

A formalin-inactivated, alum-precipitated vaccine derived from the Edmonston strain was also licensed in the United States in 1963 and used until 1967 (see Table 20-2 and Figure 20-6). This vaccine was also used in some provinces in Canada. Usually, three doses of killed vaccine or two doses of killed and one dose of live vaccine were administered at monthly intervals with few side effects.67,266,369,372,384–392 Use of killed vaccine was eventually discontinued when it became apparent that this vaccine produced short-lived immunity and placed many recipients at risk for atypical measles infection.403 It has been estimated that between 600,000 and 900,000 persons in the United States received the 1.8 million doses of killed measles vaccine that were administered (see Table 20-2 and Figure 20-6).402

**Figure 20-4** Attenuation history of selected measles vaccine strains. Cell cultures in which strains were passaged during attenuation: CAM, chick chorioallantoic membrane; CE, chick embryo intra-amniotic cavity; CEF, chick embryo fibroblast; GPK, guinea pig kidney; HA, human amnion; HK, human kidney; JQ, Japanese quail; MK, monkey kidney; SK, sheep kidney; WI-38, human diploid cell line.
Further attenuated live vaccines

Many further attenuated vaccines have been developed and are in active use worldwide (Table 20-3, see Figure 20-4). Most were derived from the Edmonston strain. These further attenuated vaccines differ in the viral isolate of origin, the number and temperature of cell culture passages, the type of cell culture used for the passage and production, and whether plaquings were performed during the passages.

Although differences in plaque size, subgenomic particles, temperature sensitivity, and pathogenicity in severe combined immune-deficient mice containing human thymic tissue implants have been described among the further attenuated vaccine strains, their significance is uncertain. Nucleotide sequence analysis of the F, H, N, and M genes showed no more than 0.6% variability among vaccine strains derived from the Edmonston strain. Complete genomic sequence analysis of different measles vaccine strains have been compared with the Edmonston wild-type virus. AIK-C, Moraten, Rubeovax, Schwarz, and Zagreb were all found to be of the Edmonston lineage, whereas CAM-70, Changchun-47, Leningrad-4, and Shanghai-191 were derived from four different wild-type isolates. However, all the vaccine strains, whether derived from Edmonston or from other wild-type viruses, are members of the same genotype, genotype A. Studies have identified nucleotide sequence substitutions in the H gene that appear to mediate some of the biologic characteristics of the Moraten strain of vaccine. Comparison of the noncoding regions of a low-passage Edmonston wild-type strain and five Edmonston vaccine viruses found 21 nucleotide positions at which the wild type and one or more of the vaccine types differed. Five nucleotide substitutions were conserved in all of the vaccine strains. Comparison of protein-encoding nucleotide sequences of the N, P, M, F, H, and L genes of these vaccine strains with Edmonston wild-type virus identified amino acid substitutions in each of the genes; however, the overall level of heterogeneity did not exceed 0.3%. The role that these sequence differences in both the coding and noncoding regions of the genome play in attenuation of measles viruses is being characterized by using specialized genetics systems.
Two further attenuated live measles vaccines derived from the Edmonston strain were licensed in the United States, the Schwarz strain in 1965 and the Moraten strain in 1968 (see Table 20-2 and Figure 20-4). The Schwarz vaccine was derived from Edmonston virus passaged an additional 85 times at 32°C (89.6°F) in chicken embryo cells. The Moraten strain was also passaged at this lower temperature, but only an additional 40 times. Compared with the Edmonston B vaccine, the frequency and severity of side effects attributed to these and other further attenuated vaccines were significantly lower (see Figure 20-5). A temperature of 39.4°C (103°F) or higher occurred in only 5% to 15% and rash in only 3% to 5% of vaccinees. Simultaneous administration of specially titered IG in a low dose (0.02, 0.1, or 0.2 mL/kg) further reduced the incidence of high fever and rash to approximately 3% each (see Figure 20-5). These doses of IG did not interfere with seroconversion, but the peak geometric mean antibody titer was lower than that observed without IG administration. The further attenuated vaccines are used without IG.

The Moraten vaccine (Attenuvax; Merck, Whitehouse Station, NJ) is now the only measles vaccine used in the United States; the Schwarz vaccine is the predominant product in many other nations.

Several different further attenuated measles vaccines, including AIK-C, Schwarz F88, CAM-70, and TD97, have been developed and are being used in Japan. The vaccine developed by Smorodintsev (Leningrad-16) was introduced in Russia in 1967 and was the principal vaccine virus strain in eastern Europe. The CAM-70 and TD97 vaccines were derived from the Tanabe strain; these vaccines, as well as those in use in China since 1965, are the few not derived from the Edmonston virus.

Whereas most measles vaccines were attenuated and are produced in chick embryo fibroblasts, a few currently used vaccines were attenuated in human diploid cells. The Edmonston-Zagreb vaccine, used extensively in the former Yugoslavia since 1969, is now produced by several other manufacturers and is the most widely used vaccine in developing countries. Other vaccine strains have been adapted to MRC-5 and R-17 human diploid cells in Iran and in China.
Dosage and route of administration

According to current regulations in the United States, measles vaccine must contain at least 1,000 median tissue culture infective doses [TCID\textsubscript{50}] at the end of the expiration date of the vaccine.\textsuperscript{413} The vaccine is administered in a 0.5-mL dose. The minimum dose required to immunize a seronegative child has been found to be as low as 20 TCID\textsubscript{50} in some studies but higher in others.\textsuperscript{419–422} The dose in the commercial product is designed to compensate for some of the virus deterioration that may result either from improper storage or reconstitution or from exposure to light or heat before injection.

The recommended route of administration is subcutaneous injection. Although there are only limited data on the intramuscular route, it appears to be as effective as subcutaneous vaccination.\textsuperscript{423} Studies with the Edmonston B and further attenuated vaccines have examined the effectiveness of other routes of administration, such as intranasal and conjunctival inoculation.\textsuperscript{11,15,30,53,54,384,424–425} Most of the results were not favorable. In contrast, aerosol administration, which was evaluated during the early 1960s and 1970s showed promising results.\textsuperscript{426} During the 1980s, studies were undertaken to determine whether aerosol administration of measles vaccine could overcome maternal antibody and immunize younger infants.\textsuperscript{426–431} Many of these studies have found the Edmonston-Zagreb vaccine strain to be more immunogenic than the Schwarz strain when it is administered by aerosol.\textsuperscript{432} However, whereas some investigators reported high seroconversion rates after administration by this route in young infants,\textsuperscript{427–431} others found it inferior to subcutaneous administration.\textsuperscript{430}

Aerosol administration of measles vaccine in South Africa\textsuperscript{432} and of combined measles and rubella vaccines in Mexico\textsuperscript{434} resulted in boosting of antibody responses among schoolchildren. These studies have led to enthusiasm about the possible use of aerosol administration as a less invasive alternative to needle-and-syringe administration during mass vaccination campaigns, especially among schoolchildren. Subsequently, aerosol administration of the Edmonston-Zagreb strain has been shown to induce a primary immunization response at 9 months of age.\textsuperscript{435} However, the antibody and T-cell responses were lower in the infants who received aerosolized vaccine when compared with those vaccinated subcutaneously, possibly because of the lower dose contained in the aerosol preparation. The challenge remains to demonstrate immunization safety with this new approach and license an aerosol device together with an existing measles vaccine strain [see “Future vaccines”].

Combination with rubella, mumps, and varicella vaccines

In the United States, vaccination against measles is accomplished with combined live vaccines that also contain attenuated rubella and mumps vaccine viruses. Combined vaccines were licensed in the United States in 1971. They contain at least 1,000 TCID\textsubscript{50} of the measles Moraten strain, at least 5,000 TCID\textsubscript{50} of the mumps Jeryl Lynn strain, and at least 1,000 TCID\textsubscript{50} of the RA27/3 strain of rubella vaccine virus. The RA27/3 strain of rubella vaccine replaced the HPV-77 rubella strain as the rubella component in 1979. Currently, the only licensed MMR vaccine is produced by Merck [M-M-R II]. In September 2005, a combined measles, mumps, rubella, and varicella [MMRV] vaccine produced by Merck was licensed for use in the United States.\textsuperscript{436} The measles, mumps, and rubella vaccine viruses in this quadrivalent vaccine are identical and of equal titer to those in MMR vaccine. The titer of Oka/Merck varicella-zoster virus is higher in MMRV vaccine than in single-antigen varicella vaccine [see Chapter 37 on “Varicella vaccine”].

Combination products have been developed as other countries began vaccinating children against rubella or mumps along with measles.\textsuperscript{31–34,37,437} For example, GlaxoSmithKline [Research Triangle Park, NC] produces a vaccine that contains Schwarz measles vaccine, RIT 4,385 mumps vaccine strain [derived from the Jeryl Lynn strain], and the RA27/3 strain of rubella vaccine. Sanofi Pasteur [Swiftwater, PA] produces a combined formulation with Schwarz measles vaccine, Urbane mumps vaccine, and RA27/3 rubella vaccine. In Japan, several formulations of combined vaccines are available, including one containing the A1K-C measles virus, the Hoshino mumps virus, and the Takahashi rubella virus strains.\textsuperscript{438} Two other combined vaccines are also licensed: one containing the CAM-70 measles strain and one containing the Schwarz F88 strain. The MMR vaccine containing the Urbane mumps strain is no longer being produced in Japan. A triple vaccine with the Edmonston-Zagreb strain of measles vaccine is being produced by the Institute of Immunology [Zagreb],\textsuperscript{439} Berna Biotec [Berne; formerly the Swiss Serum Institute],\textsuperscript{440} and the Serum Institute of India [Mumbai; Leningrad-Zagreb mumps strain and RA27/3 rubella strain].

Safety and immunogenicity data indicate that combining the measles antigen with rubella and mumps antigens\textsuperscript{437–439} in the MMR vaccine is both safe and efficacious. Initial results also showed similar safety and efficacy for MMRV vaccine compared with MMR given with varicella vaccine at the same time but at different injection sites.\textsuperscript{439–441} However, when given as the first dose to young children, more recent studies have shown the risk of febrile seizures\textsuperscript{442–445} appears to be higher after MMRV compared with MMR and varicella vaccine administered simultaneously at separate sites.\textsuperscript{442} [see “Adverse effects”]. Based on the increased risk of febrile seizures when MMRV is used as the first dose in young children, the Advisory Committee on Immunization Practices [ACIP] has modified its recommendations for use of MMRV [see “General immunization guidelines”].

Production and constitution of vaccine

Preparation methods for the Merck vaccine provide generally applicable information regarding the production and constitution of measles vaccines.\textsuperscript{446} Although there are minor differences in dose, antibiotic content, and other details among manufacturers, there are no reports of significant differences in side effects or vaccine effectiveness.

The vaccine virus is cultured in primary chick embryo cells. After an initial cell growth phase, the cultures are inoculated with the further attenuated Moraten strain of measles virus. After several days’ incubation at 32°C (89.6°F), the cells are washed to remove fetal bovine serum, and the medium is replaced with one containing 50 μg/mL of neomycin, sucrose, buffered salts, amino acids, and human albumin. Fluids containing virus can be removed from the cultures for a period of time as the cells are maintained at the same temperature. These fluids are frozen until determinations of the virus titer have been performed on retained aliquots. Harvested virus fluids having sufficient virus potency and satisfactorily passing tests are thawed, pooled, sampled for safety testing, clarified, dispensed, and refrozen.

When bulk vaccine has passed all quality control tests, portions of the vaccine are thawed, dispensed into vials, and lyophilized. At the time of use, the vaccine is reconstituted with fluid [sterile distilled water] provided by the manufacturer. A preservative-containing reconstitution fluid is not recommended for general use because it may inactivate the vaccine. Each vaccine dose contains approximately 25 μg of neomycin. Sorbitol and hydrolyzed gelatin are added as stabilizers. When reconstituted with the provided diluent, the vaccine is clear and yellow in color.
Stability of vaccine

Measles vaccine is extremely stable between −70° C (−94° F) and −20° C (−4° F). Although measles vaccine is affected adversely by higher temperatures, the introduction of more heat-stable vaccines in 1979 has led to increased stability under normal working conditions, which is especially important in the developing world. In the United States, manufacturers must demonstrate that a minimum titer of 1,000 TCID<sub>50</sub> is maintained throughout to the labeled expiration date when the vaccine is stored at 2° C to 8° C. The WHO has a requirement that inactivated measles vaccine, after exposure to 37° C for at least 1 week, cannot lose more than 1 log<sub>10</sub> and must maintain a titer of at least 1,000 TCID<sub>50</sub>.

For the currently available vaccine in the United States, when it is stored at 2° C to 8° C (35.6° F-46.4° F), a minimum titer of 1,000 TCID<sub>50</sub> can be maintained in unreconstituted vaccine for 2 years or more. This potency can be maintained for 8 months at room temperature (20° C-25° C or 68° F-77° F) and up to 37° C (98.6° F) for 4 weeks at 37° C. Reconstituted vaccine loses 50% of its potency in 1 hour at 20° C to 25° C (68° F-77° F) and almost all its potency when it is held at 37° C (98.6° F) for 1 hour. Vaccine is also sensitive to sunlight; however, colored glass vials further minimize loss of potency. Notwithstanding its improved thermostability, the vaccine still needs to be handled with care according to the recommendations of the manufacturer.

As stated in the package insert, Merck recommends that its product be shipped at a temperature of 10° C (50° F) or less and stored, before reconstitution, at 2° C to 8° C (35.6° F-46.4° F) and protected from sunlight. Reconstituted measles vaccines (M, MR, and MMR) should be used immediately. If reconstituted vaccine is not used within 8 hours, it must be discarded. MMRV vaccine must be stored frozen at an average temperature of less than or equal to 5° F (−15° C). Unlike other measles-containing vaccines, MMRV vaccine cannot be stored at refrigerator temperature, and once reconstituted, it should be used immediately to minimize loss of potency and should be discarded if not used within 30 minutes.

Results of vaccination

The immune response

The immune response after successful vaccination is similar in most respects to that noted after natural infection. Although the interval between vaccination and an immune response is a few days shorter than that observed after natural infection, immunization induces both humoral and cellular immunity and the production of interferon. Laboratory evidence of immunity is most conveniently documented by use of antibody assays because tests for cell-mediated immunity are not standardized. However, even with antibody assays, results of studies on vaccine-induced immunity may vary, depending on the sensitivity of the antibody assay used. Although the presence of antibodies detected by HI, ELISA, or CF correlates with immunity, 

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in 124 children receiving their first dose of MMR. However, a study of the immune response to measles vaccination at 9 months of age among 55 Peruvian children found that 93% developed a humoral response, and only 23% had lymphoproliferative responses. Gans and colleagues studied the ability of infants ages 6, 9, or 12 months to respond to measles vaccine and found that, unlike humoral responses, T-cell responses can be established despite the presence of passive antibodies. Outbreak investigations have documented vaccination before the first birthday as a risk factor for vaccine failure, suggesting that vaccine-induced cell-mediated immune responses can be established despite the presence of passive antibodies. Antibody responses by the cell-mediated immune system correspond to an initial T-helper 1 [Th1]-type response with a shift to a Th2-type response.

Vaccination suppresses cell-mediated immune function [as does natural infection]. This manifests in vitro as suppression of lymphocyte stimulation or in vivo as suppression of cutaneous delayed hypersensitivity to various antigens. Fireman and colleagues noted suppressed cellular immune function up to 4 weeks after administration of live vaccine. Suppression did not occur after receipt of killed vaccine. A study of Bangladeshi infants found that delayed-type hypersensitivity reactions to Candida antigen were significantly reduced at 6 weeks postvaccination. Data suggest that this suppression is due to down-regulation of interleukin-12, which is needed for cell-mediated immunity.

One would assume that the presence of a rash after parenteral injection of vaccine would be associated with viremia. The generalized stimulation of T and B lymphocytes after vaccination also suggests viremia. Few studies documented viremia after vaccination. Early studies with the canine cell vaccine isolated vaccine virus from blood, but more recently, van Binnendijk and colleagues have isolated Schwarz strain vaccine virus from monkeys 7 to 9 days after vaccination. There are no reports of isolation of vaccine virus from blood in normal humans. Although Mitus and associates did isolate vaccine virus from the throat and conjunctiva of a susceptible leukemic patient who died of giant cell pneumonia after administration of Edmonston B vaccine, they failed to isolate virus from the blood. The apparent difficulty of isolating vaccine virus may reflect the low level of viremia after vaccination.

