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211 Measles (Rubeola)

TABLE 210-3 Recommendations for Poliovirus Vaccination of Adults

1. Most adults in the United States have little risk for exposure to polioviruses, and most are immune as a result of vaccination during childhood. Vaccination with IPV is recommended for those at greater risk for exposure to polioviruses than the general population: a. travelers to areas or countries where polio is epidemic or endemic; b. laboratory workers who handle specimens that might contain polioviruses; c. health care workers or other caregivers who have close contact with patients who might be excreting wild-type polioviruses; and d. adults who are identified by public health authorities as being part of a group or population at increased risk because of an outbreak.
2. Adults who are unvaccinated or whose vaccination status is unknown and who are at increased risk should receive three doses of IPV. Two doses of IPV should be administered at intervals of 4–8 weeks; a third dose should be administered 6–12 months after the second.
3. Adults who have had a primary series of polio vaccine and who are at increased risk should receive another dose of IPV. Currently, data do not indicate a need for more than a single lifetime booster dose with IPV for adults. Abbreviation: IPV, inactivated poliovirus vaccine. Source: From https://www.cdc.gov/vaccines/vpd/polio/hcp/recommendations.html. As the frequency of wild-type polio declines and reports of polio asso ciated with circulating VDPV increase, the World Health Organization is investigating whether IPV can be produced from OPV strains that require less biocontainment, ultimately replacing OPV. OPV and IPV induce antibodies that persist for at least 5 years. Both vaccines induce IgG and IgA antibodies. Compared with recipients of IPV, recipients of OPV shed less virus and less frequently develop reinfection with wild-type virus after exposure to poliovirus. Although IPV is safe and efficacious, OPV offers the advantages of ease of admin istration, lower cost, and induction of intestinal immunity resulting in a reduction in the risk of community transmission of wild-type virus. Because of progress toward global eradication of polio and the contin ued occurrence of cases of vaccine-associated polio, an all-IPV regi men was recommended in 2000 for childhood poliovirus vaccination in the United States, with vaccine administration at 2, 4, and 6–18 months and 4–6 years of age. The risk of vaccine-associated polio should be discussed before OPV is administered. Recommendations for vaccina tion of adults are listed in Table 210-3. PART 5 Infectious Diseases There are concerns about discontinuing vaccination in the event that endemic spread of poliovirus is eliminated. Among the reasons for these concerns are that poliovirus is shed from some immunocom promised persons for >25 years, that vaccine-derived poliovirus can circulate

and cause disease, and that wild-type poliovirus is present in research laboratories and vaccine manufacturing facilities. Antivirals and monoclonal antibodies are in development to reduce or terminate shedding of poliovirus by long-term virus excretors. Pocapavir was shown to reduce shedding of OPV type 1 in a clinical trial, but rapid development of resistance with virus transmission, despite reduced shedding, indicates that combination therapy with other antivirals and/ or monoclonal antibodies will be needed. PARECHOVIRUSES Human parechoviruses (HPeVs), like enteroviruses, are members of the family Picornaviridae. The 19 serotypes of HPeV commonly cause infections in early childhood. Infections with HPeV type 1 (HPeV-1) occur throughout the year, while other parechovirus infections occur more commonly in summer and fall. Infections with HPeVs present similarly to those due to enteroviruses and may cause generalized disease of the newborn, aseptic meningitis, encephalitis, seizures, paralysis, exanthems, respiratory tract disease, rash, hepatitis, and gas troenteritis. While HPeV-1 is the most common serotype and generally causes mild disease, deaths of infants in the United States have been associated with HPeV-1, HPeV-3, and HPeV-6. HPeVs can be isolated from the same sites as enteroviruses, including the nasopharynx, stool, and respiratory tract secretions. PCR using pan-enterovirus primers does not detect HPeVs, and while PCR assays are performed by the

