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Measles

William J. Moss¹, Diane E. Griffin² and W. Harry Feinstone²

¹Department of Epidemiology, International Health and Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
²Department of Molecular Microbiology and Immunology, John Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

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ABSTRACT

Measles is a highly contagious disease characterized by a prodromal illness of fever, cough, coryza, and conjunctivitis followed by the appearance of a generalized maculopapular rash. Measles virus is a nonsegmented, single-stranded, negative-sense RNA virus and a member of the Morbillivirus genus in the family of Paramyxoviridae. Although RNA viruses have high mutation rates, measles virus is an antigenically monotypic virus and the surface proteins responsible for inducing protective immunity have retained their antigenic structure. The public health significance is that measles vaccines developed decades ago from a single measles virus strain remain protective worldwide. Prior to the development and widespread use of measles vaccine, 30 million cases of measles were estimated to occur each year, resulting in more than 1 million deaths. Several live, attenuated measles vaccines are available, either as single-antigen vaccines or in combination with rubella and mumps vaccines (MR and MMR vaccines). Most of the currently used measles vaccines were derived from the Edmonston strain of measles virus that was isolated by Enders and Peebles in 1954.
Measles vaccines are recommended for all susceptible children and adults for whom the vaccine is not contraindicated. Despite progress in reducing measles mortality, measles remains a major cause of vaccine-preventable death and an important cause of morbidity and mortality in children, particularly sub-Saharan Africa and in Asia. The ideal measles vaccine would be inexpensive, safe, heat-stable, immunogenic in neonates or very young infants, and administered as a single dose without needle or syringe. A number of vaccine candidates with some of these characteristics are undergoing preclinical studies, including DNA vaccines and various viral and bacterial vectored vaccines. The high infectivity of measles virus is a characteristic suitable to a biothreat agent. However, increasingly high levels of measles vaccination coverage throughout the world as part of accelerated measles control efforts would protect many from the deliberate use of measles virus as a biothreat agent. Genetic engineering of a measles virus strain that was not neutralized by antibodies induced by the current attenuated measles vaccines would likely have reduced infectivity, as suggested by the fact that wild-type measles viruses have not mutated to alter their neutralizing epitopes. Measles virus meets many of the biological criteria for disease eradication. Measles virus has no nonhuman reservoir, can be accurately diagnosed, and measles vaccination is a highly effective intervention. Where measles virus differs from smallpox and polio viruses is that it is more highly infectious, necessitating higher levels of population immunity to interrupt transmission. It remains unclear whether the threat from bioterrorism precludes stopping measles vaccination after eradication, but provision of a second opportunity for measles vaccination likely could be stopped following eradication.

INTRODUCTION

Measles is a highly contagious disease characterized by a prodromal illness of fever, cough, coryza, and conjunctivitis followed by the appearance of a generalized maculopapular rash. Deaths from measles are due largely to an increased susceptibility to secondary bacterial and viral infections, attributed to a prolonged state of immune suppression. Despite the development of an effective attenuated vaccine, measles remains a leading vaccine-preventable cause of childhood mortality worldwide, particularly sub-Saharan Africa and in Asia, and continues to cause outbreaks in communities with low vaccination coverage rates in industrialized nations.

HISTORY OF MEASLES

Measles is one of the most important infectious diseases of humans and has caused millions of deaths
since its emergence thousands of years ago. Measles virus most closely resembles rinderpest virus, a pathogen of cattle, and likely evolved as a zoonotic infection in communities where cattle and humans lived in close proximity. Measles virus is believed to have become established in human populations about 5000–10,000 years ago when human populations achieved sufficient size in Middle Eastern river valley civilizations to maintain virus transmission.

Abu Becr, an Arab physician also known as Rhazes, is generally credited with distinguishing smallpox from measles in the 9th century. He dated the first description of measles to the 6th century. However, epidemics identified as measles were not recorded until the 11th and 12th centuries, and measles was first mentioned as a childhood disease in 1224. The name “morbilli” was derived from the Italian meaning “little diseases” to distinguish it from plague, “il morbo.” Sanvages in 1763 defined morbilli as measles, but called it rubeola, leading to confusion with rubella.