Because wild-type virus is so highly transmissible, both virologic and clinical studies with susceptible contacts were conducted in early vaccine investigations. These studies showed no evidence of virus excretion or transmission by vaccinees. Measles virus was isolated from a throat swab taken from a 3-year-old boy who presented with fever only 12 days after vaccination with MMR vaccine. This case report suggests that subcutaneous vaccination with live attenuated measles virus can result in respiratory excretion of the vaccine virus. Person-to-person transmission of vaccine virus has never been documented.

**Table 20-4 Antibody Response 21 to 28 Days After Measles Vaccination with or without Immune Globulin**

<table>
<thead>
<tr>
<th>Vaccination regimen</th>
<th>Total number</th>
<th>Seroconversion (%)</th>
<th>GMT†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edmonston B vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>171</td>
<td>96</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>–</td>
<td>1 : 208</td>
</tr>
<tr>
<td>Immune globulin, 0.02 mL/kg</td>
<td>185</td>
<td>99</td>
<td>1 : 96</td>
</tr>
<tr>
<td>Further attenuated vaccine‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>121</td>
<td>99</td>
<td>1 : 56</td>
</tr>
<tr>
<td>Immune globulin, 0.1 mL total</td>
<td>89</td>
<td>95</td>
<td>1 : 32</td>
</tr>
<tr>
<td>Immune globulin, 0.2 mL total</td>
<td>452</td>
<td>98</td>
<td>1 : 32</td>
</tr>
<tr>
<td>Immune globulin, 0.02 mL/kg</td>
<td>193</td>
<td>95</td>
<td>1 : 24</td>
</tr>
</tbody>
</table>

*Neutralizing titer of 1:400/0.1 mL.
†Complement fixation assay geometric mean antibody titer.
‡Schwarz strain.

**Table 20-5 Antibody Response 28 Days After Attenuated and Further Attenuated Measles Vaccine**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Total number</th>
<th>Seroconversion (%)</th>
<th>GMT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edmonston B†</td>
<td>258</td>
<td>99</td>
<td>1 : 25</td>
</tr>
<tr>
<td>Schwarz‡</td>
<td>250</td>
<td>98</td>
<td>1 : 16</td>
</tr>
<tr>
<td>Moraten‡</td>
<td>273</td>
<td>98</td>
<td>1 : 16</td>
</tr>
</tbody>
</table>

*Hemagglutination-Inhibition assay.
†Attenuated vaccine.
‡Further attenuated vaccine.
GMT, Geometric mean antibody titer.

Response to revaccination

The immune response after revaccination depends on the results of the initial vaccination. Persons who have no response to initial vaccination typically generate a primary immune response to revaccination, with a significant rise in antibody titer and the production of IgM antibody. After revaccination of a person with some level of immunity, a fourfold or greater rise in antibody may appear sooner than that seen after initial vaccination, but there are usually no clinical signs of infection. IgG antibodies are first detected within 5 to 6 days and peak around 12 days. IgM antibodies are not usually detected. As is the case with immunity after natural infection, these are the characteristics of an anamnestic immune response. Such a boost is more likely to occur in the presence of a low or undetectable pre-existing antibody titer, whereas persons with a high level of circulating antibody may not boost. Krugman and colleagues reported that, after revaccination, a significant increase in HI titer occurred in only 1 of 6 children with HI titers of 1 : 16 or 1 : 32 but in 25 of 36 children with titers of 1 : 8 or less. Similar findings were noted in vaccinees exposed to wild-type virus.
Despite the fact that any detectable level of measles antibody of protection from measles (ie, as a correlate of protection). The booster phenomenon is not unique to vaccine-induced immunity. It can also be observed after exposure to measles or after vaccination in persons who have had measles, but it occurs less frequently because antibody titers after natural infection are usually higher than those after vaccination.\textsuperscript{55,67} Stokes and colleagues\textsuperscript{68} reported that, on reexposure to wild-type virus, 6 of 12 naturally immune persons with preexposure NT titers ranging from 1:2 to 1:8 experienced a boost in titer. However, such boosts were not seen in any of 22 persons with titers between 1:16 and 1:128. These data indicate that subclinical reinfection may occur after both natural infection and successful vaccination.

Studies of the response to revaccination\textsuperscript{18,514,517-519} have shown that a high proportion of vaccinated persons who lack detectable antibody to measles will respond to the second dose. Among persons initially vaccinated after 12 months of age, at least 95% will respond.

**Effectiveness of protection**

**Measures of protection**

A person's risk of measles is the product of his or her susceptibility to measles and risk of exposure to measles virus. Measles vaccine provides both personal immunity to prevent disease when exposed to measles virus and population immunity through decreased intensity of transmission as the proportion of immune persons in a population increases. The population immunity effect decreases the risk of measles among immunized as well as unimmunized persons.

The most direct method of measuring the personal immunity effect of measles vaccine would be to challenge vaccinees and controls with wild-type measles virus and document the clinical outcome. Such studies are not done in humans because of the harmful effects of exposure to measles virus. In studies in animals challenged with wild-type measles virus, vaccinated animals have significant decreases in clinical symptoms and measles virus replication compared to controls.\textsuperscript{520} These studies are performed to evaluate the response to new vaccines in terms of clinical protection, reduced viral load, and development of serologic and cellular immunity.\textsuperscript{521-522}

Because tests of cell-mediated immunity to measles are less widely available, antibody titers are most often used as evidence of protection from measles [ie, as a correlate of protection]. Despite the fact that any detectable level of measles antibody has been interpreted as evidence of protection after vaccination, the development of more sensitive antibody tests\textsuperscript{527} has raised concerns that low levels of antibody\textsuperscript{529} may not be protective. A school blood drive before a measles outbreak permitted correlation of preexposure measles antibody titers by using the PRN test with the level of clinical protection.\textsuperscript{525-526} Eight of nine students with low but detectable levels of measles antibody immediately before the outbreak [PRN titer ≤ 1:20] developed typical measles compared with none of 71 with preexposure PRN titers of greater than 120. Seven of 11 students with preexposure PRN titers of 216 to 874 had a fourfold or greater rise in antibody titer compared with none of 7 with a preexposure PRN titer of 1,052 or greater, indicating that high titers were associated with protection against both infection and disease. Although many persons with low antibody titers may not develop disease after exposure, available data suggest that these low levels of antibody may not be fully protective.

Protection also can be evaluated by examining the immune response of vaccinees challenged with vaccine virus through revaccination.\textsuperscript{517,518,520,523,525} Such challenges most often result in an anamnestic immune response (see “Response to revaccination”).

The most commonly used method to quantify the protective effect of measles vaccine is to identify persons with similar likelihood of exposure to measles virus and compare the attack rate of disease in unvaccinated and vaccinated persons. The decrease in attack rate among vaccinated compared with unvaccinated persons is called vaccine effectiveness or vaccine efficacy.\textsuperscript{526,527} [Refer to Chapter 67 for a more detailed discussion of this topic, including formulas and methods for calculating vaccine effectiveness.] In outbreak settings in which a high proportion of the population is vaccinated, the proportion of cases that are vaccinated will also be high, and it may appear erroneously that the vaccine effectiveness is low.\textsuperscript{514,529} However, approximately 50% of cases can be expected to be vaccinated, with vaccine effectiveness and vaccine coverage each 90%.\textsuperscript{525} This proportion of cases will increase to 60% with a 95% coverage rate. The majority of available data indicate vaccine effectiveness in the United States of 90% to 95% or greater,\textsuperscript{510,511} consistent with seroconversion data.

Reduction in the occurrence of measles after the introduction of vaccine is a common measure of vaccine-induced protection at the population level. Both Krugman and colleagues\textsuperscript{266} and Baba and colleagues\textsuperscript{531} noted virtual elimination of measles from a population of institutionalized children after vaccination became routine, despite high levels of infection in the surrounding community. Similarly, nationwide surveillance in many countries with high levels of immunization has documented a significant reduction in reported measles cases after vaccine licensure, and many have eliminated endemic transmission of measles.\textsuperscript{22-41} For more examples of the impact of measles vaccination on measles incidence, see “Experiences with measles control” and “Elimination in various countries” later in this chapter.

Monitoring the reproductive rate, or R value, is another method of assessing the impact of vaccination on a population. The basic reproductive rate [R\textsubscript{0}] is the average number of cases that would be expected to spread from a single case of measles in a completely susceptible population. Measles is a highly infectious disease, and R\textsubscript{0} has been estimated as 12.5 to 18.\textsuperscript{512} The effective reproductive rate [R] incorporates the level of immunity in a population with the factors that determine R\textsubscript{0}. In a completely susceptible population, R = R\textsubscript{0}. In populations with partial immunity, the difference between R and R\textsubscript{0} is the effect of population immunity. When R is greater than 1, the number of cases increases from one generation to the next and an epidemic begins. As the spread of disease increases immunity in the population, R falls below 1, the number of cases decreases from one generation to the next, and the epidemic ends. To achieve interruption of endemic transmission of measles, it is necessary to achieve a level of population immunity that maintains R less than 1 [see Chapter 71]. In the United States, assessment of the reproductive rates through surveillance data documented R less than 1 for the period from 1992 to 1999.\textsuperscript{533} Analysis of vaccination programs in Western Europe found that four of eight countries had vaccine coverage sufficiently high to eventually eliminate measles.\textsuperscript{534}

Because tests of cell-mediated immunity to measles are less widely available, antibody titers are most often used as evidence of protection from measles [ie, as a correlate of protection]. Despite the fact that any detectable level of measles antibody has been interpreted as evidence of protection after vaccination, the development of more sensitive antibody tests has raised concerns that low levels of antibody may not be protective. A school blood drive before a measles outbreak permitted correlation of preexposure measles antibody titers by using the PRN test with the level of clinical protection. Eight of nine students with low but detectable levels of measles antibody immediately before the outbreak [PRN titer ≤ 1:20] developed typical measles compared with none of 71 with preexposure PRN titers of greater than 120. Seven of 11 students with preexposure PRN titers of 216 to 874 had a fourfold or greater rise in antibody titer compared with none of 7 with a preexposure PRN titer of 1,052 or greater, indicating that high titers were associated with protection against both infection and disease. Although many persons with low antibody titers may not develop disease after exposure, available data suggest that these low levels of antibody may not be fully protective.
serum IgG antibodies to measles. However, 19% of those born between 1967 and 1976 were seronegative. This time frame represents the early implementation phase of measles vaccination in the United States, when high coverage levels had not been achieved, yet the incidence of measles was significantly decreased; therefore, a proportion of children grew up without getting measles or vaccination. This pocket of susceptibility has not been a major focus of measles transmission, however, it may have a significant impact on the amount of antibodies mothers born in these years pass on to their infants. In a follow-up survey conducted 1999 to 2004 in the United States, the lowest levels of seropositivity were again found in persons born in early vaccine implementation years of 1967 to 1976. Serosurveys in some other countries have demonstrated low levels of seropositivity in persons born in the early vaccine implementation years. Serosurveys have also been used to plan vaccine strategies or assess their impact. More recently, oral fluid surveys have assessed population IgG antibodies to measure the impact of mass campaigns on population immunity and susceptibility in Kenya and Ethiopia.

Mathematical modeling can be used to compile and interpret the factors related to measures of vaccine protection, including patterns of transmission, vaccination coverage estimates, measles antibody surveys, and effects of primary and secondary vaccine failure.

**Correlates of immunity**

Plaque reduction neutralization antibody titers at the time of exposure to virus have been most closely correlated with immunity against measles. In one study, no one with a titer of greater than or equal to 120 at the start of an outbreak developed measles. Further information on correlates of immunity is provided in the preceding section on “Measures of protection”.

**Host factors affecting protection**

The quality and durability of measles vaccine-induced immunity is dependent on a number of factors that relate both to the vaccine and to the host. In considering factors affecting protection, it is important to distinguish between primary vaccine failure, that is, a failure to seroconvert after vaccination, and secondary vaccine failure, that is, loss of protection after demonstrated seroconversion.

**Maternal antibody and age at vaccination**

A number of host factors may be responsible for primary vaccine failure. The most important and well described is maternal antibody. Passively acquired measles antibodies may neutralize vaccine virus before a complete immune response develops. The most common sources of these antibodies are maternal transfer, IgG, and other blood products. The presence of maternally derived transplacental antibody is particularly important in evaluating the immunogenicity of live measles vaccine in early childhood. The effect of maternal antibodies in breast milk on response to measles vaccination is unknown.

As noted by Orenstein and colleagues, recommendations for the age at vaccination must balance two factors: (1) the earliest age at which high rates of seroconversion can be obtained and (2) the age group with the greatest risk of severe infection. A balance must be met that optimizes vaccine-induced protection while minimizing the risk of morbidity and mortality that would occur by delaying vaccination. The age at vaccination that achieves this balance is lower in developing countries than in developed nations because of the increased risk of measles exposure among infants and because of earlier loss of maternally derived antibody. The reasons for the variation in duration of passive protection from maternal antibody include differences in (1) levels of measles antibody in mothers, (2) efficiency of transport of IgG across the placenta, and (3) rate of loss of passively acquired antibody by the infant.

Early in the clinical investigations of live measles virus vaccine, it was recognized that maternal antibody interfered with seroconversion by in vivo neutralization of vaccine virus before adequate replication had occurred. On the basis of data available at the time, it appeared that maternal antibody rarely persisted beyond 7 months of age and that an adequate immune response could be achieved if vaccination was limited to infants 9 months of age and older. Whereas only 60% to 70% of infants younger than 9 months seroconverted, 95% or more of older infants produced antibodies.

Accordingly, when vaccine was licensed in 1963 in the United States, the recommended age for routine vaccination was 9 months.

In the first few years after licensure, it became apparent, however, that maternal antibodies actually persisted in many infants until 11 months of age. In the early years of vaccine implementation, it became apparent that maternal antibody interfered with seroconversion by in vivo neutralization of vaccine virus before adequate replication had occurred. Thus, in 1965, the recommended age for vaccination was raised to 12 months. The importance of this change is illustrated by Krugman et al. data showing that only 86% of 123 infants 9 months of age seroconverted after administration of Edmonston B vaccine and Ig, compared with 97% of 899 children vaccinated at 12 months of age or older.

In 1965, it was also recommended that children vaccinated before 1 year of age be revaccinated because a large proportion of these children were susceptible and were expected to respond well to revaccination. A number of studies confirmed these findings, but there are also some data indicating that early vaccination may alter the immune response after revaccination. Wilkins and Wehrle first raised concerns by reporting that 19 (51.4%) of 37 children who did not respond when they were initially vaccinated at 6 to 10 months of age did not have detectable HI antibodies 8 months after revaccination. All 37 did, however, have detectable Nt antibody. Similarly, Linnemann and colleagues reported that 29 (40.3%) of 72 children vaccinated before 10 months of age were HI negative at a mean of 4.8 years after revaccination. In contrast, Lampe and colleagues did not find any difference in seroconversion rates in children vaccinated once at 15 months of age or later, compared with children revaccinated after first being vaccinated before 1 year of age. By using an EIAs assay, Murthy and colleagues observed high seroprevalence rates at a mean of 6 months after vaccination in 302 children revaccinated after early vaccination and in 300 vaccinated once at 15 months of age or older (98% for both groups). However, they did observe that the titers in the revaccinated group were lower than those in the children vaccinated once. These findings were confirmed by McGraw.

One of the most complete descriptions of an altered immune response is provided by Stetler and colleagues. These authors reported that children revaccinated after an initial vaccination before 1 year had no difficulty seroconverting, postrevaccination HI antibody was detected in 116 (95.9%) of 121 children lacking HI antibody before revaccination. Eight months later, HI antibodies were undetectable in 58 (47.9%) children, but, after retesting with a cytopathic effect neutralization (CPEN) test, only 5 (4.2%) of 120 sera were negative. Successful priming in some of the early vaccinees was also suggested by the finding that IgM was detected in the sera of only 22.2% of 63 revaccinated children lacking HI, EIA, and CPEN antibody, compared with 74.0% of 50 random control vaccinees. These findings were similar to those noted by Black and colleagues.