CDC and research laboratories, many commercial laboratories do not perform the test. REOVIRUSES Reoviruses are double-stranded RNA viruses encompassing three sero types. Serologic studies indicate that most humans are infected with reoviruses during childhood. Most infections either are asymptomatic or cause mild upper respiratory tract symptoms. Reovirus is consid ered a rare cause of mild gastroenteritis or meningitis in infants and children. Speculation regarding an association of reovirus type 3 with idiopathic neonatal hepatitis and extrahepatic biliary atresia is based on an elevated prevalence of antibody to reovirus in some affected patients and the detection of viral RNA by PCR in hepatobiliary tissues in some studies. Orthoreoviruses have been associated with human disease—e.g., Melaka and Kampar viruses with fever and acute respi ratory disease in Malaysia and Nelson Bay virus with acute respiratory disease in a traveler from Bali. ■ ■FURTHER READING Lee SE et al: Progress toward poliomyelitis eradication – Worldwide, January 2021–March 2023. MMWR Morb Mortal Wkly Rep 72:517, 2023. Link-Gelles R et al: Public health response to a case of paralytic poliomyelitis in an unvaccinated person and detection of poliovirus in wastewater - New York, June–August 2022. Morb Mortal Wkly Rep 19;1065, 2022. Ma KC et al: Increase in acute respiratory illnesses among children and adolescents associated with rhinoviruses and enteroviruses, including enteroviris D68–United States, July–September 2022. MMWR Morb Mortal Wkly Rep 71:1265, 2022. Pallansch MA: Circulating poliovirus in New York—new instance of an old problem. N Engl J Med 387:1725, 2022. Tomatis Souverbielle C et al: Update on nonpolio enterovirus and parechovirus infections in neonates and young infants. Curr Opin Pediatr 35:380, 2023. Alex C. Kong, William J. Moss

Measles (Rubeola) ■ ■DEFINITION Measles is a highly contagious viral disease characterized by a pro dromal illness of fever, cough, coryza, and conjunctivitis followed by the appearance of a generalized maculopapular rash. Before the wide spread use of measles vaccines, it was estimated that measles caused

> 2 million deaths worldwide each year. ■ ■GLOBAL CONSIDERATIONS Remarkable progress has been made in reducing global measles incidence and mortality rates through measles vaccination. In the Americas, intensive vaccination and surveillance efforts—based in part on the successful Pan American Health Organization strategy of periodic nationwide measles vaccination campaigns (supplementary immunization activities [SIAs])—and high levels of routine measles vaccine coverage interrupted endemic transmission of measles virus. The World Health Organization's (WHO's) Region of the Americas was declared to have eliminated measles in September 2016—the first region in the world to do so. However, endemic measles virus trans mission was reestablished, and the region lost its measles elimination status. As such, no WHO region has achieved and sustained measles elimination status, highlighting the importance of maintaining high measles vaccination coverage.

In the United States, high-level coverage with two doses of measles vaccine eliminated endemic measles virus transmission in 2000. How ever, imported cases and low measles vaccine coverage in some com munities threaten this goal. The 1274 measles cases reported in the United States in 2019 represent the highest count since 1992. Histori cally low levels of measles cases were reported early after the COVID-19 pandemic began but were not sustained, with resurgence of measles globally and in the United States. Progress also has been made in reducing measles incidence and mortality rates in sub-Saharan Africa and Asia because of increasing routine measles vaccine coverage and provision of a second dose of measles vaccine through mass measles vaccination campaigns and routine childhood immunization programs. From 2000 to 2022, the estimated annual number of global measles deaths per year decreased 82%, from 772,854 (95% confidence interval [CI]: 580,969−1,064,580) to 136,216 (95% CI: 97,058−190,234). Measles vaccination prevented an estimated 57.2 million deaths over this period. Despite this progress, the fact that >100,000 children die each year from a preventable disease such as measles attests to the need for greater resources and efforts to identify and reach unvaccinated children. The COVID-19 pandemic caused severe disruptions to immuniza tion activities, further threatening progress toward measles control and elimination. Almost 40 million children were estimated to have missed a dose of measles vaccine in 2021, including 25 million children who missed their first dose. Large-scale measles outbreaks occurred in 22 countries in 2021 and 37 countries in 2022. Over the same period, the estimated number of measles cases and deaths increased by 18% and 43%, respectively. The Measles and Rubella Partnership (MRP)—formerly the Measles and Rubella Initiative (MRI)—is working to improve immunization coverage and address setbacks caused by the pandemic. Since its incep tion in 2001, MRI has played an important role in reducing global measles incidence and mortality rates, providing governments and communities in 88 countries with technical and financial support for routine immunization activities, mass vaccination campaigns, and dis ease surveillance systems. In 2023, MRI was rebranded as MRP, and the partnership that had historically been led by the American Red Cross, the United Nations Foundation, UNICEF, and the U.S. Centers for Disease Control and Prevention (CDC) expanded to formally include longtime partners Gavi, the Vaccine Alliance and the Bill and Melinda Gates Foundation as core partners. ■ ■ETIOLOGY Measles virus is a spherical, nonsegmented, single-stranded, negativesense RNA virus and a member of the Morbillivirus genus in the family