Introduction of measles into previously unexposed populations has been associated with high mortality. One quarter of the population on the Fiji Islands died after the introduction of measles virus in 1875. Millions died as a result of European exploration of the New World, largely due to the introduction of diseases such as smallpox and measles into native Amerindian populations. The high mortality from these diseases facilitated European conquest of the Americas (McNeill, 1976).

Many of the basic principles of measles epidemiology and infection were elucidated by Peter Panum, a Danish physician who was sent to the Faroe Islands in 1846 during a large measles epidemic (Panum, 1938). Panum deduced the highly contagious nature of the disease, the 14-day incubation period, the lifelong immunity following infection, and postulated a respiratory route of transmission. Measles virus first was isolated from the blood of David Edmonston and others by Enders and Peebles (1954). The development of vaccines against measles soon followed.

### MEASLES VIRUS

Measles virus is a spherical, nonsegmented, single-stranded, negative-sense RNA virus and a member of the *Morbillivirus* genus in the family of Paramyxoviridae. Other members of the *Morbillivirus* genus are rinderpest virus and canine distemper virus. Although RNA viruses have high mutation rates, measles virus is an antigenically monotypic virus, meaning that the surface proteins responsible for inducing protective immunity have retained their antigenic structure. The public health significance is that measles vaccines developed decades ago from a single measles virus strain remain protective worldwide. Measles virus is killed by ultraviolet light and heat. Attenuated measles vaccine viruses retain these characteristics, necessitating a cold chain for transportation and storage.

The measles virus RNA genome consists of approximately 16,000 nucleotides and is enclosed in a lipid-containing envelope derived from the host cell. The genome encodes eight proteins, two of which (V and C) are nonstructural proteins and are transcribed from the phosphoprotein (P) gene. Of the six structural proteins, P, large protein (L), and nucleoprotein (N) form the nucleocapsid housing the viral RNA. The hemagglutinin protein (H), fusion protein (F), and matrix protein (M), together with lipids from the host cell membrane, form the viral envelope.

The H protein interacts with F to mediate fusion of the viral envelope with the host cell membrane (Malvoisin and Wild, 1993). The primary function of the H protein is to bind to the host cellular receptors for measles virus. The two identified receptors are CD46 and CD150 (SLAM). CD46 is a complement regulatory molecule expressed on all nucleated cells in humans. SLAM, an acronym for signaling lymphocyte activation molecule, is expressed on activated T and B lymphocytes and antigen-presenting cells. The binding sites on H for these receptors overlap and strains of measles virus differ in the efficiency with which each is used. Wild-type measles virus binds to cells primarily through the cellular receptor SLAM whereas most vaccine strains bind to CD46; however, most measles virus strains can use both CD46 and SLAM as receptors during acute infection (Schneider et al., 2002). Additional, as yet unidentified receptors for measles virus exist on human endothelial and epithelial cells (Andres et al., 2003).

Other measles virus proteins are involved in viral replication. The P protein regulates transcription, replication, and the efficiency with which the N assembles into nucleocapsids (Spahner et al., 1997). The M protein links ribonucleoproteins with envelope proteins during virion assembly. The functions of V and C proteins have not been clearly defined, but both appear to contribute to the virulence of measles virus by regulating transcription and sensitivity to the antiviral effects of interferon (IFN) α/β (Valsamakis et al., 1998; Patterson et al., 2000).