Although there may be some alteration of the immune response, the most reliable indicator of the actual effectiveness

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SECTION TWO • Licensed vaccines
of revaccination of these children is the evaluation of their risk of infection. Although revaccination may not provide 100% protection, available data indicate that revaccination is effective.556,560 Shabas and colleagues555 reported that, in an outbreak, the attack rate in 73 children vaccinated once before 12 months of age was 35.6%, whereas the attack rate in 55 children revaccinated after 12 months of age was only 1.8%. Davis and colleagues noted that none of 80 students revaccinated after their first vaccination before 12 months of age became infected during an outbreak. For comparison, the attack rate in children vaccinated twice at 12 months of age or older was 1.4% (2 of 138), that in children vaccinated once at 12 months of age or older was 1.8% (21 of 1,191), and that in unvaccinated children was 57.1% (4 of 7). Hutchins and colleagues566 reported a vaccine effectiveness of 99.5% for children vaccinated with a first dose at age 6 to 11 months and a second dose after age 12 months. Thus, the available data indicate that revaccination of children first vaccinated before 1 year of age will result in good vaccine-induced protection, although it may be associated with an altered immune response, manifested as a lower antibody titer. This conclusion is especially important because vaccination of US children as young as 6 months, with subsequent revaccination, is recommended in certain outbreak situations and for children traveling internationally.211,212

The recommended age at vaccination was again changed in 1976 from 12 months to 15 months because newer data indicated that children vaccinated at 15 months of age and older were even more likely to make and maintain antibodies and were less likely to be infected in outbreak situations than those children vaccinated earlier.529 Although some studies provide contrary results, examination of data on seroconversion rates and prevalence of antibodies after vaccination indicates that, in general, 79% to 89% of children vaccinated at 12 months of age have detectable antibodies, compared with 87% to 99% of those vaccinated at 15 months or later.475–477,479,538,555,564–566 Similarly, a number of studies measuring the risk of measles in vaccinated and unvaccinated children indicated that measles occurred in children vaccinated at 12 months of age approximately 1.5 to 5.0 times more frequently than in those vaccinated later than 12 months.495–499,520,555,556

Data on measles antibody titers in umbilical cord blood and in infants suggests that infants whose mothers have vaccine-induced immunity may be receiving less maternal antibody than infants whose mothers had natural measles.523,567 Mothers born in the vaccine era may be acquiring maternal measles antibody from birth onward. In 2009, greater than 99% of women giving birth in the United States were born after 1963, the year measles vaccine was licensed.571 Infants whose mothers were born in the vaccine era are susceptible to disease at a younger age and are more likely to respond to vaccination at an early age. In a 1992 cohort study in the United States, Papania and colleagues documented a greater than 2.5 relative risk of measles among infants whose mothers were born in the vaccine era compared with infants whose mothers were born before 1963. Higher rates of seroconversion at 12 months also have been found in children born to women with vaccine-induced immunity.567–569 Based on these findings, in 1994, the recommended age of vaccination in the United States was changed again to between 12 and 15 months.212

Factors that alter the efficiency of transport of IgG across the placenta also can affect the amount of antibody infants receive. Maternal measles antibody is transferred across the placenta from mother to infant via an active transport system, which results in a higher antibody titer in the infant than in the mother. Because the majority of the maternal measles antibody transfer occurs late in the third trimester, infants born prematurely often have low antibody titers.573 Several diseases that affect the mother, most importantly HIV infection and possibly malaria, have been shown to decrease the placental transfer of maternal measles antibody and result in lower infant titers.574,575

Because infants in developing countries may lose maternal measles antibody at an early age and may be exposed to measles virus at an early age as a result of intense transmission, the WHO recommendations indicate that 9 months is the most appropriate age for delivery of the first dose of measles vaccine in most developing countries76 (see “Indications”).

Studies of early measles vaccination regimens have found that infants 6 months of age had lower seroconversion rates and geometric mean titers than older infants or toddlers. This effect was evident even among 6-month-old infants who lacked maternal measles antibody, suggesting an age-related delay in maturation of humoral immunity unrelated to passively transferred maternal antibody.576 In contrast, markers of cell-mediated immunity (eg, T-cell proliferation) were equivalent after vaccination at 6, 9, or 12 months, regardless of the presence of passive antibodies. In addition, infants initially vaccinated at 6 or 9 months experienced increases in both humoral and cell-mediated responses after administration of a second dose. Although the cell-mediated immunity resulting from a dose at 6 months alone may not be protective, early vaccination may prime the humoral response to the second dose, thereby providing clinical benefit.578

Intercurrent illness and malnutrition

There is a theoretic concern that interferon produced by an intercurrent infection may interfere with successful vaccination.317,379 Studies addressing this question, which have been conducted in developing and in developed countries, have produced discordant results. Two studies in developing countries found no differences in seroconversion rates in ill and well children after receipt of measles vaccine.345,540 A small study in the United States found that 80% of children with rhinorrhea seroconverted, compared with 98% of well children.361 Subsequent studies conducted in the United States and Canada have found equivalent seroconversion rates among children with respiratory infections or mild illness and well children.542–544 In a study of 128 mildly ill and 258 well children given MMR, seroconversion to measles was 97% in well children compared with 99% in those with mild illnesses, mostly upper respiratory tract infection;545 no differences were observed in seroconversion to mumps or rubella. A study conducted in Wisconsin found no association between vaccine failure and vaccination during the high-risk season for respiratory infections.566 One study conducted in Thailand found lower geometric mean antibody titers for children vaccinated at 9 months of age among those who experienced an upper respiratory tract infection in the 2 weeks after vaccination.567 However, the benefits of vaccinating mildly ill children outweigh any theoretic risk of lower seroconversion rates.557 Several studies have found seroconversion rates in malnourished children similar to those in children who are well nourished.344,345,558,559

Immunosuppression and HIV infection

Measles vaccination is not recommended for most immunocompromised patients, and as a result, few data are available on the immune response in such patients. However, the increasing number of children with HIV infection, the high risk of severe measles in these children, and the limited side
effects to measles vaccine found in HIV-infected children have resulted in recommendations for vaccination. Studies in the United States have found that HIV-infected children have poor responses to vaccination, lose antibody more quickly after vaccination, and respond poorly to revaccination. Retrospective studies have found that only 12% of 24 and 59% of 37 vaccinated children with HIV infection had detectable measles antibody. Seroconversion rates in prospective studies range from 33% of 39 children to 60% of 25 children. In the Democratic Republic of Congo, seroconversion rates after vaccination at 9 months were 77% in asymptomatic HIV-infected children and 36% in symptomatic HIV-infected children [36%]. In two other studies in Africa, seroconversion rates after vaccination at 6 months were greater than 75% in HIV-infected children. A study in Thailand found that, by age 9 months, 100% of 30 infants of HIV-infected mothers had lost their maternally acquired antibodies and that, by 12 weeks postvaccination, HIV-positive infants had lower seroconversion and median antibody levels when compared with HIV-negative infants. A recent study in Zambia found 88% of HIV-infected infants vaccinated at 9 months of age developed protective antibody levels; by 27 months after vaccination only 50% of children who survived had maintained protective antibody titers. HIV-infected children may respond better when they are vaccinated at earlier ages, before they become severely immunocompromised.

Adults who were vaccinated in childhood before becoming infected with HIV appear to retain protective levels of measles antibody. High seroprevalence of measles antibody in HIV-infected adults in the United States has been documented, and antibody levels are maintained, even as immunosuppression progresses. In one study, measles seronegative HIV-infected adults who were vaccinated while on highly active antiretroviral therapy (HAART) responded to measles vaccine but lost antibody rapidly after vaccination.

Vitamin A supplementation

Investigators in Indonesia found a lower rate of seroconversion among children vaccinated at 6 months of age who received supplementary vitamin A compared with children not receiving such a supplement. Subsequent studies conducted in Guinea-Bissau, India, and West Java found similar rates of seroconversion among 9-month-old children receiving and not receiving vitamin A supplements. Among malnourished children in the Indian study, the postvaccination geometric mean antibody titer was significantly higher in the group receiving vitamin A compared with the placebo group. A large multicenter clinical trial confirmed the safety of vitamin A supplementation administered with routine immunizations at 6, 10, and 14 weeks of age and at 9 months with measles immunization. The balance of evidence supports the WHO recommendation that, in vitamin A–deficient countries, infants should receive a vitamin A supplement at the time of measles immunization.

Other host factors

Even after receipt of potent vaccine, approximately 2% to 5% of vaccinees will fail to respond for unknown reasons. A group of investigators at the Mayo Clinic has explored the role of genetic factors and found associations with particular human lymphocyte antigen (HLA) types and nonresponse or hyperresponse to measles vaccination. A study of monozygotic and dizygotic twins found a high degree of heritability of measles antibody level and subsequently showed associations between homozygosity for class I and class II HLA alleles and poor response to measles vaccination. Of importance, two doses of MMR vaccine appear to induce sufficient antibody levels and lymphoproliferative responses against measles regardless of homozygosity status, suggesting genetically related nonresponse to the first dose is overcome by administration of a second dose.

Although there may be some exceptions in the very young, revaccination has been found in both epidemiologic and serologic studies to induce the same high rate of immune response that follows initial vaccination.

Vaccine factors affecting protection

Vaccine antigen and strain

Although most further attenuated measles vaccines have been found to be equally immunogenic in older children, differences in the ability of vaccine strains to immunize young infants have been reported. High measles morbidity and mortality among infants younger than the recommended age for vaccination (9 months) in developing countries has stimulated research on strategies for immunization of younger infants. In the early 1980s, investigators administered aerosol administration of two measles vaccines, the Edmonston-Zagreb and Schwarz strains. Their finding of higher seroconversion rates after Edmonston-Zagreb than after Schwarz vaccine focused attention on this vaccine strain. Several subsequent studies found that the Edmonston-Zagreb strain was more immunogenic than the Schwarz vaccine in this age group when given by injection (see paragraph on “Vaccine dose” below). The AIK-C strain of measles vaccine also has been found to be highly immunogenic in young infants and, in some studies, more immunogenic than either Schwarz or Edmonston-Zagreb vaccines. The reasons for these differences are not known.

Vaccine dose

Small doses of vaccine can effectively immunize older infants and children, however, the dose of vaccine administered has been shown to be important in immunizing young infants. Increasing the Edmonston-Zagreb vaccine dose from 10,000 to 40,000 plaque-forming units (PFU) in the Gambia resulted in an increase in response rate from 73% to 100% in 4- to 6-month-old infants. In Mexico, serologic response to vaccination of 6-month-old infants increased for both Schwarz and Edmonston-Zagreb vaccines, with a 100-fold increase in dose, the effect was greater for Schwarz than for Edmonston-Zagreb vaccine. Because of these data and interest in a vaccination strategy for children younger than 1 year in developing countries, in 1990 the WHO recommended that a higher dose (initially defined as > 100,000 PFU and later changed to > 50,000 PFU) Edmonston-Zagreb vaccine be administered at 6 months of age in areas where measles mortality in young infants was a major health problem. However, problems with vaccine availability resulted in little use of the vaccine on a large scale. Questions were raised regarding the safety of high-dose measles vaccine in several developing countries, with a higher mortality rate in girls who received high-titer vaccines compared with those who received standard-titer vaccines. Increased mortality rates after vaccination with a high-titer vaccine were not observed in developed countries or in countries with an infant mortality rate less than 100 per 1,000 births. High-titer measles vaccines are not currently recommended.

Vaccine handling

Primary vaccine failures with live vaccine have stemmed from improper handling. Loss of potency of live vaccines can result from poor shipping or storage practices. Although
administration of impotent vaccine had previously been implicated in outbreaks of measles in vaccinated persons, the likelihood of this occurring now has been greatly reduced by the introduction of new stabilizers discussed previously. 421, 467

Persistence of immunity

The majority of data suggest that a dose of live vaccine properly administered to an appropriate host that results in seroconversion will afford lifelong protection to nearly all vaccinees. 629 The duration of vaccine-induced immunity has been documented by studying the persistence of measurable antibody, the clinical characteristics and serologic response of measles cases in vaccinated persons, the effects of vaccine challenge, and the attack rate in vaccinees as a function of the time since vaccination.

Although vaccine-induced antibody titers are lower than those achieved after natural infection, this difference does not appear to result in decreased personal protection from measles. Serologic studies limited to children vaccinated at 12 months of age or older indicate that, although antibody titers do decline over time, detectable antibodies are present in most vaccinees.5 Because titers can fall to levels undetectable with some assays, the test used is important in the assessment of immune status. Furthermore, many persons lacking detectable antibody manifest a secondary immune response on revaccination or exposure to wild-type virus, indicating persistence of some level of immunity. 275

Krugman et al.427, 428 followed the serologic status of a population of institutionalized children for 16 years. The HI geometric mean antibody titer in 70 persons who received further attenuated vaccine was 1:333 at 1 month but, in the absence of exposure, had fallen to 1:6 after 16 years (Figure 20-7). 268 Thirteen percent had a HI titer of 1:4, 10% had a titer of 1:2, and 13% had no detectable antibody. In contrast, whereas 47 naturally infected children had a comparable 1-month HI geometric mean antibody titer of 1:410, 16 years after disease, the geometric mean titer was 1:22 (see Figure 20-7). Only 4% had a HI titer of 1:2, and none had undetectable antibodies. Sixteen sera with HI titers ranging from less than 1:2 to 1:4, obtained from persons vaccinated 6 to 15 years earlier, were retested with the more sensitive PRN assay; 277 the PRN titers ranged from 1:4 to 1:46. 268 Typical responses after revaccination of some of the HI-negative persons were also found.

Dine and associates431 followed up adults vaccinated in a vaccine trial in the 1970s. The 56 participants, who were all seropositive by HI tests after vaccination, all had detectable measles antibody by PRN at least 26 years after vaccination. PRN titers greater than 1:120 were found in 92% of the subjects, and the strongest predictor of lower titers was lower HI titers in the original study. None of the subjects had been revaccinated in the interim period, or had had measles or known exposure to measles. Fewer than five cases were reported annually from Cincinnati, the study setting, over the 12 years before the follow-up study began. Therefore, boosting of antibody titers from exposure to wild-type measles virus was unlikely to play a major role in sustaining antibody titers in most of the study subjects.

Seroprevalence studies also provide useful information about duration of immunity, but, because information on seroconversion is lacking, one cannot be sure whether persons are seronegative because of primary or secondary vaccine failure. In addition, sensitivity of the assay procedure is important. These variables account for some discrepancies in reported findings. For example, Bass and colleagues432 reported that HI antibodies were detectable in 73% of 40 children more than 8 years after vaccination; however, 98% had detectable antibody. Epstein and colleagues434 reported that the seroprevalence among 1,871 high-school students (10th, 11th, and 12th graders), 98.1% of whom had been vaccinated at 14 months of age or older and who had no history of measles, was 86.9% by an HI assay. However, 98.8% were positive with both the HI assay and the same PRN assay used in the Krugman study. 277 Orenstein and colleagues466 further documented the specificity of the PRN assay by vaccinating HI-negative children. IgM was detected in 14 of 16 students with a PRN titer less than 1:4 but in only 1 of 68 who were PRN positive.

Although live-virus vaccine-induced immunity is accepted as durable, there have been case reports of measles in persons who had a previously documented seroconversion after vaccination, which indicates that secondary vaccine failure can occur. 170, 172, 432 Also, there have been reports of measles, or modified measles, occurring in vaccinees who had laboratory evidence of infection, although IgM was not detected, which suggests a secondary immune response. 160, 169, 171 A secondary immune response indicates a preexisting level of immunity, although such reports are limited by the sensitivity of the assays used to detect IgM antibody. These studies also suggest that the clinical reinfection can be mild and may be more likely to occur in persons vaccinated at younger than 12 months. One study that provides data on the risk of clinical reinfection after vaccination was conducted in Canada; 5% (9 of 175) of persons who initially seroconverted after receipt of measles vaccine developed measles within 10 years of vaccination.176 In this study, persons who developed measles had lower postvaccination titers than those who did not.

In epidemiologic studies of persons vaccinated with live measles vaccine at 12 months of age or older, some studies have shown that persons with increased time since vaccination have slight increases in attack rates compared with those more recently vaccinated; however, none has yet documented a significant increase (Table 20-6). 497, 530, 556, 576, 579, 633, 635 During outbreaks, observed attack rates in persons vaccinated 15 years or more before infection have been on the order of 5% or less, and calculated vaccine effectiveness has been 90% to 95% or greater. These results are consistent with the expected frequency of primary vaccine failure that occurs in everyday practice. Data from the United Kingdom, the United States, and other countries,440, 459, 461, 464, 467 have not found increases in vaccine failures with time since vaccination. With overall incidence of measles in the United States at record low levels and no evidence of increasing incidence among previously vaccinated persons, waning immunity does not appear to constitute

Figure 20-7. Measles geometric mean hemagglutination-inhibition antibody titers after natural infection and immunization with live, further attenuated vaccine. (Courtesy of S. Krugman.)