Paramyxoviridae. Measles was originally a zoonotic infection, arising from animal-to-human transmission of an ancestral morbillivirus thousands of years ago, when human populations attained sufficient size to sustain virus transmission. Although RNA viruses typically have high mutation rates, measles virus is an antigenically monotypic virus, i.e., the surface proteins responsible for inducing protective immunity retained their antigenic structure across time and distance because of their key role in binding cellular receptors. The public health signifi cance of this stability is that measles vaccines developed decades ago from a single strain of measles virus remain protective worldwide. Both wild-type and attenuated measles viruses are inactivated by ultraviolet light and heat, necessitating a cold chain for vaccine transport and storage. ■ ■EPIDEMIOLOGY Measles virus is one of the most highly contagious directly transmit ted pathogens. Outbreaks can occur in populations in which <10% of persons are susceptible. Chains of transmission are common among household contacts, school-age children, and health care workers. There are no latent or persistent measles virus infections that result in a prolonged infectious period, nor are there animal reservoirs for the virus. Thus, measles virus can be maintained in human populations only by an unbroken chain of acute infections, which requires a contin uous supply of susceptible individuals. Newborns become susceptible

to measles virus infection when passively acquired maternal antibodies are lost, generally before 6–9 months of age. When not immunized, these infants account for the bulk of new susceptible individuals that sustain measles virus transmission.

Endemic measles has a typical temporal pattern characterized by yearly seasonal epidemics superimposed on longer epidemic cycles of 2–5 years or more. In temperate climates, annual measles outbreaks typically occur in the late winter and early spring. These annual out breaks are probably attributable to social networks facilitating trans mission (e.g., congregation of children at school) and environmental factors favoring the viability and transmission of measles virus. Measles cases continue to occur during interepidemic periods in large popula tions but at low incidence. The longer epidemic cycles occurring every several years result from the accumulation of susceptible persons over successive birth cohorts and the subsequent decline in the number of susceptibles following an outbreak. Secondary attack rates among susceptible household and institu tional contacts generally exceed 90%. The average age at which measles occurs depends on rates of contact with infected persons, protective maternal antibody decline, and vaccine coverage. In densely popu lated urban settings with low-level vaccination coverage, measles is a disease of infants and young children. The cumulative incidence can reach 50% by 1 year of age, with a significant proportion of children acquiring measles before 9 months—the age at which the first of two routine vaccine doses are administered in many countries, in line with the schedule recommended by the WHO’s Expanded Programme on Immunization. As measles vaccine coverage increases or population density decreases, the age distribution shifts toward older children. In such situations, measles cases predominate in school-age children. Infants and young children, although susceptible if not protected by maternal antibodies or vaccination, are not exposed to measles virus at a rate sufficient to cause a heavy disease burden in this age group. As vaccination coverage increases further, the age distribution of cases may be shifted into adolescence and adulthood. This distribution is seen in measles outbreaks in the United States and necessitates targeted measles vaccination programs for these older age groups. Some coun tries have a bimodal distribution, with measles cases predominantly in young infants and adults. CHAPTER 211 Measles (Rubeola) Persons with measles are infectious for several days before and after the onset