Variability within the genome is sufficient to allow for molecular epidemiologic investigation. Genetic characterization of wild-type measles viruses is based on sequence analysis of the genes encoding the

### III. VIRAL VACCINES
N and H proteins. One of the most variable regions of the measles virus genome is the 450-nucleotide sequence at the carboxy-terminal of the N protein, with up to 12% variability between wild-type viruses. The World Health Organization (WHO) recognizes 8 clades of measles virus (designated A through H) and 23 genotypes (World Health Organization, 2006). New genotypes likely will be identified with enhanced surveillance and molecular characterization. As measles control efforts intensify, molecular surveillance of circulating measles virus strains can be used to document interruption of measles virus transmission and to identify the source and transmission pathways of measles virus outbreaks (Rota and Bellini, 2003). Molecular epidemiologic tools also would be important in documenting deliberate bioterrorist introductions of wild-type or genetically modified measles virus strains.

**Immune Responses to Measles Virus**

Host immune responses to measles virus are essential for viral clearance, clinical recovery, and the establishment of long-term immunity. The early nonspecific (innate) immune responses that occur during the prodromal phase of the illness include activation of natural killer (NK) cells and production of IFN-γ and β. These innate immune responses contribute to the control of measles virus replication before the onset of more specific adaptive immune 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 following administration of antimeasles virus immune globulin (Black and Yannet, 1960). The first measles virus-specific antibodies produced after infection are of the IgM subtype, followed by a switch to predominantly IgG3 and then to IgG1 and IgG4 isotypes (Isa et al., 2002). IgA antibodies to measles virus are found in mucosal secretions. The most abundant and rapidly produced antibodies are against N, and the absence of antibodies to N is the best indicator of seronegativity to measles virus. Antibodies to H and F proteins contribute to virus neutralization and are sufficient to provide protection against measles virus infection.

Evidence for the importance of cellular immunity to measles virus is demonstrated by the ability of children with agammaglobulinemia to fully recover from measles, whereas children with severe defects in T-lymphocyte function often develop severe or fatal disease (Good and Zak, 1956). Monkeys depleted of CD8+ T-lymphocytes and challenged with wild-type measles virus had a more extensive rash, higher measles virus loads, and longer duration of viremia than control animals, further confirming the importance of cellular immunity in measles virus clearance (Permar et al., 2003). CD4+ T-lymphocytes also are activated in response to measles virus infection and secrete cytokines capable of modulating the humoral and cellular immune responses. Plasma cytokine profiles show increased levels of IFN-γ during the acute phase, followed by a shift to high levels of interleukin (IL)-4 and IL-10 during convalescence (Moss et al., 2002). The initial predominant Th1 response (characterized by IFN-γ) is presumed to be essential for viral clearance, while the later Th2 response (characterized by IL-4) promotes the development of measles virus-specific antibodies.

The duration of protective immunity following wild-type measles virus infection is generally thought to be lifelong. The immunologic mechanisms involved in sustaining high levels of neutralizing antibody to measles virus are not completely understood, although general principles of immunologic memory probably govern this process. Immunologic memory to measles virus includes both continued production of measles virus-specific IgG antibodies and the circulation of measles virus-specific CD4+ and CD8+ T-lymphocytes (Ovsyannikova et al., 2003). Although immune protection is assessed by measurement of antimeasles virus antibodies, long lasting cellular immune responses almost certainly play an important role in protection from infection and disease.

Young infants in the first months of life are protected against measles by maternally acquired IgG antibodies. An active transport mechanism in the placenta is responsible for the transfer of IgG antibodies from the maternal circulation to the fetus starting at about 28 weeks gestation and continuing until birth (Crowe, 2001). Three factors determine the degree and duration of protection in the newborn: (1) the level of maternal antimeasles antibodies; (2) the efficiency of placental transfer; and (3) the rate of catabolism in the child. Although providing passive immunity to young infants, maternally acquired antibodies can interfere with the immune responses to the attenuated measles vaccine by inhibiting replication of vaccine virus. In general, maternally acquired antibodies are no longer present in the majority of children by 9 months of age, the time of routine measles vaccination in many countries. Women with vaccine-induced immunity tend to have lower antimeasles virus antibody titers than women with naturally acquired immunity, and their children may be susceptible to measles at an earlier age. 