See references 67, 267, 268, 473, 474, 477, 480, 482, 484–486, 491, 630.
programs. Vaccine (MMR) as part of routine childhood immunization today along with rubella and mumps vaccines as a combined vaccine is likely to be MMR.

Exposure to measles is not a contraindication to measles immunization. Available data suggest that live virus measles vaccine, if given within 72 hours of measles exposure, will prevent, or modify disease. Although the vaccine should induce protection against subsequent measles exposures should the initial exposure fail to result in measles and protection. Therefore, vaccine is the intervention of choice for persons older than 12 months of age who are exposed to measles in most settings (eg, healthcare facilities, schools, colleges, health care facilities), unless contraindicated (see “Precautions and contraindications”).

Studies consistently show that combinations of measles, mumps, and rubella antigens, regardless of the virus strain, elicit the same high rates of seroconversion seen with each component individually and that there is no increased risk of reactions in persons susceptible to all three antigens [Tables 20-7 and 20-8]. Furthermore, vaccination of persons already immune to one or more of the antigens, from either previous vaccination or infection, is not associated with any increased risk of vaccine-associated adverse events.

Table 20-6 Epidemiologic Studies of Duration of Measles Vaccine-Induced Immunity

<table>
<thead>
<tr>
<th>Study</th>
<th>Attack rate (%) by years since vaccination*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-4 yr</td>
</tr>
<tr>
<td>Shasby et al198</td>
<td>9.4 (3/32)</td>
</tr>
<tr>
<td>Nikowane et al199</td>
<td>0 (0/18)</td>
</tr>
<tr>
<td>Davis et al200</td>
<td>1.1 (2/187)</td>
</tr>
<tr>
<td>Marks et al201</td>
<td>4.0/1000</td>
</tr>
<tr>
<td>Hutchins et al202</td>
<td>0 (0/33)</td>
</tr>
<tr>
<td>Robertson et al203</td>
<td>0 (0/2)</td>
</tr>
<tr>
<td>Guris et al204</td>
<td>11.8 (2/17)</td>
</tr>
<tr>
<td>Lynn et al205</td>
<td>0 (0/40)</td>
</tr>
</tbody>
</table>

*Single vaccination at 15 months of age or older except for Shasby, Nikowane, and Davis (12 months of age or older).

†Years since vaccination: 5 to 8 and 9 or more.

‡Projected from a 25% random sample.

<table>
<thead>
<tr>
<th>Study</th>
<th>Attack rate (%) by years since vaccination*</th>
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<tbody>
<tr>
<td></td>
<td>0-4 yr</td>
</tr>
</tbody>
</table>

Although there are reports of directly mixing vaccine with DTP; this should not be done routinely. Rather, the vaccines should be administered in separate syringes and at separate sites.

Immunization against varicella along with measles, rubella, and mumps, either as two vaccines [varicella and MMR] or as a quadrivalent vaccine [MMRV], has been studied. Concomitant administration of MMRV, Haemophilus influenzae b/hepatitis B [Hib/HepB], and diphtheria-tetanus-acellular pertussis [DTaP] vaccines was found to be immunogenic and well tolerated.

Postexposure prophylaxis

Routine vaccination before exposure to measles provides the best protection against measles. However, persons without measles immunity who are exposed can receive some protection through measles vaccination or IG administration after exposure.

Use of vaccine

Exposure to measles is not a contraindication to measles immunization. Available data suggest that live virus measles vaccine, if given within 72 hours of measles exposure, will prevent, or modify disease. Also, the vaccine should induce protection against subsequent measles exposures should the initial exposure fail to result in measles and protection. Therefore, vaccine is the intervention of choice for persons older than 12 months of age who are exposed to measles in most settings (eg, healthcare facilities, schools, colleges, health care facilities), unless contraindicated (see “Precautions and contraindications”). Infants 6 to 11 months of age may receive measles vaccine instead of IG if the initial exposure is detected within 72 hours. Infants vaccinated before age 12 months must be revaccinated on or after the first birthday with two doses of MMR vaccine separated by at least 28 days [see “Indications”].
Table 20-7 Antibody Response after Administration of Measles Vaccine Alone, in Combination with Mumps and Rubella Vaccines, and in Combination with Mumps, Rubella, and Varicella Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Total number</th>
<th>Measles</th>
<th>Mumps</th>
<th>Rubella</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>GMT</td>
<td>%</td>
<td>GMT</td>
</tr>
<tr>
<td>Measles</td>
<td>23</td>
<td>100</td>
<td>82</td>
<td>–</td>
</tr>
<tr>
<td>Measles, mumps, rubella (RA27/3)</td>
<td>91</td>
<td>96</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>Measles, mumps, rubella (HPV-77:DE-5)</td>
<td>85</td>
<td>99</td>
<td>77</td>
<td>89</td>
</tr>
</tbody>
</table>


Use of immune globulin

Current US recommendations are to give human immune globulin, as an intramuscular injection (IGIM), to susceptible persons exposed to measles and for whom vaccine either is contraindicated or was not given within 72 hours of initial exposure. Measles is infectious during the prodrome and often is not diagnosed until the rash onset. Therefore, many exposed persons are not identified until more than 72 hours after initial exposure, which is too late for prophylaxis with measles vaccine. Human IGIM provides measles antibodies to prevent or modify the disease when given up to 6 days after exposure. However, any immunity conferred is temporary (lasting approximately 3 to 4 weeks) unless modified or typical measles occurs. IGIM should not be used to control measles outbreaks.

Postexposure prophylaxis with IGIM is especially important for exposed persons at increased risk for complications from measles (ie, infants less than 12 months of age, pregnant women, and immunocompromised persons). The recommended dose of IGIM is 0.25 mL/kg within 6 days of initial exposure. The dose should be increased to 0.50 mL/kg for immunocompromised persons. The maximum dose in all cases is 15 mL.

Infants younger than 5 to 6 months of age usually have partial or complete immunity to measles because of passive maternal antibody. However, infants whose mothers develop measles are not protected by maternal antibody and should receive IGIM. Also, in some countries up to 19% of women of childbearing age do not have measurable measles antibody titers. IGIM is not indicated for persons who have received at least one dose of measles vaccine at 12 months of age or older unless they are immunocompromised. All immunocompromised persons (including anyone with HIV infection and children of unknown infection status born to HIV-infected women) who are exposed to wild-type measles should receive IGIM postexposure prophylaxis (0.5 mL/kg, maximum dose 15 mL) regardless of their immunization status. An exception is the patient receiving IGIV at regular intervals, whose last dose of at least 100 mg/kg was received within 3 weeks before exposure. IGIV and IGSC are commonly used in immunocompromised patients with primary immunodeficiency, HIV infection, or B-cell chronic lymphocytic leukemia. The FDA-required minimum standards for measles antibody titers are lower for IGIV and IGSC than for IGIM preparations. However, the IGIV doses commonly used (200–400 mg/kg) for immunocompromised patients should be sufficient to prevent measles for 3 weeks. An additional dose of IGIV should be considered for persons on maintenance IGIV therapy who are exposed to measles more than 3 weeks after receiving a standard dose of IGIV.

Human IGSC is given in weekly doses that are calculated to provide similar mean immunoglobulin G levels as IGIV doses given every 4 weeks. There are currently no published guidelines as to whether persons on IGSC therapy should receive IGIM injection if exposed to measles. Because current immune globulin preparations may contain lower levels of measles neutralizing antibodies than in the past, there is active discussion as to whether recommended dosages should be modified. As of mid 2012, the ACIP has not recommended any changes. Should there be any changes to the recommended doses, they will be posted at HYPERLINK "http://www.cdc.gov/vaccines" www.cdc.gov/vaccines under the recommendations section.

Adverse effects

Adverse reactions after receipt of live, further attenuated measles vaccines (alone and in combination) are generally mild. With the exception of hypersensitivity reactions, adverse reactions are...
Table 20-8 Proportion of Children with Fever and Rash After Administration of Measles Vaccine Alone, in Combination with Mumps and Rubella Vaccines, and in Combination with Mumps, Rubella, and Varicella Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Total number</th>
<th>Fever ≥ 39.4° C (%)</th>
<th>Rash (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>43</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Measles, mumps, rubella (RA27/3)</td>
<td>141</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Measles, mumps, rubella (HPV-77:DE-5)</td>
<td>142</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Placebo</td>
<td>42</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Fever ≥ 38.9° C</th>
<th>Rash</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles, mumps, rubella, and varicella</td>
<td>982</td>
<td>33.1</td>
</tr>
<tr>
<td>Measles, mumps, rubella, and varicella</td>
<td>2,839</td>
<td>39.1</td>
</tr>
</tbody>
</table>

*During 6 weeks after vaccination.
†Moraten strain.
‡Jeryl Lynn strain.
§RA27/3 strain.
¶Oka/Merck strain.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Total Number</th>
<th>Fever ≥ 38.9° C %</th>
<th>Rash %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles, mumps, rubella, and varicella given separately</td>
<td>1,000</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella, and varicella</td>
<td>2,877</td>
<td>5.7</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Fever ≥ 39.4° C</th>
<th>Rash</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>5.9%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Immediate hypersensitivity reactions, including hives and anaphylaxis, occur rarely. The rate of anaphylaxis is approximately 1 to 3.5 per million doses administered. The rate of other immediate hypersensitivity reactions is estimated to be about 10 per million doses. Measles vaccine is produced in chick embryo tissue culture, and for many years, there were concerns about administering these vaccines to children with egg allergy. However, several studies using sensitive methods have demonstrated that there is no evidence of egg protein in measles vaccine. Although rare cases of anaphylaxis have been reported in children with egg hypersensitivity, the allergen in the vaccine responsible for these reactions is uncertain. The majority of children with immediate hypersensitivity reactions to measles-containing vaccines have evidence of allergy to the gelatin stabilizer. Children with immediate hypersensitivity to eggs can be safely immunized with measles vaccines, and no special precautions are necessary.
Febrile seizures are the most commonly reported neurologic adverse event after measles vaccination. Fever from any source lowers the threshold for seizures, and a febrile seizure is not a sign of central nervous system (CNS) infection or disease. Febrile seizures occur primarily in the second and third year of life and are not associated with long-term sequelae. The risk of febrile seizures is increased approximately threefold in the 8 to 14 days after receipt of MMR. The increased rate of fever associated with MMRB results in an additional febrile seizure in about 1 in every 2,500 children compared with administering MMR and varicella vaccine separately. The rates of fever and febrile seizures after administering measles vaccines are much lower than the rates after measles disease. There has been no increased risk of adverse neurologic events observed in children who received measles vaccine combined with rubella and mumps vaccines (MMR) compared with measles vaccine administered alone.

Postinfectious encephalitis is a recognized complication of measles, but there is uncertainty as to whether or not encephalitis is caused by further attenuated measles vaccines in normal hosts. In children who have died during the rash phase of measles, measles virus has been found in brain tissue, but measles virus rarely has been found in brain tissue from postinfectious encephalitis, which is thought to be the result of an altered immune response to myelin proteins. Encephalitis has been reported after measles immunization at a rate of approximately 1 case per 1 million vaccine recipients. This rate is lower than the background rate of encephalitis of unknown etiology in unvaccinated children in the general population. There is temporal clustering of reports in the 5 to 15 days after immunization when other adverse effects from the vaccine occur. There has been one report of a vaccine isolate recovered from the cerebrospinal fluid of a normal person who received Edmonston B strain vaccine. There have been no cases of vaccine-strain virus identified as the cause of encephalitis in persons with intact immune systems confirmed by neuropathologic studies. Nine cases of encephalitis after administering measles-containing vaccines were reported in the United States during 1979 to 1986, when 22.7 million doses of measles antigen-containing vaccine were distributed, for a rate of 1 per 2.5 million doses (0.4 per 1 million doses). In Albania, 2 cases of encephalitis were identified after 867,000 doses of MR were administered during a mass vaccination campaign. This observed rate is lower than that noted for several neurologic disorders of unvaccinated children of the same age range, suggesting a possible chance temporal association. In Finland and the United States, there was no evidence of an increased risk of encephalitis after measles vaccine. In the United Kingdom, studies have found an increased rate of serious neurologic disease in the 6 to 11 days after vaccination. However, some of the increase was due to complex febrile seizures, and other viruses known to cause encephalitis (herpes simplex virus, HHV-6 and HHV-7) were identified in some affected patients. The Institute of Medicine concluded, in 1994, that there was inadequate evidence to accept or reject a causal relation between measles vaccine and encephalitis or encephalopathy. However, in a 1998 study, done by Weibel and colleagues, the authors found a clustering of 17 cases of encephalopathy on days 8 and 9 after MMR vaccination, but they stated that with the large denominator and random association of encephalopathy with measles vaccination, this result needs clarification. There have been no additional reports of encephalopathy in children vaccinated throughout 23 years, encephalopathy would be an extremely rare complication (0.06 per 100,000 vaccinees). If measles vaccines do cause acute encephalitis, the rate is at least 1,000 times less than the rate after natural infection. There are case reports but no evidence of increased risk or causal associations of several other disorders after measles vaccines, including Reye syndrome, oculomotor palsy, optic neuritis, retinopathy, hearing loss, cerebellar ataxia, arthralgia, arthritis, and soft-tissue reactions. There is no increased risk of Guillain-Barré syndrome after measles vaccine. In a cohort study of 167,240 children, no significant association between timing of the receipt of measles vaccine and asthma was found. SSPE is caused by persistence of defective measles virus in the CNS through as-yet undefined mechanisms. Analyses of data from the United Kingdom and the United States have shown the true incidence of SSPE to be approximately 4 to 11 cases of SSPE per 100,000 cases of measles, with higher rates in children who had measles at an early age. No specific immune deficiency has been identified in children with SSPE to explain the failure of the immune system to eliminate the virus. There was an initial concern that measles vaccine virus might cause a persistent CNS infection because some patients with SSPE who have received vaccine had no history of disease. However, when investigated carefully, most of these patients have histories of measles-like illnesses and/or known exposures to measles followed by administration of passive Ig. Genetic sequencing of viruses obtained from the brains of patients with SSPE, including patients with no history of having had measles, has revealed only viruses of wild-type origin. Case-control studies and the marked decline of SSPE in parallel with the decline in measles after the introduction and widespread use of measles vaccine in the general population demonstrate that the vaccine protects against SSPE. It is not known if measles virus persists in immunologically normal persons who do not develop SSPE. Measles virus genomic RNA was detected frequently in persons who had been immunized or exposed to measles more than 2 months before testing in one study, and one group of investigators found evidence for persistence of measles virus nucleocapsid in a variety of tissues many years after measles. An HIV-infected intravenous drug user developed progressive measles retinitis and subsequent progressive CNS disease diagnosed as SSPE at 30 years of age. His illness resembled measles encephalitis in immunocompromised persons. He had a history of measles at 2 years of age, and HIV infection most likely occurred in later life, secondary to intravenous drug abuse or sexual contact.

Measles encephalitis in immunosuppressed children, including children with HIV infection or leukemia, is sometimes referred to as subacute or inclusion body measles encephalitis and is caused by progressive measles virus infection. Onset is usually 5 weeks to 6 months after acute measles, and virus has been identified in brain tissues of patients with progressive measles encephalitis. Virus isolated from brain tissue specimens from several patients has been shown to be wild-type measles virus. One patient with an undefined immune disorder who developed this disorder at 21 months of age was found to have measles vaccine virus in brain tissue. The Institute of Medicine concluded in 2011 that there was adequate evidence to accept a causal relation between measles vaccine and measles inclusion body encephalitis in persons with demonstrated immunodeficiencies (causation is attributed to the measles component of the vaccine).