of rash, when levels of measles virus in blood and body fluids are highest and when cough, coryza, and sneezing that facilitate virus spread are most severe. The contagiousness of measles before the onset of recognizable disease hinders the effectiveness of isolation measures. Medical settings are well-recognized sites of measles virus trans mission. Children may present to health care facilities during the prodrome, when the diagnosis is not obvious, although the child is infectious and is likely to infect susceptible contacts. Susceptible health care workers can acquire measles from infected children and transmit measles virus to others. Nosocomial transmission can be reduced by maintenance of a high index of clinical suspicion particularly during outbreaks, use of appropriate isolation precautions when measles is suspected, administration of measles vaccine to susceptible children and health care workers, and documentation of health care workers' immunity to measles (i.e., proof of receipt of two doses of measles vaccine or detection of IgG antibodies to measles virus). As efforts at measles control are increasingly successful, public per ceptions of the risk of measles diminish and may be replaced by con cerns about possible adverse events associated with measles vaccine. Consequently, measles outbreaks have occurred because of opposition to vaccination on religious or philosophical grounds or unfounded fears of serious adverse events (see "Active Immunization," below, and Chap. 3). ■ ■PATHOGENESIS Measles virus is transmitted primarily by respiratory droplets over short distances and, less commonly, by small-particle aerosols that remain suspended in the air for long periods. Airborne transmission appears to be important in certain settings, including schools, physicians' offices, hospitals, and enclosed public places. The virus can

be transmitted by direct contact with infected secretions but does not survive for long on fomites.

The incubation period for measles is ~10 days to fever onset and 14 days to rash onset. This period may be shorter in infants and longer (up to 3 weeks) in adults. Infection is initiated when measles virus is deposited in the respiratory tract, oropharynx, or conjunctivae (Fig. 211-1A). During the first 2–4 days after infection, measles virus proliferates locally in the respiratory mucosa, primarily in dendritic cells and lymphocytes, and spreads to draining lymph nodes. Virus then enters the bloodstream by budding from infected lymphocytes, producing the viremia that disseminates infection throughout the body. Replication of measles virus in the target organs, together with the host's immune response, are responsible for the signs and symp toms of measles that occur 8–12 days after infection and mark the end of the incubation period (Fig. 211-1B). Thymus Liver Skin Virus titer (pfu) Severity of clinical symptoms Lung Respiratory epithelium Local lymph nodes Blood Spleen Lymphatic tissue PART 5 Infectious Diseases

A Days after infection Rash Conjunctivitis Cough Fever Koplik's spots Koplik's spots

B Days after infection CD4+ T cells Immune suppression CD8+ T cells IgM IgG Immune response

Days after infection C FIGURE 211-1 Measles virus infection: pathogenesis, clinical features, and immune responses. A. Spread of measles virus, from initial infection of the respiratory tract through dissemination to the skin. B. Appearance of clinical signs and symptoms, including Koplik's spots and rash. C. Antibody and T-cell responses to measles virus. The signs and symptoms of measles arise coincident with the host immune response. (Reproduced with permission from WJ Moss and DE Griffin: Global measles elimination. Nat Rev Microbiology 4:900, 2006.)