**III. Viral Vaccines**
EPIDEMIOLOGY

Prior to the development and widespread use of measles vaccine, 30 million cases of measles were estimated to occur each year, resulting in more than 1 million deaths. Despite progress in reducing measles mortality, measles remains the most frequent cause of vaccine-preventable death and an important cause of morbidity and mortality in children, particularly in sub-Saharan Africa and in Asia (Henao-Restrepo et al., 2003).

The disease burden due to measles decreased over the past several decades due to a number of factors. Measles mortality declined in developed countries in association with economic development, improved nutritional status and supportive care, particularly antibiotic therapy for secondary bacterial pneumonia. Remarkable progress in reducing measles incidence and mortality has been, and continues to be, made in resource-poor countries as a consequence of increasing measles vaccine coverage, provision of a second opportunity for measles vaccination through supplementary immunization activities, and efforts by the WHO, the United Nations Children's Fund (UNICEF) and their partners to target 45 countries for accelerated and sustained measles mortality reduction. Specifically, this targeted strategy aims to achieve >90% measles vaccination coverage in every district of the 45 countries and to ensure that all children receive a second opportunity for measles immunization (World Health Organization, 2001). Provision of vitamin A through polio and measles vaccination campaigns has contributed further to the reduction in measles mortality (World Health Organization, 2005).

In 2003, the World Health Assembly endorsed a resolution urging member countries to reduce the number of deaths attributed to measles by 50% by the end of 2005 compared with 1999 estimates. Overall global measles mortality in 2005 was estimated to be 345,000 deaths (uncertainty bounds 247,000 and 458,000 deaths) (Wolfson et al., 2007). This estimate represents a 60% decrease from 1999, when the global number of measles deaths was estimated to be 873,000 (uncertainty bounds 634,000 and 1,140,000 deaths). The largest decrease in measles mortality was in Africa, contributing 72% of the global reduction in measles mortality.

Measles incidence has a typical temporal pattern characterized by annual, seasonal epidemics superimposed upon 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 outbreaks are likely the result of social networks facilitating transmission (e.g., congregation of children at school) and environmental factors favoring the viability and transmission of measles virus (Fine and Clarkson, 1982). Measles cases continue to occur during the interepidemic period in densely populated communities but at low incidence. The longer 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. In the absence of a vaccination program these longer epidemic cycles tend to occur every 2–4 years.

Measles vaccination programs that achieve coverage rates in excess of 80% extend the interepidemic period to 4–8 years by reducing the number of susceptible individuals.

Humans are the only reservoir for measles virus, a characteristic important for the potential eradication of measles. Nonhuman primates may be infected with measles virus and develop an illness similar to measles in humans, with rash, coryza, and conjunctivitis. However, populations of wild monkeys are not of sufficient size to maintain measles virus transmission.

Measles virus is transmitted primarily by respiratory droplets small enough to traverse several feet but too large to remain suspended in the air for long periods of time. The symptoms induced during the prodrome, particularly sneezing and coughing, enhance transmission. Measles virus also may be transmitted by the airborne route, suspended on small particles for a prolonged time. Direct contact with infected secretions can transmit measles virus, but the virus does not survive long on fomites as it is quickly killed by heat and ultraviolet radiation. The average incubation period for measles, the time from infection to clinical disease, is approximately 10 days to the onset of fever and 14 days to the onset of rash (range 7–18 days). The incubation period may be shorter in infants and following a large inoculum of virus, and longer in adults. During this seemingly quiescent period, the virus is rapidly replicating and infecting target tissues.