In persons with severe immune suppression, there is an increased risk of progressive measles virus replication and severe complications, including fatal pneumonia. HIV infection has not been associated with increased risks of adverse events in the few weeks after measles vaccination (see Chapter 133). However, with the large denominator of HIV-infected persons, only one well-documented instance of a severe complication after measles vaccine in an HIV-infected person has been reported. Measles vaccine virus was identified in the lung of a 20-year-old man who died of progressive pneumonitis that was recognized about 9 months after receiving a second dose of measles vaccine. One HIV-infected child who had received MMR vaccine at 15 months of age was found to have characteristic inclusion bodies on brain biopsy at 18 months of age, but no specific testing was performed to determine the cause of the encephalitis.
determine the source or identity of the virus. Also, a 19-year-old HIV-infected man with hemophilia had paramyxovirus nucleocapsids in intranuclear inclusion bodies, and there was evidence of measles antigen on immunohistochemical staining, but the virus was not sequenced. He had received measles vaccine at 10 years of age, and there was no history of measles exposure in the year preceding the biopsy. The ages at which he acquired HIV infection and possible subsequent exposures to measles were not reported. The WHO recommends measles vaccine for asymptomatic HIV-infected children and those with early signs of HIV-induced immunosuppression because of the high risk of serious complications from measles in HIV-infected persons.

In the United States, where the risk of measles exposure is low, the ACIP recommends withholding measles vaccine from persons with severe immunosuppression. Severe immunosuppression is defined as (1) a CD4+ count of less than 200 cells/mm³ for persons 6 years of age and older, a CD4+ count of less than 500 cells/mm³ for children 1 to 5 years old, and a CD4+ count of less than 750 cells/mm³ for children younger than 12 months of age; or (2) CD4+ cells less than 15% of total lymphocytes for children younger than 13 years.

After bone marrow transplantations, advisory committees recommend waiting 2 years to administer measles vaccine to allow immune reconstitution. However, in a study of 51 patients, vaccination 1 year after transplantation was not associated with any increased rate of adverse events.

The possibility that measles virus persists in selected tissues after measles has been proposed by investigators who found evidence for measles antigen or genomic material in human tissues, including brain, lung, intestine, and bone, years after measles disease. The investigators proposed that these viruses contribute to or cause inflammatory diseases in these organs, including Paget disease, otosclerosis, and inflammatory bowel disease. However, other investigators have found no evidence for measles viruses or measles genomic material in tissues from affected or normal patients.

The hypothesis that measles vaccine given in combination with mumps and rubella vaccines (MMR) caused inflammatory bowel disease and autism was promoted by one particular investigator who had unrevealed conflicts of interest. A later review of the clinical records from the original 12 patients found evidence of fraud in the data, and the article has been withdrawn.

Some of the other reports of persistent measles virus genomic material in children with autism were based upon PCR methods that amplified host genomic material, not measles virus. In-depth reviews conducted by the Institute of Medicine concluded that the evidence favors rejection of the MMR-autism hypothesis, and an expert review by the AAP concluded that the evidence does not support either of these hypotheses. A systematic review of the literature by the Cochrane Collaboration reached similar conclusions.

Advisory committees in many countries recommend the use of MMR to protect against these three diseases.

**Indications**

**General**

The goal of measles vaccination programs is to protect persons from the severe consequences of measles infection by providing lifelong individual immunity to vaccinees and by reducing susceptibility to measles in the population to prevent transmission of this disease. The major source of measles susceptibility in a population is the birth of children, who will all lose their maternal antibody and become susceptible in the first or second year of life. Maternal antibody interferes with the response to live measles vaccines. The most critical task of any vaccination program is the timely delivery of the first dose of measles vaccine to young children. The timing of the first dose must balance the proportion of infants who have lost maternal antibody and become susceptible in the first or second year of life.

The WHO recommends measles vaccine be administered at 9 months of age in countries with ongoing transmission of measles in which the risk of measles mortality among infants is high. In countries with low rates of measles transmission (ie, those near elimination) the WHO recommends the first dose of measles vaccine be given at 12 months to take advantage of higher seroconversion rates achieved at this age.

![Figure 20-8 Subacute sclerosing panencephalitis (SSPE) cases and measles notifications in the United States, 1960 to 2000. (Adapted from Campbell et al. Int J Epidemio 36:1334-1348, 2007.)](image-url)
the WHO recommended that a two-dose measles immunization schedule should be the standard of care for all countries. The second dose may be offered either at a scheduled age through routine services or periodically through mass campaigns, depending on which strategy achieves the higher coverage.206,731

Many developed and some developing countries now have schedules for two routine doses of measles vaccine. In developed countries, the first dose is usually recommended early in the second year of life; the age for the second dose varies.20,30–33,121,566

The following section provides detailed recommendations of measles vaccination for the United States.

General immunization guidelines

In general, use of licensed combination vaccines, such as MMR, is preferred over separate injections with equivalent component vaccines, to minimize the number of injections and reduce missed opportunities to protect through vaccination. ACIP, AAP, and American Academy of Family Physicians (AAFP) recommend that combination vaccines may be used whenever any components of the combination are indicated and its other components are not contraindicated.108,735 Single antigen measles, mumps, or rubella vaccines are no longer available in the United States.

MMR or MMRV vaccine may be administered simultaneously with other vaccines to persons at the recommended age to receive these vaccines. Neither theoretic considerations nor practical experience indicate that the simultaneous administration at separate anatomic sites of MMR or MMRV and other live or inactivated vaccines will produce a diminished immune response or increase the incidence of adverse events among vaccinated persons.212

The combined live attenuated measles, mumps, rubella, and varicella (MMRV) vaccine was licensed in 2005 in the United States and recommended in 2006 for use in children 12 months to 12 years of age.206 In May 2010, ACIP updated its 2006 MMRV recommendations157 based on study results showing a roughly twofold increased risk for febrile seizures after the first dose of MMRV compared with the first dose of MMR and varicella vaccine administered separately at the same visit.458,459,738,739

The routinely recommended age for the first dose of measles, mumps, rubella, and varicella vaccines is age 12 to 15 months; children not vaccinated according to the routine schedule may receive the first dose of MMRV vaccine up to age 12 years. For the first dose of measles, mumps, rubella, and varicella vaccine administered to children younger than 12 months is not contraindicated. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMR vaccine, MMRV vaccine and varicella vaccine or MMRV vaccine may be used. Providers who are considering administering MMRV vaccine should discuss the benefits and risks of both vaccination options with the parents or caregivers. Unless the parent or caregiver expresses a preference for MMR vaccine, MMRV vaccine and varicella vaccine should be administered as separate vaccines for the first doses in this age group. Use of MMR vaccine and varicella vaccine avoids the increased risk for fever and febrile seizures after MMRV vaccine. The 47-month cutoff was selected on the basis of the epidemiology of febrile seizures. Approximately 97% of febrile seizures occur in children ages less than or equal to 47 months.458,459,738

Although the routinely recommended age for the second dose of measles, mumps, rubella, and varicella vaccines is 4 to 6 years, the second dose may be administered before age 4 years, provided greater than or equal to 3 months have elapsed since the first dose. MMRV vaccine is licensed for use among children from age 12 months through age 12 years. For the second dose of measles, mumps, rubella, and varicella vaccines at any age (15 months to 12 years) and for the first dose at age greater than or equal to 48 months, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines [ie, MMR vaccine and varicella vaccine]. Catch-up vaccination is recommended to ensure a second dose for all children, adolescents, and adults who previously had received one dose.737

At least 1 month should elapse between doses of any live virus vaccines. For children ages 12 months to 12 years at least 3 months should elapse between doses of varicella-containing vaccines. Simultaneous administration of the most widely used live and inactivated vaccines has produced seroconversion rates and dose ratios similar to those observed when the vaccines are administered separately.739,740 Therefore, MMRV may be administered simultaneously with other vaccines recommended at ages 12 months and 12 years, although data are absent or limited for the concomitant use of MMRV vaccine with DTP, inactivated polio, pneumococcal conjugate, influenza, and hepatitis A vaccines.741 Additional information regarding MMRV is provided in the chapters on “Varicella vaccine” (Chapter 37) and “Combination vaccines” (Chapter 40).

Specific criteria for documentation of measles immunity have been established to identify the appropriate level of immunity for different groups. Persons can generally be presumed immune to measles if they have documentation of adequate vaccination, laboratory evidence of immunity to measles, or documentation of physician-diagnosed measles or were born before 1957 [few persons in the United States born before 1957 escaped natural infection]. Physician-diagnosed measles is no longer considered presumptive evidence of immunity for health care personnel [see “Health care personnel”].742

In general, one dose of MMR is considered adequate vaccination for preschool children and adults who are not at high risk of exposure to measles. Two doses of MMR are indicated for schoolchildren, students at post–high-school educational institutions, health care personnel, persons in measles outbreak settings, and international travelers because these groups are at increased risk for exposure to measles. Criteria accepted as evidence of immunity for the purpose of meeting school or college entry requirements or other government regulations may vary among state and local jurisdictions.211,212

Proper documentation of immunization is critical to ensuring that every person receives the appropriate vaccines. Vaccination status and date of administration of all vaccinations should be documented in the patient’s permanent medical record. Only doses of vaccine for which written documentation of the date of administration is presented should be considered valid. Health care professionals should provide a vaccination record for a patient only if they have administered the vaccine or documented vaccination.512

Because of reduced efficacy of measles vaccine when it is administered to young children, doses of measles vaccine administered to children younger than 12 months are not considered valid doses in the United States. Children vaccinated at ages younger than 12 months should be revaccinated at 12 to 15 months of age [provided at least 28 days have elapsed] to be considered to have received a single dose of measles vaccine.511,212

Routine vaccination schedule

Preschool children

All children should receive the first dose of MMR or MMRV at 12 to 15 months of age (Table 20–9). Children exposed to measles at high risk of exposure (eg, during an outbreak or while on international travel) may be vaccinated with MMR as early as 6 months of age.

The second dose of MMR or MMRV vaccine is recommended when children are age 4 to 6 years [ie, before a child enters kindergarten or first grade]. This recommended timing for the second dose has been adopted jointly by the Advisory Committee on Immunization Practices (ACIP), the AAP, and the AAFP.211,212 Evidence now indicates that [1] the major benefit of administering the second dose for measles is a reduction in the proportion of persons who remain susceptible because of primary
vaccine failure, [2] waning immunity is not a major cause of vaccine failure and has little influence on measles transmission, and [3] revaccination of children who have low levels of measles antibody produces only a transient rise in antibody levels.\textsuperscript{170,155}

For children greater than or equal to 12 months of age who are exposed to measles or at high risk of exposure [eg, during an outbreak or for international travel], the second dose may be given as early as 28 days after the first dose based on the principle that live-virus vaccines not administered at the same time should be separated by at least 1 month.\textsuperscript{211,212} For vaccines containing varicella antigens, a three-month interval between doses is required.

Schoolchildren

All children in school from kindergarten through 12th grade should have documentation of two doses of measles vaccine, unless vaccination is contraindicated. Children who do not have documentation of adequate vaccination against measles or other acceptable evidence of immunity should be admitted to school only after administration of the first dose of MMR vaccine. If required, the second MMR dose should be administered as soon as possible, but no sooner than 28 days after the first dose. The ACIP, AAP, and AAFP recommend the health maintenance visit at age 11 to 12 years should serve as a special opportunity to evaluate vaccination status and to administer MMR vaccine to all persons who have not received two doses at the recommended ages.\textsuperscript{214,215} As of the 2007 to 2008 school year, 49 states have state immunization requirements for two doses of measles vaccine that cover all grades, and all states require two doses for school entry.\textsuperscript{741} The estimated national two-dose coverage rate in the 2009 to 2010 school year at kindergarten entry was 94.8%,\textsuperscript{741a} state estimates ranged from 84.5% to 100%.\textsuperscript{741} However, there are limitations to the kindergarten survey data, because the methodology for collection of the data differs among the states.

Vaccination of high-risk groups

Colleges and other post–high-school educational institutions

Risks for transmission of measles at post–high-school educational institutions can be high because these institutions may bring together large concentrations of persons who may be susceptible to measles. College entry requirements for measles immunity substantially reduce the risk for measles outbreaks on college campuses where they are implemented and enforced.\textsuperscript{743} Therefore, colleges, universities, technical and vocational schools, and other institutions for post–high-school education should require that all undergraduate and graduate students have received two doses of MMR vaccine or have other acceptable evidence of immunity before enrollment. Students without documentation of any measles immunization or immunity should receive a dose on entry, followed by a second dose 4 weeks later.\textsuperscript{211,212}

Outbreak settings

During outbreaks in schools and other institutions, all students and personnel born in 1957 or later, should have documentation of two doses of measles-containing vaccine on or after the first birthday.\textsuperscript{211,212} All persons who do not have such documentation or other evidence of immunity should be vaccinated or excluded from the school until 21 days after the onset of rash in the last case of measles. Persons receiving their second dose and unimmunized persons receiving their first dose as part of the outbreak control program may be readmitted immediately to school. In outbreaks where there is increased risk of exposure for infants younger than 1 year, vaccination with MMR vaccine is recommended for infants as young as 6 months. Children who are vaccinated before their first birthday should be revaccinated when they are 12 months of age [provided at least 28 days have elapsed since the first dose given before age 12 months] and again at school entry. During outbreaks, IG should be administered to immunocompromised persons, susceptible pregnant women, and unvaccinated children younger than 12 months who are exposed to measles. However, IG should not be used to attempt to reduce measles transmission or control outbreaks. Likewise, serologic screening before vaccination generally is not recommended during an outbreak because waiting for serology results can impede the rapid vaccination needed to curb the outbreak.

Every suspected measles case should be reported immediately to the local health department, and every effort must be made to rapidly verify that the illness is measles, especially if

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**Table 20-9 Summary of Measles Vaccination Recommendations in the United States**

| Preschool children | Routine childhood schedule | First dose: 12-15 mo  
| Special circumstances | | Second dose: 4-6 yr  
| | Outbreak settings or before international travel | First dose: may be given as early as 6 mo  
| | | Repeat first dose: 12 mo  
| | | Second dose: may be given as early as 13 mo\textsuperscript{1}  
| | |  
| | HIV infection | First dose: 12 mo  
| | | Second dose: may be given as early as 13 mo\textsuperscript{1}  
| | School children and adolescents | All children in kindergarten through 12th grade should have documentation of two doses of MMR unless they have other evidence of immunity\textsuperscript{2}  
| | Adults | Adults without other evidence of immunity\textsuperscript{3} should have documentation of receipt of at least one dose of MMR  
| | Special circumstances | Students and staff in colleges and other post–high-school educational institutions, persons working in health care facilities, and international travelers should have documentation of receipt of two doses of measles vaccine unless they have other evidence of immunity\textsuperscript{4}  

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\*All recommendations exclude persons for whom measles vaccination is contraindicated.  
\textsuperscript{1}Wait at least 28 days after any dose before giving a subsequent dose.  
\textsuperscript{2}Persons who were born before 1957 or have a history of physician-diagnosed measles disease or have laboratory evidence of immunity.
this may be the first case in the community. Subsequent pre-
vvention of the spread of measles depends on prompt immu-
nization of persons at risk of exposure or already exposed who
cannot readily provide documentation of measles immunity,
including the date of immunization.211,212

If an outbreak occurs in a health care setting, all employ-
ees who were born in 1957 or later who cannot provide docu-
mentation that they have received two doses of measles vaccine
on or after their first birthday or other presumptive evidence of
immunity to measles should be offered the first dose of MMR
vaccine immediately and receive the second MMR vaccination
at least 28 days later. Some health care personnel who were born
before 1957 have acquired measles while at work. Therefore,
during an outbreak of measles, health care facilities should rec-
ommend completion of two doses of MMR vaccine for unvacci-
nated or undervaccinated personnel born before 1957 who lack
laboratory evidence of measles IgG in their serum or labora-
tory confirmation of infection.740 Health care personnel with
immunity who are not vaccinated after exposure should be removed from all patient contact and excluded from
the facility from day 5 after their first exposure through day 21
after the last exposure, even if they have received postexposure
immunoglobulin (immunoglobulin, 0.25 mg/kg [40 mg IgG/kg]).
Those with documentation of one vaccine dose may remain at
work and should receive the second dose.211,212

Health care personnel

Persons who work in health care facilities are at greater risk for
acquiring measles than the general population. During 1985 to
1989, physicians had an eightfold increased risk and nurses
a twofold increased risk of measles compared with non–health
care workers of the same age.744 In the 120 measles outbreaks
occurring during 1993 through 2001, health care facilities
were the most commonly reported settings, with 24 out-
breaks reported.745 In the postelimination years 2001 to 2008,
27 reported measles cases were transmitted in US health care
facilities, accounting for 5% of all reported US measles cases.746
Because persons working in medical settings have been infected
with measles and have transmitted the virus to patients and other
staff, the ACIP recommends that persons born in or after 1957
working in health care facilities be required to provide documented
receipt of two doses of measles-containing vaccine, laboratory
evidence of measles immunoglobulin (IgG) in serum (ie, a sin-
gle serologic test for measles IgG), or laboratory confirmation
of acute prior measles infection (ie, positive serologic test for measles
immunoglobulin M [IgM] antibody or fourfold rise in measles IgG
antibody level or documentation of seroconversion by any stan-
ard serologic assay, detection of measles RNA in a clinical speci-
men, or isolation of measles virus from a clinical specimen);746,746

During 2001 to 2008, 12.5% (1 of 8) of measles cases reported
to the Centers for Disease Control and Prevention (CDC) among
health care personnel occurred in persons born before 1957.746
Thus, because measles has occurred in persons born before
1957, health care facilities should consider vaccinating person-
nel born before 1957 who lack documented receipt of two doses
of measles-containing vaccine, laboratory evidence of measles
IgG in their serum, or laboratory confirmation of infection,
with two doses of MMR vaccine at the appropriate interval.211
During an outbreak of measles, health care facilities should rec-
ommend two doses of MMR vaccine for unvaccinated personnel
born before 1957 who lack laboratory evidence of measles IgG
in their serum or laboratory confirmation of infection.740,746

Serologic screening need not be done before vaccinating for
measles and rubella unless the medical facility considers it cost
effective.211 For health care personnel who have two docu-
mented doses of MMR vaccine or other acceptable evidence of
immunity to measles, serologic testing for immunity is not
recommended.