■ ■IMMUNE RESPONSES Host immune responses to measles virus are essential for viral clearance, clinical recovery, and the establishment of long-term protective immunity (Fig. 211-1C). Early nonspecific (innate) immune responses during the prodromal phase include activation of natural killer cells and increased production of antiviral proteins. The adaptive immune responses consist of measles virus–specific antibody and cellular responses. The protective efficacy of antibodies to measles virus is illustrated by the immunity conferred to infants from passively acquired maternal antibodies and the protection of exposed, susceptible individuals after administration of anti–measles virus immunoglobulin. The first measles virus–specific antibodies produced after infection are of the IgM subtype, with a sub sequent switch to predominantly IgG1 and IgG3 isotypes. The IgM anti body response is typically absent following reexposure or revaccination and serves as a marker of primary infection. The importance of cellular immunity to measles virus is demon strated by the ability of children with agammaglobulinemia (congenital inability to produce antibodies) to recover fully from measles and the contrasting picture for children with severe defects in T lymphocyte function who often develop severe or fatal disease (Chap. 362). The initial predominant TH1 response (characterized by interferon-γ) is essential for viral clearance, and the later TH2 response (characterized by interleukin-4) promotes the development of measles virus–specific antibodies that are critical for protection against reinfection. The duration of protective immunity following wild-type measles virus infection is generally thought to be lifelong. Immunologic mem ory to measles virus includes both continued production of measles virus–specific antibodies by long-lived plasma cells and memory B cells as well as circulation of measles virus–specific CD4+ and CD8+ T lymphocytes. However, the intense immune responses induced by measles virus infection are paradoxically associated with depressed responses to unrelated (non–measles virus) antigens. This state of immunosuppres sion persists for at least several weeks to months beyond resolution of the acute illness, enhances susceptibility to secondary infections with bacteria and viruses that cause pneumonia and diarrhea, and is thus responsible for a substantial proportion of measles-related morbidity and deaths. Delayed-type hypersensitivity responses to recall antigens, such as tuberculin, are suppressed, and cellular and humoral responses to new antigens are impaired. Reactivation of latent tuberculosis and remission of autoimmune diseases after measles have been described and are attributed to this period of immune suppression. Importantly, measles results in reductions in the magnitude and diversity of anti bodies against previously encountered viral and bacterial antigens, impairing immunologic memory. This mechanism may explain why child morbidity and mortality due to other infectious diseases may be increased for >2 years after measles. APPROACH TO THE PATIENT Measles Clinicians should consider measles in persons presenting with fever and generalized erythematous rash, particularly when measles virus is known to be circulating or the patient has a history of travel to endemic areas. Appropriate precautions must be taken to prevent nosocomial transmission. The diagnosis requires laboratory confirmation except during large outbreaks in which an epidemiologic link to a confirmed case can be established. Care is largely supportive and consists of the administration of vitamin A and antibiotics for secondary bacterial infections (see “Treatment,” below). Complications of measles, including bacterial infections and encephalitis, may occur after acute illness and require careful monitoring, particularly in immunocompromised persons. ■ ■CLINICAL MANIFESTATIONS In most persons, the signs and symptoms of measles are highly char acteristic (Fig. 211-1B). Fever and malaise beginning ~10 days after exposure are followed by cough, coryza, and conjunctivitis. These

signs and symptoms increase in severity over 4 days. Koplik's spots (see Fig. A1-2) develop on the buccal mucosa ~2 days before the rash appears. Koplik's spots are pathognomonic of measles and consist of bluish white dots ~1 mm in diameter surrounded by erythema. The lesions appear first on the buccal mucosa opposite the lower molars but rapidly increase in number and may involve the entire buccal mucosa. They fade with the onset of rash. The characteristic rash of measles (see Fig. A1-3) begins 2 weeks after infection, when the clinical manifestations are most severe, and signal the host's immune response to the replicating virus. Headache, abdominal pain, vomiting, diarrhea, and myalgia may be present. The rash of measles begins as erythematous macules behind the ears and on the neck and hairline. The rash progresses to involve the face, trunk, and arms, with involvement of the legs and feet by the end of the second day. Areas of confluent rash appear on the trunk and extremi ties, and petechiae may be present. The rash fades slowly in the same order of progression as it appeared, usually beginning on the third or fourth day after onset. Resolution of the rash may be followed by des quamation, particularly in undernourished children. Because the characteristic rash of measles is a consequence of the cellular immune response, it may not develop in persons with impaired cellular immunity. These persons have a high case–fatality rate and fre quently develop giant cell pneumonitis caused by measles virus. ■ ■DIFFERENTIAL DIAGNOSIS The differential diagnosis of measles includes other causes of fever, morbilliform rash, and conjunctivitis, including rubella, Kawasaki dis ease, infectious mononucleosis, roseola, scarlet fever, Rocky Mountain spotted fever, enterovirus or adenovirus infection, and drug sensitivity. Rubella is a milder illness without cough and with distinctive posterior auricular or suboccipital lymphadenopathy. The rash of roseola (exan them subitum) (see Fig. A1-5) appears after fever has subsided. The atypical lymphocytosis in infectious mononucleosis contrasts with the leukopenia commonly observed in children with measles. ■ ■DIAGNOSIS Measles is readily diagnosed on clinical grounds by clinicians famil iar with the disease, particularly during outbreaks. Koplik's spots are especially helpful because they appear early and are pathognomonic. Clinical diagnosis is more difficult (1) during the prodromal illness;