Measles virus is one of the most highly contagious infectious agents and outbreaks can occur in populations in which less than 10% of persons are susceptible. Chains of transmission commonly occur among household contacts, school children, and health care workers. Generally, persons with measles are infectious for several days before and after the onset of rash, when titers of measles virus in the blood and body fluids are highest. As with many other acute viral infections (SARS-coronavirus being an exception), the fact that measles virus is contagious prior to the onset of recognizable disease hinders the effectiveness of quarantine measures. Measles virus can be isolated in tissue culture from the urine as late as 1 week after rash onset. Detection of measles virus in body fluids in the late period following the rash is not diagnostic of new transmission and may or may not represent infectious virus.
fluids by a variety of means, including identification of multinucleated giant cells in nasal secretions or the use of reverse transcriptase-polymerase chain reaction (RT-PCR), suggests the potential for a prolonged infectious period in persons immunocompromised by severe malnutrition or human immunodeficiency virus type 1 (HIV-1) infection (Dossetor et al., 1977; Permar et al., 2001; Riddell et al., 2007). However, whether detection of measles virus by these methods indicates prolonged contagiousness is unclear.

In densely populated urban settings with low vaccination coverage rates, measles is a disease of young children. The cumulative distribution can reach 50% by 1 year of age, with a significant proportion of children acquiring measles virus infection before 9 months, the age of routine vaccination. 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 younger children, although susceptible if not protected by immunization, are not exposed to measles virus at a rate sufficient to cause a large disease burden in this age group. As vaccination coverage increases further, the age distribution of cases may be shifted into adolescence and young adulthood, as seen in measles outbreaks in the United States, Brazil, and Australia (Hutchins et al., 1996; de Quadros et al., 1998; Lambert et al., 2000), necessitating targeted measles vaccination programs for these older age groups.

The high infectivity of measles virus is a characteristic suitable to a biothreat agent. However, increasingly high levels of measles vaccine coverage throughout the world as part of accelerated measles control efforts would protect many from the deliberate use of measles virus as a biothreat agent. Genetic engineering of a measles virus strain that was not neutralized by antibodies induced by the current attenuated measles vaccines would likely have reduced infectivity, as suggested by the fact that wild-type measles viruses have not mutated to alter their neutralizing epitopes.

### CLINICAL DISEASE

Clinically apparent measles begins with a prodrome characterized by fever, cough, coryza, and conjunctivitis. Koplik’s spots, small white lesions on the buccal mucosa inside the mouth, may be visible during the prodrome and allow the astute clinician to diagnose measles prior to the onset of rash. The prodromal symptoms intensify several days before the onset of rash. The characteristic erythematous and maculopapular rash appears first on the face and behind the ears, and then spreads in a centrifugal fashion to the trunk and extremities. The rash lasts for 3–4 days and fades in the same manner as it appeared.

In uncomplicated measles, clinical recovery begins soon after appearance of the rash. Complications occur in up to 40% of measles cases, and the risk of complication is increased by extremes of age, malnutrition, and vitamin A deficiency (Morley, 1969). Complications of measles have been described in almost every organ system. The respiratory tract is a frequent site of complication, with pneumonia accounting for most measles-associated deaths (Duke and Mgone, 2003). Pneumonia is caused by secondary viral or bacterial infections, or by measles virus itself. Pathologically, measles virus infection of the lung is characterized by multinucleated giant cells, formed when measles virus proteins on the cell surface allow cells to fuse. Other respiratory complications include laryngotracheobronchitis and otitis media. Mouth ulcers, or stomatitis, may hinder children from eating or drinking. Many children with measles develop diarrhea, which further contributes to malnutrition. Keratoconjunctivitis is common after measles, particularly in children with vitamin A deficiency, and was a frequent cause of blindness.

Because the rash of measles is a consequence of the cellular immune response, persons with impaired cellular immunity, such as those with the acquired immunodeficiency syndrome (AIDS), may not develop the characteristic measles rash. These persons have a high case fatality and may develop a giant cell pneumonia due to measles virus (Moss et al., 1999). T-lymphocyte defects due to causes other than HIV-1 infection, such as cancer chemotherapy, are also associated with increased severity of measles.