International travelers

Measles is endemic in many countries including industrialized
countries in Europe and Asia. Of the 222 measles cases reported
in the United States in 2011, 200 (90%) were associated with
importations. Almost half of the imported cases occurred in peo-
ple who acquired measles in Europe.746 Protection against mea-
sles is especially important for persons planning international
travel. Before their departure from the United States, children 12
months of age or older should have received two doses of MMR
vaccine separated by at least 28 days, with the first dose adminis-
tered on or after the first birthday. Children ages 6 to 11 months
should receive a dose of MMR vaccine before departure. For
infants vaccinated before 12 months of age, revaccination should
be at 12 to 15 months of age (12 months of age for those remain-
ing in areas of endemic or epidemic measles). The second dose
should be administered at least 28 days after the first dose.211,212

Because the risk of complications from measles is increased in
adults, it is also important to protect susceptible adults. Most per-
sons born in the United States before 1957 are likely to be immune.
However, for persons born after 1956 who travel internationally,
two doses of measles vaccine should be administered separated by
at least 28 days, unless there is documentation of receipt of two
doses, other evidence of immunity, or a contraindication.211,212

Persons infected with human immunodeficiency virus

HIV-infected persons are at increased risk for severe compli-
cations if infected with measles.211,212 Among HIV-infected per-
sons who did not have evidence of severe immunosuppression,
no increase in serious or unusual adverse events have been
reported after measles vaccination.749,750 Therefore, MMR vac-
cination is recommended for all asymptomatic HIV-infected
persons who do not have evidence of severe immunosuppres-
sion and for whom measles vaccination would otherwise be
indicated. MMR vaccination also should be considered for all
asymptomatic HIV-infected persons who do not have evidence
of severe immunosuppression. Testing asymptomatic persons
for HIV infection is not necessary before administering MMR
or other measles-containing vaccines.211,212

Because the immunologic response to live and killed-anti-
gen vaccines may decrease as HIV disease progresses, vaccina-
tion early in the course of HIV infection may be more likely to
induce an immune response.749 Therefore, HIV-infected infants
without severe immunosuppression (as defined in “Adverse
effects”) should routinely receive MMR vaccine at 12 months
of age if infected with measles in Europe.740 Among those who
did not have evidence of severe immunosuppression, revaccination
should be considered for measles cases reported after measles vaccination.749,750 Therefore, MMR vac-
cination is recommended for all asymptomatic HIV-infected
persons who do not have evidence of severe immunosuppres-
sion and for whom measles vaccination would otherwise be
indicated. MMR vaccination also should be considered for all
asymptomatic HIV-infected persons who do not have evidence
of severe immunosuppression. Testing asymptomatic persons
for HIV infection is not necessary before administering MMR
or other measles-containing vaccines.211,212

Consideration should be given to administering the second
dose of MMR vaccine as soon as 28 days (ie, 1 month) after the first
dose rather than waiting until the child is ready to enter kinder-
garten or first grade. In addition, if at risk for exposure to
measles, (eg, in an outbreak setting or for international travel),
HIV-infected infants who are not severely immunocompro-
mised should be administered MMR vaccine at age 6 to 11
months.211,212,566 These children should receive another dose as
soon as possible on reaching the first birthday, provided at least
1 month has elapsed since the administration of the previous
dose of measles-containing vaccine. An additional dose of MMR
vaccine can be administered as early as 28 days after the second
dose. Newly diagnosed HIV-infected adults and children ages 12
months or older without acceptable evidence of measles immu-
nity should receive MMR vaccine as soon as possible after diag-
nosis, unless they have evidence of severe immunosuppression.

Close contacts of immunosuppressed patients

To minimize the risk of exposure to measles among patients
with immunosuppression, including HIV infection, all family
and other close contacts of these patients should be vaccinated.
with two doses of MMR vaccine, unless they are immunosuppressed, have other contraindications, or have other acceptable evidence of measles immunity.\textsuperscript{211,112} No transmission of measles virus from a vaccinee to a contact has ever been documented, which suggests that the risk of exposure to vaccine virus among immunosuppressed contacts is very low. However, because of the extreme vulnerability of hematopoietic cell transplants (HCT) recipients, vaccine recipients who develop a fever and/or postvaccination should be excluded from visiting the HCT center while symptomatic and should avoid close contact with HCT recipients in the home setting.\textsuperscript{752}

Patients treated with chemotherapy, organ transplant, or bone marrow transplant

When cancer chemotherapy or immunosuppressive treatment is being considered, measles vaccination ideally should precede the initiation of chemotherapy or immunosuppression by at least 2 weeks.\textsuperscript{754} Persons who were not immune to measles when diagnosed with leukemia may receive measles-containing vaccine during remission. Measles vaccination is contraindicated during the period of immunosuppression, and at least 3 months should elapse after termination of chemotherapy before measles vaccination.\textsuperscript{212} Patients exposed to measles or at high risk of exposure while immunosuppressed should be given IG regardless of previous immunization status (see “Postexposure prophylaxis”). Routine vaccination with MMR is recommended for all children and seronegative adults who have received hematopoietic stem cell transplants. The first dose should be given 24 months after transplantation if the recipient is presumed to be immunocompetent, is not on immunosuppressive medications, and is not affected by graft versus host disease. A second dose should be given 6 to 12 months after the first dose.\textsuperscript{752-753} Regular testing of long-term HCT survivors for maintenance of measles antibody levels is recommended approximately every 4 to 5 years. The need for revaccination has to be assessed on an individual basis.\textsuperscript{752}

Revaccination of persons vaccinated according to earlier recommendations

Anyone vaccinated at any age with inactivated (killed) measles vaccine alone or killed vaccine followed by live vaccine within a 3-month period, and anyone vaccinated between 1963 and 1967 with a vaccine of unknown type, should be revaccinated with the current live vaccine to ensure protection and to prevent atypical measles illness. Revaccinating persons who received an unknown type of vaccine is recommended because Edmonston B, inactivated, and further attenuated live vaccines all were in use during this interval (see Figure 20-6). As noted previously, vaccination of an immune person is not associated with any increased risk of adverse events. However, revaccination of recipients of killed vaccine may be associated with local reactions of pain, swelling, erythema, and regional lymphadenopathy lasting 1 to 2 days.\textsuperscript{75,76,119,120,644,645,736} These reactions have been reported to occur in 4% to 55% of vaccinees. More severe reactions have been noted, but only rarely.\textsuperscript{75} Whereas revaccination has not been proved to totally eliminate the risk for atypical measles,\textsuperscript{199} available data suggest that the risk is reduced considerably.\textsuperscript{773,774,782} Thus, the risk of these reactions is outweighed by the risk associated with atypical measles.\textsuperscript{212}

A dose of further attenuated live vaccine with IG administered simultaneously should not be considered adequate vaccination. This recommendation is based on the theoretic consideration that passively derived antibody might interfere with seroconversion. Whereas low doses of IG do not appear to interfere with seroconversion, there is no information available about the dose used in general practice shortly after the introduction of further attenuated vaccines in the United States. Furthermore, at least one study has suggested that there is an increased rate of seronegativity when further attenuated vaccine was administered with IG.\textsuperscript{555} Finally, and perhaps most important, revaccination is indicated if there is any uncertainty about the validity of doses in the vaccination record.\textsuperscript{499}

Precautions and contraindications

In general, measles vaccination is contraindicated for patients with acute severe illness, immunosuppression, pregnancy, or a personal history of an anaphylactic reaction to measles-containing vaccines. For the rare patient with a personal history of an anaphylactic reaction to gelatin or neomycin, measles vaccine should be administered with extreme caution and in consultation with an allergist. After administration of IG (by IM, IV, or SC route) or other blood products, vaccination should be delayed for the recommended interval, unless the patient is exposed to measles or at high risk of exposure.\textsuperscript{212} Clinical judgment must be used in deciding whether to vaccinate a patient with a history of thrombocytopenia, but recent studies suggest that the risk of stimulating a recurrence of ITP is very low.\textsuperscript{756,757} Mild illness, personal or family history of seizures, steroid therapy that is not immunosuppressive, and allergic reactions to eggs, chicken, feathers, or penicillin are not contraindications to measles vaccination. Persons with contraindications to measles vaccination should receive IG if they are exposed to measles or at high risk of exposure. Unfortunately, this only provides protection for a short time (see “Passive immunization”). To reduce the risk of exposure to measles in persons for whom the vaccine is contraindicated, their household contacts should be immune to measles or be vaccinated (unless contraindicated). To prevent nosocomial exposure to measles in patients with contraindications, all health care personnel should be immune to measles or be vaccinated (unless contraindicated) (see “Indications”).

Severe illness

Measles-containing vaccines should not be administered to patients with acute severe illnesses, including those with significant fever or evolving neurologic conditions. To avoid confusing the evolution of the illness with possible adverse events resulting from measles vaccine, vaccination should be deferred until the acute severe illness is resolved.

Withholding vaccination for false contraindications is a major cause of late vaccination and low vaccine coverage. Measles vaccination should not be deferred in the presence of mild conditions, such as mild upper respiratory infections, otitis media, or diarrhea.\textsuperscript{555} Multiple large studies, in the United States and in other countries, have documented that children with mild illness have similar serologic responses to measles vaccination compared with well children. These studies also showed that the ill children had no increased risk of adverse events after vaccination compared with well children.\textsuperscript{212,570,582,584}

Tuberculosis

Because of a theoretic concern that measles vaccination might exacerbate tuberculosis, patients with untreated active tuberculosis should begin antituberculosis therapy before measles vaccination. This theoretic concern is based on the reputed role of measles disease as an aggravating factor in tuberculosis and the similar suppression of delayed hypersensitivity for up to 4 to 6 weeks seen after both measles disease and measles vaccination.\textsuperscript{501,503} However, a 1976 review of studies examining the effect of measles disease on tuberculosis patients concluded that none of the studies provided conclusive evidence that measles disease has a deleterious effect on tuberculosis.\textsuperscript{104} A review of the incidence of tuberculosis after a measles outbreak in Korea did not reveal an increased risk of tuberculosis.\textsuperscript{793} In several small
studies in the 1960s, measles vaccine did not exacerbate tuberculosis in children receiving antituberculosis therapy.\textsuperscript{506,509,749} However, there are no data available on the effect of measles vaccine on patients with untreated tuberculosis.

Tuberculin skin testing is not a prerequisite for measles immunization. In patients for whom tuberculin skin testing is indicated, such testing can be undertaken at the same time that vaccine is administered. If skin testing is not done at that time, it is advisable to wait 4 to 6 weeks after vaccination before administering a tuberculin skin test.\textsuperscript{211,212}

\textbf{Immunosuppression}

Live virus measles vaccine should not be administered to persons who are immunosuppressed because of medication (eg, high-dose steroids, alkylating agents, and antimitoticals), other therapy such as radiation, or underlying illness (eg, congenital immunodeficiency, leukemia, lymphoma, generalized malignant disease) (see “Indications”). Although patients with severe immunosuppression related to HIV infection should not receive measles vaccine, HIV-infected persons who are not severely immunosuppressed may be vaccinated.\textsuperscript{711} Immunosuppressed patients who are exposed to measles or at risk of exposure should receive IG regardless of their history of measles disease, vaccination, or serology, because they are at high risk of complications and death from measles (see “Passive immunization”). Replication of live vaccine virus may be augmented and prolonged in patients who are immunocompromised, and adverse events after vaccination, including death, are more common in immunocompromised patients (see “Adverse effects”).

Systemic corticosteroid treatment can result in immunosuppression. Because the minimum dose and duration of steroid therapy necessary to induce immunosuppression are not well defined, clinical judgment must be used to assess whether a patient on steroid therapy is immunosuppressed. Most experts would consider a steroid dose equivalent to or greater than a prednisone dose of 2 mg/kg of body weight per day (or a total of 20 mg/day administered daily or on alternate days) or 14 days or more to be sufficiently immunosuppressive to contraindicate measles vaccination.\textsuperscript{212} Patients receiving immunosuppressive doses of steroids should not receive measles vaccine until 1 month after the end of steroid therapy. Vaccination is not contraindicated in persons receiving topical, localized (eg, intra-articular, bursal, or tendon injection); low- to moderate-dose steroids, or physiologic steroid replacement. Patients who receive high-dose steroids for less than 14 days generally can be vaccinated immediately after cessation of steroid therapy. Measles vaccine is contraindicated in any patient on any dose of steroids with clinical or laboratory evidence of immunosuppression or an underlying disease that is immunosuppressive.\textsuperscript{211,711}

MMR and other measles-containing vaccines are not recommended for HIV-infected persons with evidence of severe immunosuppression (as defined above) because of the risk of adverse events, the impaired immune response to MMR vaccination, and the current low risk of exposure to measles in the United States.\textsuperscript{211,212,722} One case of fatal vaccine-associated pneumonitis has been documented in a severely immunocompromised patient with HIV infection (see “Adverse events”).\textsuperscript{720} Available data suggest that persons with HIV infection who are not severely immunosuppressed may be vaccinated safely.\textsuperscript{211,594,595,722} Because measles has been documented to be severe in HIV-infected persons in both the United States and developing countries,\textsuperscript{742} measles vaccine is recommended routinely for asymptomatic HIV-infected children and adults without evidence of measles immunity and should be considered for those with symptomatic HIV infections who are not severely immunosuppressed. Asymptomatic patients at risk for HIV infection do not need to be screened for HIV before vaccination (see “Indications”).\textsuperscript{211,212,566,722}

\textbf{Pregnancy}

On theoretic grounds, live-virus vaccines, including measles vaccine, should not be administered to a pregnant woman. However, in contrast to rubella and mumps vaccines, measles vaccine virus has not been shown to cross the placenta and infect the fetus. ACIP recommends that susceptible women of childbearing age be asked if they are currently pregnant or attempting to become pregnant before administering MMR vaccine. Vaccination should be deferred for those who answer “yes.” Those who answer “no” should be vaccinated and advised to avoid pregnancy for 1 month after vaccination because of the theoretic risks to the fetus.