(2) when the rash is attenuated by passively acquired antibodies or prior immunization; (3) when the rash is absent or delayed in immu nocompromised children or severely undernourished children with impaired cellular immunity; and (4) in regions where the incidence of measles is low and other pathogens are responsible for most illnesses with fever and rash. The CDC case definition for measles requires (1) a generalized maculopapular rash of at least 3 days' duration; (2) fever of at least 38.3°C (101°F); and (3) cough, coryza, or conjunctivitis. Serology is the most common method of laboratory diagnosis. The detection of measles virus–specific IgM in a single specimen of serum or oral fluid is considered diagnostic of acute infection, as is a four fold or greater increase in measles virus–specific IgG antibody levels between acute- and convalescent-phase serum specimens. Primary infection in the immunocompetent host results in antibodies that are often detectable within 1–3 days of rash onset and reach peak levels in 2–4 weeks. However, measles virus–specific IgM antibodies may not be detectable until 4–5 days or more after rash onset, resulting in falsenegative test results if the specimen is obtained too early, and usually fall to undetectable levels within 4–8 weeks of rash onset. Several methods for measurement of antibodies to measles virus are available. Neutralization tests are sensitive and specific, and the results are highly correlated with protective immunity. However, these tests require propagation of measles virus in cell culture and thus are expensive and laborious. Commercially available measles IgM enzyme immunoassays are most frequently used. Measles can also be diagnosed by isolation of the virus in cell culture from respiratory secretions, nasopharyngeal or conjunctival swabs,

blood, or urine. Direct detection of giant cells in respiratory secretions, urine, or tissue obtained by biopsy provides another method of diagnosis.

For detection of measles virus RNA by reverse-transcription poly merase chain reaction, primers targeted to highly conserved regions of measles virus genes are used. Extremely sensitive and specific, this assay may also permit identification and characterization of measles virus genotypes for molecular epidemiologic studies and can distin guish wild-type from vaccine virus strains.

TREATMENT Measles There is no specific antiviral therapy for measles. Treatment con sists of general supportive measures such as hydration and adminis tration of antipyretic agents. Because secondary bacterial infections are a major cause of morbidity and death attributable to measles, effective case management involves prompt antibiotic treatment for patients who have clinical evidence of bacterial infection, including pneumonia and otitis media. Vitamin A (available in oral and parenteral formulations) is effective for the treatment of measles and can markedly reduce rates of morbidity and mortality. The WHO recommends administration of once-daily oral doses of 200,000 IU of vitamin A for 2 consecu tive days to all children with measles who are ≥12 months of age. Lower doses are recommended for younger children: 100,000 IU per day for children 6–11 months of age and 50,000 IU per day for children <6 months old. A third dose is recommended 2–6 weeks later for children with evidence of vitamin A deficiency. While such deficiency is not a widely recognized problem in the United States, many American children with measles do, in fact, have low serum levels of vitamin A, and these children experience increased measles-associated morbidity. CHAPTER 211 Anecdotal reports have described the recovery of previously healthy pregnant and immunocompromised patients with measles pneumonia and of immunocompromised patients with measles encephalitis after treatment with aerosolized and IV ribavirin. However, the clinical benefits of ribavirin in measles have not been conclusively demonstrated in clinical trials. Measles (Rubeola) ■ ■COMPLICATIONS Most complications of measles involve the respiratory tract and include the effects of measles virus itself and secondary bacterial infections. Giant cell pneumonitis due to replication of measles virus in the lungs can develop in immunocompromised persons. Acute laryngotracheo bronchitis (croup) can occur during measles and may result in airway obstruction, particularly in young children. Many children with mea sles develop diarrhea, which contributes to and can exacerbate existing undernutrition. Most complications of measles result from secondary bacterial infections of the respiratory tract that are attributable to a state of immune suppression after acute measles. Otitis media and broncho pneumonia are most common. Recurrence of fever or failure of fever to subside with the rash suggests secondary bacterial infection. Severe complications of measles involve the central nervous system (CNS). Post-measles encephalomyelitis complicates ~1 in 1000 cases, affecting mainly older children and adults. Encephalomyelitis occurs within 2 weeks of rash onset and is characterized by fever, seizures, and a variety of neurologic abnormalities. The finding of periventricular demyelination, the induction of immune responses to myelin basic protein, and the absence of measles virus in the brain suggest that postmeasles encephalomyelitis is an autoimmune disorder triggered by measles virus infection. Rarer CNS complications that occur months to years after acute infection are measles inclusion body encephalitis (MIBE) and subacute sclerosing panencephalitis (SSPE). In contrast to post-measles encephalomyelitis, MIBE and SSPE are caused by per sistent measles virus infection. MIBE is a rare but fatal complication that affects individuals with defective cellular immunity and typically occurs months after infection. SSPE is a slowly progressive disease characterized by seizures and progressive deterioration of cognitive and motor functions, with death occurring 5–15