Rare but serious complications of measles involve the central nervous system. Postmeasles encephalomyelitis complicates approximately 1 in 1000 cases, mainly older children and adults. Encephalomyelitis occurs within 2 weeks of the onset of rash and is characterized by fever, seizures, and a variety of neurological 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. Other central nervous system complications that occur months to years after acute infection are measles inclusion body encephalitis (MIBE) and subacute sclerosing panencephalitis (SSPE). In contrast to postmeasles encephalomyelitis, MIBE and SSPE are caused by persistent 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, progressive deterioration of cognitive and motor functions followed by death that occurs 5–15 years after measles virus infection, most often in persons infected with measles virus before 2 years of age.

There are conflicting and inconclusive data suggesting that measles virus infection causes or contributes to the development of chronic diseases, including multiple sclerosis, Paget’s disease, inflammatory bowel disease, and otosclerosis (Perry and Halsey, 2004). However, no causal association has been established between measles and these conditions.

The characteristic clinical features of measles are of sufficient specificity and sensitivity to have high predictive value in regions where measles is endemic. However, laboratory diagnosis is necessary where measles virus transmission rates are low or in immunocompromised persons who may not have the characteristic clinical manifestations. Infection with rubella, parvovirus B19, human herpes virus 6, and dengue viruses may mimic measles. Detection of IgM antibodies to measles virus by enzyme immunoassay (EIA) is the standard method of diagnosing acute measles (Bellini and Helfand, 2003). Alternatively, seroconversion using IgG-specific EIA, hemagglutinin inhibition, complement fixation, or virus neutralization assays can be used to diagnose acute measles based on testing serum or plasma obtained during the acute and convalescent phases.

Measles virus can be isolated in tissue culture from white blood cells, respiratory tract secretions, and urine, although the ability to isolate measles virus diminishes quickly after rash onset. Amplification and detection of measles virus RNA by RT-PCR from blood, urine, and nasal discharge is highly sensitive in detecting measles virus RNA and allows sequencing of the measles virus genome for molecular epidemiologic studies.

### TREATMENT

No specific antiviral drug is used routinely to treat measles virus infection, although the broad antiviral agent ribavirin has been used to treat immunocompromised persons or persons with SSPE, alone or in combination with IFN-α or intravenous immunoglobulin (Forni et al., 1994; Solomon et al., 2002). The major components of case management include provision of vitamin A, prompt treatment of secondary bacterial infections, and nutritional support. Several placebo-controlled trials have demonstrated marked reductions in morbidity and mortality in hospitalized children with measles treated with vitamin A. The WHO recommends administration of two daily doses of 200,000 IU of vitamin A to all children with measles 12 months of age or older. Lower doses (100,000 IU) are recommended for children less than 12 months of age. Overall, this regimen resulted in a 64% reduction in the risk of mortality (RR = 0.36, 95% CI 0.14–0.82) (D’Souza and D’Souza, 2002). Pneumonia-specific mortality is reduced, and the impact is greatest in children less than 2 years of age (D’Souza and D’Souza, 2002).

Secondary bacterial infections are a major cause of morbidity and mortality following measles (Duke and Mgone, 2003), and effective case management involves prompt treatment with antibiotics. Various strategies have been used to guide antibiotic therapy in children with measles. Antibiotics are indicated for children with measles who have clinical evidence of bacterial infection, including pneumonia, otitis media, skin infection, eye infection, and severe mouth ulcers. *Streptococcus pneumoniae* and *Haemophilus influenza* type b are the most common causes of bacterial pneumonia following measles, and antibiotic therapy should be directed against these pathogens. Whether all children with measles, or all hospitalized children with measles, should be given prophylactic antibiotics remains controversial. Limited evidence suggests that antibiotics administered as prophylaxis to all children presenting with measles may reduce the incidence of pneumonia but not mortality (Duke and Mgone, 2003). The potential benefits of antibiotic prophylaxis need to be weighed against the risks of accelerating antibiotic resistance.

Vitamin A has been widely distributed through polio and measles supplemental immunization activities as well as through routine child health services. Pooled analysis of community-based studies of vitamin A supplementation of apparently healthy children resulted in a 39% reduction in measles-associated mortality (Villamor and Fawzi, 2000). Thus, vitamin A is not only effective in reducing mortality when used to treat hospitalized children with measles but community-based supplementation programs also can result in measles mortality reduction.