\textbf{Allergies}

Severe immediate hypersensitivity reactions (urticaria, angioedema, wheezing, hypotension, and shock) are very rare serious complications after measles vaccination. From 1991 to 2000, the US Vaccine Adverse Event Reporting System received reports of events that were classified as probable or possible anaphylaxis at an average of two reports per million doses of MMR distributed.\textsuperscript{848,945} A detailed review of patients enrolled with maintenance organizations in the US Vaccine Safety Datalink Project found three cases of anaphylaxis among 848,945 persons who received MMR vaccine (two had also received other vaccines at the same visit) for an estimated risk of 3.5 episodes of anaphylaxis per million doses of MMR administered.\textsuperscript{704,681} In China, the rate was 6.5 per million doses administered.\textsuperscript{681} No anaphylaxis deaths have been reported in association with measles vaccination in the United States, but anaphylaxis can be life threatening. Persons with a history of anaphylaxis or other serious allergic reactions after measles-containing vaccines should be evaluated by using standardized procedures to try to determine the offending allergen and the need for and acceptability of administering additional doses of vaccine.\textsuperscript{704} Most patients with anaphylactic reactions after measles vaccination do not have clinically evident risk factors for anaphylaxis. Adequate treatment for hypersensitivity reactions, including epinephrine injection, should be available for immediate use whenever measles vaccines are administered, along with staff trained in treatment of anaphylactic reactions.\textsuperscript{211}

Measles vaccines typically contain hydrolyzed gelatin as a stabilizer. Allergic reaction to gelatin has been recognized as a major cause of anaphylaxis after MMR vaccination.\textsuperscript{764,765} Persons who are allergic to gelatin contained in vaccines should be vaccinated with extreme caution and in consultation with an allergist or immunologist.\textsuperscript{522} Vaccine skin testing may be useful in these patients, but there is no protocol available. Patients with severe immediate hypersensitivity reactions have been shown to have high levels of anti-gelatin IgE and IgG and increased gelatin-specific T-cell responses.\textsuperscript{762,763} In a study in Japan, 24 of 26 children who had allergic reactions to vaccines had anti-gelatin IgE. Only two of the children had allergic reactions to gelatin in food before vaccination.\textsuperscript{764} In contrast, substantially fewer children (6 of 22) with severe allergic reactions to MMR in the United States had anti-gelatin IgE, and none had a reported history of allergic reactions to gelatin in food.\textsuperscript{764} Measles vaccines contain trace amounts of the antibiotic neomycin. Allergic reactions to topical or systemic neomycin are rare and typically consist of delayed or cell-mediated reactions such as contact dermatitis. The rare patients with systemic allergic reactions to either topical or systemic administration of neomycin should be vaccinated with extreme caution and in consultation with an allergist or immunologist.\textsuperscript{211} Vaccine skin testing may be useful in these patients, but there is no protocol available. Patients with severe immediate hypersensitivity reactions have been shown to have high levels of anti-gelatin IgE and IgG and increased gelatin-specific T-cell responses.\textsuperscript{762,763} In a study in Japan, 24 of 26 children who had allergic reactions to vaccines had anti-gelatin IgE. Only two of the children had allergic reactions to gelatin in food before vaccination.\textsuperscript{764} In contrast, substantially fewer children (6 of 22) with severe allergic reactions to MMR in the United States had anti-gelatin IgE, and none had a reported history of allergic reactions to gelatin in food.\textsuperscript{764} Measles vaccines contain trace amounts of the antibiotic neomycin. Allergic reactions to topical or systemic neomycin are rare and typically consist of delayed or cell-mediated reactions such as contact dermatitis. The rare patients with systemic allergic reactions to either topical or systemic administration of neomycin should be vaccinated with extreme caution and in consultation with an allergist or immunologist.\textsuperscript{211} Vaccine skin testing may be useful in these patients, but there is no protocol available. Patients with severe immediate hypersensitivity reactions have been shown to have high levels of anti-gelatin IgE and IgG and increased gelatin-specific T-cell responses.\textsuperscript{762,763} In a study in Japan, 24 of 26 children who had allergic reactions to vaccines had anti-gelatin IgE. Only two of the children had allergic reactions to gelatin in food before vaccination.\textsuperscript{764} In contrast, substantially fewer children (6 of 22) with severe allergic reactions to MMR in the United States had anti-gelatin IgE, and none had a reported history of allergic reactions to gelatin in food.\textsuperscript{764}
protein in the MMR vaccine currently licensed in the United States. Because some children with egg allergy have had anaphylactic reactions to measles vaccines,\textsuperscript{770} previous recommendations included an algorithm of vaccine skin testing and desensitization for children who have had anaphylactic reactions after egg ingestion.\textsuperscript{771} However, more than 1,200 children with severe allergic reactions to eggs have been vaccinated safely in two studies.\textsuperscript{772,773} Vaccine skin testing and desensitization are no longer recommended for persons with severe egg allergies.\textsuperscript{211} These persons may be vaccinated by using the same precautions (treatment for anaphylaxis immediately available) as for persons without severe egg allergy. Also, persons with less severe allergic reactions to eggs, or allergy to chicken or feathers, may be vaccinated as usual.\textsuperscript{211,772}

**Administration of immune globulin and other blood products**

Because passively derived antibody may interfere with vaccine seroconversion, vaccination should be deferred for 3 to 11 months after receipt of IG (by IM, IV, or SC route) and other blood products, depending on the dose of the blood product received.\textsuperscript{211,775,776} In addition, vaccination should precede receipt of IG by at least 2 weeks whenever possible. However, unvaccinated persons may not be fully protected by the passive antibodies received during the entire interval recommended prior to vaccination after receipt of blood products. Therefore, additional doses of IG or measles vaccine may be necessary if the patient is repeatedly exposed to measles or at high risk of exposure to measles. If measles vaccination is given before the recommended interval has elapsed, the dose should be repeated (at least 1 month after the measles vaccination and after the recommended interval from the time of blood product administration has elapsed).

**Thrombocytopenia**

Oski and Naiman\textsuperscript{777} reported significant depression of platelet counts without clinical symptoms after vaccination with Edmonston B vaccine, including one infant who had thrombocytopenia repeatedly after three doses. Previous immunity to measles did not prevent depression of the platelet count. ITP has been associated with measles-containing vaccines currently in use.\textsuperscript{674} The increased risk of ITP after MMR vaccination is estimated at three to four cases for every 100,000 doses.\textsuperscript{776,777} There are no reports in which ITP solely associated with measles vaccines has resulted in death.

Two cases of recurrent MMR-associated ITP have been reported in patients with ITP associated with a previous MMR dose,\textsuperscript{778,779} and one case of MMR-associated exacerbation of chronic ITP was reported in a 19-year-old female whose onset of chronic ITP was associated with rubella vaccination in the second year of life.\textsuperscript{781} In a study including 21 children with ITP before their first dose of MMR, Miller and colleagues\textsuperscript{770} reported that none had a recurrence of ITP after vaccination. A recent review identified 131 children with a history of ITP who received MMR without a recurrence, including 26 children whose ITP followed a first dose of MMR.\textsuperscript{675} Advisory committees recommend caution when administering measles-containing vaccines to children with thrombocytopenia or a past history of ITP especially when the prior episode of ITP was associated with measles vaccination.\textsuperscript{211,772} Serologic assessment of immunity may be useful in assessing the risk and benefits of immunization in such patients.

**Family or personal history of seizures**

Measles vaccination, like other causes of fever, may cause febrile seizures in young children. The 5% to 7% of children who have either a personal or family history of seizures may have an increased risk of febrile seizures after measles vaccination.\textsuperscript{781}

Febrile seizures after vaccination do not increase the risk of epilepsy or other neurologic disorders. The benefits of administering measles vaccine to children with personal or family history of seizures substantially outweigh the risks, and these children should be vaccinated following the standard recommendations. Their parents should be advised of the benefits of the vaccination and the minimal increased risk of febrile seizures. Because the fever induced by measles vaccine occurs between 6 and 12 days after vaccination and seizures may occur with the onset of fever, it is difficult to use antipyretics to prevent febrile seizures after measles vaccination. Patients taking anticonvulsants should continue these medications after measles immunization.\textsuperscript{211,772}

**Future vaccines**

Although measles vaccines are highly effective, the need to delay immunization until passively acquired maternal antibodies have declined has been an impediment to the global control and eradication of measles.\textsuperscript{782} Research continues to develop new vaccines that might effectively immunize children at younger ages or be administered by routes that allow easy delivery during mass campaigns. Advances have been made in the development of subunit DNA and vectored measles vaccines that may be immunogenic in young infants in the presence of maternal antibody.\textsuperscript{783-786} For example, a DNA vaccine expressing measles virus hemagglutinin and fusion glycoproteins induced long-lasting, high-avidity neutralizing antibodies in neonatal mice born to measles-immune mothers despite the presence of high levels of maternal antibodies.\textsuperscript{783} Studies in the monkey model for atypical measles reveal that a DNA vaccine expressing hemagglutinin did not prime for atypical measles.\textsuperscript{786} However, some vaccine constructs did induce antibodies of poor avidity.\textsuperscript{786}

Oral vaccination using an enteric-coated live, attenuated measles vaccine was not successful in monkeys.\textsuperscript{787} However, oral administration of a measles peptide incorporated into a vesicle induced a cell-mediated immune response to measles and orally administered adenovirus modified to express measles nucleocapsid antigen induced both measles antibody and cytotoxic T-cell responses.\textsuperscript{789}

Aerosol administration of live attenuated measles vaccines has been studied for more than 30 years. In recent studies, aerosol administration was equally or more immunogenic than the same vaccines administered by injection.\textsuperscript{805,790} Standardization of administration techniques with practical devices have improved as have the immune response rates.\textsuperscript{792} Aerosol administration of the Edmonston-Zagreb strain as a second dose to older children and adults induces a booster response stronger than that seen with vaccination by injection.\textsuperscript{792} The use of the Schwarz strain via the aerosol route is no longer being pursued because of low response rates. Aerosol administration could help simplify administration of vaccine to large numbers of children in community-based campaigns similar to those used in the polio eradication effort.\textsuperscript{815,790,792} The WHO, CDC, and the American Red Cross have established a Measles Aerosol Project with the goal of completing the necessary research and regulatory requirements to license aerosol delivery of measles vaccine in the developing world.\textsuperscript{794}

**Public health considerations**

**Epidemiologic results of vaccination**

Measles is one of the most contagious diseases of humans and is a classic communicable disease of childhood. The goal of measles vaccination is to prevent illness and death caused
by measles directly among vaccinated persons and indirectly among unvaccinated persons as a result of decreased transmission. In the absence of vaccination, measles occurs in epidemic cycles. The magnitude and frequency of the epidemics depends on the population size, contact rates between persons, and the rate at which new susceptible persons are added to the population through births or migration. In England and Wales in the 1940s, epidemics occurred every second year, starting in the large cities of London, Manchester, and Liverpool and spreading outward to towns and rural villages.19,794 In the large population centers, chains of transmission were sustained during the periods between epidemics, and these cities were the reservoirs of measles. In towns and villages, transmission died out after an epidemic and had to be reintroduced for each subsequent epidemic. Epidemic cycles of measles also can be described in terms of the effective reproduction number, \( R \), defined as the average number of secondary cases produced by a typical case in a population (see Chapter 7).152,799,800 When \( R \) is less than 1, the average case gives rise to less than one case, and the number of cases occurring subsequently begins to decrease. Introduction of measles vaccination leads to a reduction in the size of epidemics and a decrease in the interval between measles epidemics.199 The widened interepidemic interval has been referred to as the “honeymoon period”.401 Vaccination of successive cohorts of young children results in a decrease in incidence among vaccinated cohorts, an overall decline in measles incidence in all age groups (because of dampened transmission), and, when outbreaks occur, an increase in the proportion of cases among older children.145,151,401 Susceptibility to measles among older cohorts occurs most often because these persons missed natural disease as young children and either missed getting vaccinated (program failure) or failed to respond to vaccination (primary vaccine failure). Waning of vaccine-induced immunity (secondary vaccine failure) has been found to occur in 0% to 5% of vaccinees but does not appear to play a major role in reducing overall population immunity to measles.151,152,629,637 As vaccination coverage increases among successive birth cohorts, measles transmission decreases, reducing the risk of measles even among unvaccinated persons. At some vaccine-induced immunity level lower than 100%, measles virus transmission is interrupted.401,404 Mathematical models have estimated the herd immunity threshold for measles in the United States at 92% to 95%.97 If this level of population immunity is maintained by a vaccination program, endemic transmission of measles will die out and measles elimination is achieved. Elimination does not result in zero measles cases because importations of measles from endemic areas continue to occur. However, spread from these importations is short lived and will end without intervention. Documenting the elimination of measles is challenging. De Serres and associates99 have proposed using the proportion of cases imported and the distribution of outbreak sizes to monitor elimination. These surveillance parameters can be used to estimate \( R \), which must be maintained at less than 1 to achieve elimination. Global eradication of measles will occur when the last chain of transmission of measles virus is interrupted and can be defined as the simultaneous achievement of measles elimination in every country.

In industrialized countries, a single dose of measles vaccine administered in the first year of life induces immunity in about 95% of vaccinees.531 With a primary vaccine failure rate of 5%, 100% of the population would have to be vaccinated to reach a 95% immunity level with a single-dose strategy. Approximately 95% of persons who fail to respond to the first dose respond to a second dose,111 and with high vaccine coverage, the herd immunity target can be reached if two doses are administered.

In developing countries, high morbidity and mortality resulting from measles among infants led to a recommendation to vaccinate infants at 9 months of age, a time when maternal antibody may interfere with seroconversion.863 Studies have found the median seroconversion rate with vaccination at age 9 months to be 85% [range, 70% to 98%].869 This leaves three times more infants susceptible (15% of vaccinees) than does a rate of 95%. After a single dose with 90% coverage and 85% seroconversion, 77% of the population would be immune. To improve immunity, some have considered providing a second dose, usually through routine health services at an older age, when seroconversion is 95%. However, if only first-dose recipients were revaccinated through routine health services, given 90% coverage with both doses, immunity levels could rise to only 90%, leaving 10% susceptible. Alternatively, if vaccination activities were intensified both within and outside the routine health services, such that many children never vaccinated could receive a first dose while previously vaccinated children receive a second dose, the resulting population immunity level would be much higher. This is known as a second opportunity strategy. For example, if the second opportunity reached 90% coverage of prior first-dose recipients and previously unvaccinated children, population immunity would increase to greater than 95%. In countries with poor access to preventive services, the second opportunity for measles vaccination is most often provided through nationwide supplementary immunization activities or mass campaigns, because these are more effective at reaching children who have never been vaccinated.

The impact of measles vaccination on overall childhood mortality in developing countries was questioned by one study that reported replacement mortality [ie, later death from other causes].115 However, several subsequent studies have documented that measles vaccination increases overall child survival.810–813 In Bangladesh, investigators found that the overall mortality rate in measles-vaccinated children was 45% lower than in unvaccinated children and that this difference persisted for several years after vaccination.810 A similar large impact of measles vaccination on overall child mortality was found in rural India, where children who received measles vaccination in infancy had 27% lower mortality.811 A comparison of the proportion of all-cause mortality resulting from measles, among children ages less than 5 years, found measles accounted for about 7% of all child deaths in 1990 and 1% in 2008, contributing 23% to the overall reduction in mortality in this age group.814

Experiences with measles control and elimination in various countries

**Industrialized countries**

Experience in industrialized countries has shown that a single dose of measles vaccine, widely administered, can reduce measles transmission, but a two-dose strategy is necessary for elimination of indigenous transmission.815–818 Many countries introduced measles vaccine as a single-dose schedule and then added a second opportunity for vaccination because of the persistence of outbreaks despite high single-dose coverage (Table 20-10). Industrialized countries have found that the costs of patient care and outbreak control outweigh the cost of a second opportunity for immunization.817 Some countries [eg, Canada, United Kingdom, Australia, and New Zealand] have adopted a two-dose schedule and have conducted a one-time, nationwide vaccination campaign to reduce susceptibility among school-age children. Other countries [eg, the United States, Finland, and Sweden] have relied on a two-dose schedule alone.

In the United States, the distribution and use of more than 350 million doses of live measles vaccine between the year of licensure (1963) and the end of 2010 (see Figure 20-6) has been associated with a marked reduction in measles [Figure 20-9] and its associated complications and estimated savings of billions
of dollars.\textsuperscript{26,276} Whereas approximately 4 million cases occurred annually in prevaccine years, on average 400,000 to 500,000 cases were reported. In 2010, only 64 confirmed cases were reported, with 87.5% of these linked to importations. This represents a reduction of more than 99.9% compared with years preceding vaccine licensure. The reported occurrence of SSPE also has declined greatly (see Figure 20-8) and was virtually eliminated in the late 1980s and early 1990s. A small number of cases had been reported each year during the late 1990s as a result of the resurgence of measles during 1989 to 1991.

The United States has embarked on three elimination efforts (see Figure 20-9).\textsuperscript{22,23,805,820} The first, in 1966, was based on a single-dose strategy with vaccination at 1 year of age (see Table 20-10). The second, announced in 1978, had three components: (1) a high level of population immunity through vaccination with a single dose of measles vaccine, (2) disease surveillance, and (3) prompt response to outbreaks.\textsuperscript{22,25} To reach high coverage, vaccination requirements for school entry were enacted and enforced in every state. These requirements, which mandated not only measles vaccination but also other childhood vaccinations, have become the major legacy of this elimination initiative. Although sustained interruption of transmission of measles was not achieved, measles was eliminated from most of the country, 54% of counties in the United States were measles free for the entire decade from 1980 to 1989, and only 17 (0.5%) counties reported measles every year during that period.\textsuperscript{821} During this interval, outbreaks continued to occur in schools among school-age persons with histories of vaccination and among unvaccinated preschool-age children.\textsuperscript{338,499,556,560,633,822} In 1989, the United States introduced a routine second dose of measles vaccine at 4 to 6 years or 11 to 12 years to address the problem of school outbreaks (see Table 20-10).