years after measles

virus infection. SSPE most often develops in persons infected with measles virus at <2 years of age.

■ ■PROGNOSIS Most persons with measles recover and develop long-term protective immunity to reinfection. Measles case–fatality proportions vary with the average age of infection, the nutritional and immunologic status of the population, measles vaccine coverage, and access to health care. Among previously vaccinated persons who do become infected, disease is less severe and mortality rates are significantly lower. In most developed countries, the case–fatality rate is 0.01–0.1%, but in endemic areas of sub-Saharan Africa, the measles case–fatality rate may be 5–10% or even higher. Measles is a major cause of childhood deaths in refugee camps and in internally displaced populations, where case–fatality rates have been as high as 20–30%. ■ ■PREVENTION Passive Immunization Human immunoglobulin given shortly after exposure can attenuate the clinical course of measles. In immu nocompetent persons, administration of immunoglobulin within 72 h of exposure usually prevents measles virus infection and almost always prevents clinical measles. Administered up to 6 days after exposure, immunoglobulin will still prevent or modify the disease. Prophylaxis with immunoglobulin is recommended for susceptible household and nosocomial contacts who are at risk of developing severe measles, particularly children <1 year of age, immunocompromised persons (including immunocompromised persons living with HIV who were previously immunized with live attenuated measles vaccine), and pregnant women. Except for premature infants, children <6 months of age usually will be partially or completely protected by passively acquired maternal antibody. Infants born to women with vaccineinduced measles immunity become susceptible to measles at a younger age than infants born to women with acquired immunity from natural infection. If measles is diagnosed in a household member, all unimmu nized children in the household should receive immunoglobulin. The recommended dose is 0.5 mL/kg given intramuscularly with a maxi mum total dose of 15 mL. Immunocompromised and pregnant persons should receive 400 mg/kg intravenously. IV immunoglobulin contains antibodies to measles virus, and the usual dose of 100–400 mg/kg gen erally provides adequate prophylaxis for measles exposures occurring as long as 3 weeks or more after IV immunoglobulin administration. PART 5 Infectious Diseases Active Immunization The first live attenuated measles vaccine was developed by passage of the Edmonston strain in chick embryo fibroblasts to produce the Edmonston B virus, which was licensed in 1963 in the United States but was reactogenic. Further passage of Edmonston B virus produced the more attenuated and less reactogenic Schwarz vaccine. The Moraten (“more attenuated Enders”) strain, which was licensed in 1968 and is used in the United States, is geneti cally identical to the Schwarz strain. The Edmonston-Zagreb vaccine, also derived from the Edmonston B strain, is widely used in many countries and was passaged in human diploid cells. Lyophilized measles vaccines are relatively stable, but reconstituted vaccine rapidly loses potency. Live attenuated measles vaccines are inactivated by light and heat and lose about half their potency at 20°C and almost all their potency at 37°C within 1 h after reconstitution. Therefore, a cold chain must be maintained before and after reconsti tution. Antibodies first appear 12–15 days after vaccination, and titers peak at 1–3 months. Measles vaccines are often combined with other live attenuated virus vaccines, such as those for mumps and rubella (MMR) and for mumps, rubella, and varicella (MMRV). The recommended age of first vaccination varies from 6 to 15 months and represents a balance between the optimal age for seroconversion and the probability of acquiring measles before that age. The propor tions of