### PATHOGENESIS

Respiratory droplets from infected persons serve as vehicles of transmission by carrying infectious virus to epithelial cells of the respiratory tract of susceptible hosts. During the 10–14 day incubation period between infection and the onset of clinical signs and symptoms, measles virus replicates and
spreads within the infected host. Initial viral replication occurs in epithelial cells at the portal of entry in the upper respiratory tract and the virus then spreads to local lymphatic tissue. Replication in local lymph nodes is followed by viremia (the presence of virus in the blood) and the dissemination of measles virus to many organs, including lymph nodes, skin, kidney, gastrointestinal tract and liver, where the virus replicates in epithelial and endothelial cells as well as monocytes and macrophages.

Although measles virus infection is clinically inapparent during the incubation period, the virus is actively replicating and the host immune responses are developing. Evidence of these processes can be detected. During the incubation period, the number of circulating lymphocytes is reduced (lymphopenia) (Auwaerter et al., 1999). Measles virus can be isolated from the nasopharynx and blood during the later part of the incubation period and during the several days prior to the onset of rash when levels of viremia are highest. The prodrome ends with the appearance of the measles rash. The rash results from measles virus-specific cellular immune responses and marks the beginning of viral clearance from blood and tissue. Histologic examination of the rash reveals infected capillary endothelial cells and a mononuclear cell infiltrate (Kimura et al., 1975). Clearance of infectious virus from the blood and other tissues occurs within the first week after the appearance of the rash, although measles virus RNA can be detected in body fluids of some children for at least several months using a RT-PCR-based assay (Permar et al., 2001; Riddell et al., 2007).

The intense immune responses induced by measles virus infection are paradoxically associated with depressed responses to unrelated (nonmeasles virus) antigens, lasting for several weeks to months beyond resolution of the acute illness. This state of immune suppression enhances susceptibility to secondary bacterial and viral infections causing pneumonia and diarrhea, and is responsible for much measles-related morbidity and mortality (Beckford et al., 1985; Greenberg et al., 1991). Delayed-type hypersensitivity (DTH) responses to recall antigens, such as tuberculin, are suppressed (Tamashiro et al., 1987) and cellular and humoral responses to new antigens are impaired following measles virus infection (Coovadia et al., 1978). Reactivation of tuberculosis and remission of autoimmune diseases have been described after measles and are attributed to this state of immune suppression.

Abnormalities of both the innate and adaptive immune responses have been described following measles virus infection. Transient lymphopenia with a reduction in CD4+ and CD8+ T-lymphocytes occurs in children following measles virus infection. Functional abnormalities of immune cells have also been detected, including decreased lymphocyte proliferative responses (Hirsch et al., 1984). Dendritic cells, major antigen-presenting cells, mature poorly, lose the ability to stimulate proliferative responses in lymphocytes, and undergo cell death when infected with measles virus in vitro (Servet-Delprat et al., 2000). The dominant Th2 response in children recovering from measles can inhibit Th1 responses and increase susceptibility to intracellular pathogens (Griffin et al., 1985; Griffin and Ward, 1993). The production of IL-12, important for the generation of Th1-type immune response, decreases following binding of the CD46 receptor (Karp et al., 1996) and is low for several weeks in children with measles (Atabani et al., 2001). This diminished ability to produce IL-12 could further result in a limited Th1 immune response to other pathogens. Furthermore, engagement of CD46 and CD3 on monocytes induces production of high levels of IL-10 and transforming growth factor (TGF)-β, an immunomodulatory and immunosuppressive cytokine profile characteristic of regulatory T cells (Kemper et al., 2003). The role of these cytokines in the immune suppression following measles is supported by in vivo evidence of elevated levels of IL-10 in the plasma of children after measles virus infection (Moss et al., 2002).