After relatively low incidence during the 1980s, a 3-year epidemic of measles began in 1989 and resulted in over 55,000 cases and 123 deaths.\textsuperscript{823,824} The average annual incidence during 1989 to 1991 was 7.4 per 100,000 population compared with an average incidence for 1981 to 1988 of 1.8 per 100,000. Incidence was increased in all age groups; however, the greatest increases were in children younger than 1 year and 1 to 4 years, resulting in almost half of all cases occurring in children

<table>
<thead>
<tr>
<th>Country</th>
<th>First opportunity</th>
<th>Second opportunity</th>
<th>Supplementary campaign</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First dose in schedule</td>
<td>Second dose in schedule</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Year</td>
<td>Recommended age</td>
<td>Year</td>
</tr>
<tr>
<td>United States</td>
<td>1963</td>
<td>9 mo</td>
<td>1989</td>
</tr>
<tr>
<td></td>
<td>1965</td>
<td>12 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1976</td>
<td>15 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1994</td>
<td>12-15 mo</td>
<td></td>
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<tr>
<td>Canada</td>
<td>1963</td>
<td>9 mo</td>
<td>1996</td>
</tr>
<tr>
<td></td>
<td>1968</td>
<td>12 mo</td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1968</td>
<td>12-23 mo</td>
<td>1996</td>
</tr>
<tr>
<td></td>
<td>1988</td>
<td>13-15 mo</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>1973</td>
<td>8 mo</td>
<td>1992</td>
</tr>
<tr>
<td></td>
<td>1976</td>
<td>7 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1982</td>
<td>9 mo</td>
<td></td>
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<tr>
<td>China</td>
<td>1978</td>
<td>8 mo</td>
<td>1986</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2006</td>
</tr>
<tr>
<td>WHO EPI</td>
<td>1983</td>
<td>9 mo</td>
<td>2001</td>
</tr>
<tr>
<td></td>
<td>1989</td>
<td>6 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1991</td>
<td>9 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2009</td>
<td></td>
<td>2009</td>
</tr>
</tbody>
</table>

*WHO, World Health Organization.*
younger than 5 years (see Table 20-1). This epidemic was due to low measles vaccination levels among preschool-age children, particularly in inner cities, and was part of a hemisphere-wide measles epidemic.

In 1993, the third elimination initiative was launched. In addition to the three components of the earlier strategy, this initiative focused on increasing preschool immunization levels to greater than 90% and vaccination of all school children with a second dose. To implement these vaccination strategies, between 10 and 16 million doses of measles vaccine were distributed annually between 1994 and 2005 (see Figure 20-6). In March 2000, the CDC convened a panel of experts to review the pattern of measles transmission in the United States. Evidence presented included an annual measles incidence of less than 1 case per 1 million population since 1997, and vaccination of all school children with a second dose. To implement these vaccination strategies, between 10 and 16 million doses of measles vaccine were distributed annually between 1994 and 2005 (see Figure 20-6). In March 2000, the CDC convened a panel of experts to review the pattern of measles transmission in the United States. Evidence presented included an annual measles incidence of less than 1 case per 1 million population since 1997, and vaccination of all school children with a second dose.

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In 1968, the United Kingdom introduced measles vaccine for children between the ages of 1 and 2 years, but throughout the 1970s and early 1980s coverage remained below 80%. In 1988, combined MMR vaccine was introduced in place of measles vaccine at age 13 to 15 months (see Table 20-10) and coverage improved to over 90%. In November 1994, all children ages 5 to 16 years in England and Wales were offered combined measles-rubella vaccine, regardless of prior vaccination history, in an attempt to prevent a predicted epidemic of measles. During the campaign, 6.2 million doses were administered for a reported coverage of 92%. Between 1995 and 2000, among 594 confirmed measles cases, 212 (36%) were sporadic and 382 (64%) were associated with 51 clusters. Forty-eight sporadic cases (23%) and 18 of 51 clusters (35%) were associated with an importation of infection from overseas. A wide variety of measles virus genotypes were identified during this period. The pattern of sporadic cases and small clusters associated with importations is consistent with elimination of sustained indigenous measles transmission. However, unfounded concerns about vaccine safety that began in 1998 (see “Adverse events”) have contributed to a decline in MMR coverage that has resulted in a number of large outbreaks. In 2007, measles endemicity was reestablished with genotype D4 as the predominant genotype type. Although coverage with MMR vaccine by 24 months in England and Wales has increased from 84% in 2006 to 89% in 2010, outbreaks of measles continue.

Excellent control of measles has been achieved in other industrialized countries. In 1982, Finland initiated a measles elimination program based on a two-dose vaccination strategy. Efforts to improve vaccination coverage included mass media, a registry system to track defaults, and an intensive outreach program. Measles elimination was achieved in Finland by 1996 and has been maintained as a result of consistently high (above 95%) two-dose vaccination coverage. Sweden has reported similar success with a two-dose schedule. Australia and South Korea have achieved elimination by using a two-dose routine schedule supplemented by a one-time catch-up campaign. However, in other industrialized countries (eg, Italy, Germany, France and Switzerland), measles remains endemic, with frequent large outbreaks, in part because of the perception that vaccination may be more risky than the disease itself.

The European Region of the WHO, which includes the countries of the former Soviet Union, has updated its strategic plan for eliminating measles and rubella by 2015 and identified the accelerated actions needed to achieve this goal. In addition to Finland and Sweden, a number of European countries are close to, or have already achieved, elimination (eg, Hungary, Poland, the Netherlands, Slovenia, and the Russian Federation). Although successful catch-up vaccination campaigns using combined measles-rubella vaccine have been conducted, in a number of countries, outbreaks continue to occur (eg, Ukraine, Bulgaria, and France).

Less industrialized countries

Beginning in the late 1970s, the Expanded Programme on Immunization (EPI) has played a major role in the development of immunization programs in less industrialized countries. Measles vaccination coverage in these countries rose from 18% in 1981 to 76% in 1990, and an estimated 300 million to 500 million cases were prevented in 1995 alone. During the 1990s, donor support for the EPI decreased substantially, and measles vaccination coverage levels plateaued or decreased, with the estimated annual number of measles deaths stabilizing at about 1 million.

Worldwide in 2000, measles was estimated to cause between 535,300 and 777,000 deaths (ie, 1.4% of 55.7 million total deaths). Among children less than 5 years of age, measles was the fifth leading cause of death, accounting for 5.4% of the 10.9 million total deaths in this age group. The vast majority of measles deaths (> 95%) occur in less industrialized countries because of lower measles vaccination coverage (ie, underdeveloped routine health services and lack of a second opportunity for measles vaccination) and a higher case-fatality ratio in these countries. The higher risk of death from measles in less industrialized countries compared with industrialized countries has been associated with a younger median age of cases, increased intensity of exposure, increased likelihood of secondary infections, and malnutrition, especially vitamin A deficiency. Poverty, crowded living conditions, and large family size are the underlying socioeconomic factors contributing to this epidemiologic pattern. Global immunization programs have resulted in a decrease in worldwide measles mortality to an estimated 139,300 deaths in 2010.

During the late 1980s and early 1990s in less industrialized countries, two different approaches were developed to address the problem of severe measles in children younger than 9 months, the age for vaccination recommended by the WHO (see Table 20-10). First, high-titer measles vaccines (eg, Edmonston-Zagreb measles vaccine) were developed to overcome interference by maternal measles antibody when administered at 4 to 6 months of age. For a short period from 1989 to 1991, the WHO recommended use of high-titer Edmonston-Zagreb measles vaccines for 6-month-old infants in countries where measles was a significant cause of death for infants younger than 9 months. Although high-titer vaccines were more immunogenic than standard-titer vaccines, they were unexpectedly associated with excess delayed mortality among females. For this reason, the WHO withdrew the recommendation for use of these vaccines in 1992. The second approach, developed by PAHO, was based on the observation that older siblings were often the source of measles infection for infants. The concept of a one-time nationwide mass vaccination campaign for children ages 9 months to 14 years, regardless of prior disease or vaccination status, was pioneered in Cuba in 1987. The objective of this so-called catch-up campaign was to interrupt measles virus transmission by rapidly reducing susceptibility among older children and thereby prevent transmission to infants less than 9 months of age. This approach proved highly effective and has been developed further into the PAHO strategy for measles elimination.

The PAHO strategy

In 1994, ministers of health of countries of North and South America established the goal of eliminating measles from the Western Hemisphere by the end of 2000. To accomplish this goal, PAHO developed a strategy with three essential vaccine components: (1) catch-up—a one-time mass vaccination covering all children ages 1 to 14 years, regardless of prior disease or vaccination status; (2) keep-up—achievement of 90% or greater immunization coverage in each successive birth cohort, and (3) follow-up—subsequent mass campaigns conducted every 3 to 5 years, covering all children ages 1 to 5 years irrespective of prior disease or vaccination history. After the catch-up campaigns, most countries have increased the measles vaccination age to 12 months to maximize vaccine effectiveness. In addition to the vaccination strategy, case-based surveillance with laboratory confirmation of suspected measles cases has been established in all countries of the Americas.

In Brazil, the National Immunization Program was created in 1973, and routine measles vaccination was recommended at 8 months of age. National measles control was intensified in 1980 to 1981 with campaigns focused in areas of low coverage. The minimum recommended age for measles vaccination was changed to 7 months in 1976 and then to 9 months in 1982. In 1992, with the adoption of a measles elimination goal by 2000, a second dose was recommended at age 12 to 15 months (see Table 20-10). Based on the success of statewide mass vaccination campaigns in Parana and Sao Paulo in 1987,
Brazil conducted a nationwide catch-up campaign in 1992 during which 48 million doses of measles vaccine were administered to children ages 9 months to 14 years. In 1995, the first national follow-up campaign for children ages 1 to 3 years was conducted; the state of Sao Paulo did not participate in this campaign.

In 1997, after a 4-year period of good control, Brazil experienced a major resurgence of measles, with a total of 53,385 cases and 61 deaths. Transmission was concentrated in the metropolitan area of Sao Paulo State but subsequently spread to involve all states. The highest age-specific incidence rates were among children younger than 1 year (1,577 per 100,000), young adults ages 20 to 29 years (539 per 100,000), and children ages 1 to 4 years (205 per 100,000). This age distribution was similar throughout Brazil, with 55% of cases occurring among adults ages 20 to 29 years, a cohort born between 1968 and 1977, when the vaccination program was being initiated. Characterization of measles viruses during the outbreak in 1997 identified the D6 genotype. This same genotype was identified in subsequent measles outbreaks in Argentina and Uruguay in 1998 and in Chile, Bolivia, and the Dominican Republic during 1999 to 2001.

The resurgence of measles in Brazil in 1997 led to a nationwide follow-up campaign in 1997 for children ages 6 months to 4 years. A third follow-up campaign was conducted in 2000 for children ages 1 to 4 years. After two follow-up campaigns, measles transmission appears to have been interrupted in Brazil, of 8,358 suspected measles cases reported in 2000, only 36 cases (0.4%) were confirmed. The last recorded measles outbreak, with 15 cases, was in February 2000.

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Measles elimination*  

* Data as of 12 April 2012; 1310 confirmed cases in 2011; 2011 coverage data not yet available  
Source: Country reports to FCH/IM  

Figure 20-10  

Reported measles cases, Latin America and the Caribbean, 1980 to 2011. (Data courtesy of the Immunization Unit, Family and Community Health Area, Pan American Health Organization.)

Mortality reduction strategies

In February 2001, at a meeting hosted by the American Red Cross, a new partnership was formed to advocate for reduction of measles mortality in Africa. Worldwide, during 2000 to the end of 2008, more than 650 million children received measles vaccine through supplementary immunization activities, and global routine immunization coverage with one dose of measles vaccine increased from 71% to 83%. These accelerated control efforts have resulted in a 78% decrease in the estimated number of measles deaths worldwide by the end of 2008, thereby surpassing the 2005 global goal of a 50% reduction.

The current global goal set for 2015 is to reduce measles deaths by 95% compared with 2000 levels. Based on the success of implementing the PAHO strategy in other regions of the world, a schedule that offers at least two doses of measles vaccine delivered either through routine services or mass campaigns has become the standard of care in all countries regardless of development status or routine vaccination coverage (see Table 20-10).

Measles eradication

The feasibility of measles eradication has been debated for many years. Hopkins and colleagues have proposed global measles eradication and pointed out both the similarities and differences between measles and smallpox. Measles will be
substantially more difficult to eradicate than smallpox because of its higher contagiousness, younger median age at infection, and older age at which vaccine is effective.\textsuperscript{975}

As of 2010, five of six WHO regions have established target dates for measles elimination (the Americas by 2000, Europe and the Eastern Mediterranean initially by 2010 and revised to 2015, the Western Pacific by 2012, and Africa by 2010). The Southeast Asia Region has a measles mortality reduction goal and, in 2009, passed a resolution urging member states to eliminate measles, with a target date to be established later. The Region of the Americas stopped endemic measles transmission in November 2002 and is the first region to be free of endemic measles for over 8 years. At the global level, measles control targets have been set for 2015 to increase measles immunization coverage to greater than or equal to 90\% at the national level and greater than or equal to 80\% in every district, to decrease the incidence of measles to less than five cases per million, and to reduce measles deaths by 95\% compared with 2000 levels.\textsuperscript{971}

In July 2010, the WHO convened a global technical consultation to review the feasibility of measles eradication.\textsuperscript{977} There was a comprehensive review of the biologic, programmatic, vaccine supply, economic, and health systems aspects of measles eradication compared with mortality reduction targets. An epidemiologic and economic evaluation based on data collected in Bangladesh, Brazil, Colombia, Ethiopia, Tajikistan, and Uganda found that measles eradication by 2020 was the most cost-effective measles control option both in the six countries and globally, and it would cost an additional discounted $7.8 billion.\textsuperscript{978} The report from the global technical consultation was reviewed and discussed by the Strategic Advisory Group of Experts in November 2010. They agreed that eradication of measles is technically and biologically feasible and recommended measurable progress towards existing regional elimination targets before establishing a target date for global eradication.\textsuperscript{973}

Available evidence indicates measles meets the criteria for a disease that can be eradicated: (1) there is no animal or environmental reservoir, and humans are critical to maintaining transmission; (2) accurate diagnostic tests are available; (3) measles vaccine and existing vaccination strategies are effective and safe; and (4) measles transmission has been interrupted in a large geographic area (eg, nationwide) for a prolonged period of time.\textsuperscript{979} Major challenges to global measles eradication will include (1) increasing urbanization and population density that will require very high vaccination coverage, (2) war and civil unrest, (3) the frequency of international travel and forced migrations that facilitate importations of measles, and (4) the HIV epidemic, which may reduce the effectiveness of measles vaccination and increase the transmissibility of measles.\textsuperscript{762}

Other potential impediments are lack of political will, risk of unsafe injections, and the possibility of sustained transmission among adults.

To address these challenges, research is ongoing to improve diagnostic tests for measles by using filter paper blood spots\textsuperscript{295,296} and oral fluid\textsuperscript{286} and to develop alternative routes for administration of existing measles vaccines (eg, aerosol vaccination\textsuperscript{432–435}), needle-free jet injectors to reduce the risk of unsafe injections, and new candidate vaccines that could be administered in the presence of maternal antibodies \textsuperscript{774} or by using alternative routes.\textsuperscript{774} In addition, disease surveillance and program monitoring are being strengthened to learn from recent field experience with measles mortality reduction and regional elimination activities. These efforts provide optimism that, in the future, the goal of global measles eradication may be achieved.

\section*{Acknowledgment}

Prior versions of this chapter were authored by Stephen Preblud, Samuel Katz, Lauri Markowitz, and Stephen Redd. Substantial sections of this chapter were taken from their previous work.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure20-11.png}
\caption{Reported measles cases and reported measles deaths, seven southern African countries, 1980 to 2010. (Data courtesy of the African Regional Office of World Health Organization.)}
\end{figure}