children who develop protective levels of antibody after the first measles vaccination approximate 85% at 9 months of age and 95% at 12 months. Common childhood illnesses concomitant with vac cination may reduce the level of immune response, but such illnesses are not valid reasons to withhold vaccination. Measles vaccines have

been well tolerated and immunogenic in children and adults living with HIV, although antibody levels may wane more rapidly. Because of the potential severity of wild-type measles virus infection in children living with HIV, routine measles vaccination is recommended except for those who are severely immunocompromised. Measles vaccination is contraindicated in individuals with other severe deficiencies of cel lular immunity because of the possibility of disease due to progressive pulmonary or CNS infection with the vaccine virus. The duration of vaccine-induced immunity is at least several decades, if not longer. Rates of secondary vaccine failure 10–15 years after immunization have been estimated at ~5% but are likely lower when vaccination takes place after 12 months of age. Decreasing anti body concentrations do not necessarily imply a complete loss of protec tive immunity as a secondary immune response usually develops after reexposure to measles virus, with a rapid rise in antibody titers in the absence of overt clinical disease. Standard doses of currently licensed measles vaccines are safe for immunocompetent children and adults. Fever up to 39.4°C (103°F) occurs in ~5–15% of seronegative vaccine recipients, and ~5% of vaccine recipients develop a transient rash. Mild transient thrombocytopenia has been reported, with an incidence of 1 case per ~40,000 MMR recipients. Since the publication of a report in 1998 falsely hypothesizing that MMR vaccine may cause a syndrome of autism and intestinal inflamma tion, much public attention has focused on this purported association. The events that followed publication of this report led to diminished vac cine coverage in the United Kingdom and provide important lessons in the misinterpretation of epidemiologic evidence and the communication of scientific results to the public. The publication that incited the concern was a case series describing 12 children with a regressive developmental disorder and chronic enterocolitis; 9 of these children had autism. In 8 of the 12 cases, the parents associated onset of the developmental delay with MMR vaccination. This simple temporal association was misinterpreted and misrepresented as a possible causal relationship, first by the lead author of the study and then by elements of the media and the public. Subsequently, many comprehensive reviews and additional epidemiologic studies refuted evidence of a causal relationship between MMR vaccina tion and autism, and the offending publication was retracted. ■ ■PROSPECTS FOR MEASLES ERADICATION Progress in global measles control has renewed discussion of measles eradication. In contrast to poliovirus eradication, the eradication of measles virus will not entail challenges posed by prolonged shedding of potentially virulent vaccine viruses and asymptomatic reservoirs. However, in comparison with smallpox eradication, higher levels of population immunity will be necessary to interrupt measles virus transmission, more highly skilled health care workers will be required to administer measles vaccines, and containment through case detec tion and ring vaccination will be more difficult for measles virus because of infectivity before rash onset. New tools, such as microarray patches (MAPs) to deliver measles vaccine, could facilitate mass vaccination campaigns and vaccination of hard-to-reach children such as those residing in remote rural areas. In May 2023, Micron Biomedical reported positive results in a phase 1/2 clinical trial in The Gambia comparing the results of immuniza tion by measles- and rubella-containing (MR) vaccine administered by MAP versus subcutaneous injection. This trial was the first of its kind to use microarray technology in children and found similar rates of seroconversion in MR vaccine–naïve children (92.9–100% for MAP and 89.7–100% for subcutaneous) and seroprotection in all age groups (93.2–100% for MAP and 89.8–100% for subcutaneous). Further stud ies and the

overcoming of manufacturing and regulatory hurdles will be needed before MAPs become available. Despite enormous progress, measles remains a leading vaccinepreventable cause of childhood mortality worldwide and continues to cause outbreaks in communities with low vaccination coverage rates. As the world looks to rebuild immunization services disrupted by the COVID-19 pandemic and improve these services through the ambi tious MRP agenda, measles outbreaks will continue to remind us of the challenges to be overcome.

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