III. VIRAL VACCINES

History of Measles Vaccines

Attenuation of measles virus was achieved primarily by serial passage in chick embryo cells. The first attenuated measles vaccine licensed in the United States was Edmonston B. This vaccine was immunogenic and widely used between 1963 and 1975, but was frequently associated with fever and rash. The Schwarz and Moraten (more attenuated) strains were derived from the original Edmonston strain but further attenuated through additional passage in chick embryo fibroblasts. Despite differences in their passage history, these vaccine strains have identical genomic sequences (Parks et al., 2001). The Moraten vaccine (Merck) is the only measles vaccine used in the United States, whereas the Schwarz vaccine is used in many countries throughout the world. Other attenuated measles vaccines have been produced from locally derived wild-type strains, particularly in Russia, China, and Japan. One vaccine strain, the Edmonston-Zagreb vaccine, was also passaged in human diploid cells after attenuation in chick embryo fibroblasts, which may account for its increased immunogenicity and reactogenicity. Measles vaccines
are relatively heat stable in the lyophilized (dry) form, but rapidly lose potency when exposed to heat after reconstitution.

In the 1960s, a formalin-inactivated, alum-precipitated measles vaccine (FIMV) was licensed and administered to children in the United States. Three doses of inactivated vaccine elicited a protective antibody response but antibody titers waned within months (Carter et al., 1962). Up to 60% of immunized children exposed to measles developed atypical measles, characterized by high fever, pneumonia, and a petechial rash on the extremities (Fulginiti et al., 1967; Nader et al., 1968), leading to withdrawal of the FIMV in 1967. In a rhesus macaque model, atypical measles was shown to be associated with immune complex deposition in affected tissues and a systemic and pulmonary eosinophilia (Polack et al., 1999). The antibody response consisted of high levels of complement fixing antibodies with low avidity for measles virus, characteristics that may have promoted exaggerated immune complex formation and disease.

Seroconversion rates with attenuated measles vaccines in young infants are low because of immunologic immaturity and the interference of transplacentally acquired maternal antibodies with replication of vaccine virus (Gans et al., 1998). To protect young infants against measles, high-titer preparations containing 10-100 times the standard dose of vaccine virus were evaluated in several countries. Seroconversion rates in 4-6 month old infants immunized with high-titer measles vaccine were comparable to those of 9-15 month old children vaccinated with standard-titer measles vaccine, and the protective antibody response persisted for over 2 years. However, high-titer measles vaccine resulted in a poorly understood increase in mortality in immunized girls 1-2 years after vaccination compared to girls immunized with standard-titer vaccine at 9 months of age (Holt et al., 1993; Aaby et al., 1996). The increased mortality was attributable to infections commonly associated with measles, such as diarrhea and pneumonia. Although these studies were carried out in countries with different levels of socioeconomic development, excess mortality was observed only in countries with poor socioeconomic conditions and frequent malnutrition (Senegal, Haiti, and Guinea Bissau). The basis for the increased mortality in girls is not understood.

Current Licensed Measles Vaccines

Several live, attenuated measles vaccines are available worldwide, either as single-antigen vaccines or in combination with rubella and mumps vaccines (MR and MMR vaccines). Recently, a combined measles-mumps-rubella-varicella vaccine was licensed by the United States Food and Drug Administration (ProQuad, Merck and Co., Inc.). Licensed combination vaccines do not reduce the immunogenicity of the measles component. Most of the currently used measles vaccines were derived from the Edmonston strain of measles virus that was isolated by Enders and Peebles in 1954. These vaccines have undergone different passage histories in cell culture, but nucleotide sequence analysis shows less than 0.6% genetic differences between the vaccine strains. Vaccines in widespread use that were derived from the Edmonston measles virus strain include the Schwarz, Edmonston-Zagreb, and Moraten strains. Vaccines derived from other measles virus strains include CAM-70, Leningrad-16, and Shanghai 191.

The live, attenuated measles vaccines are typically cultured in primary chick embryo or human diploid (e.g., Edmonston-Zagreb) cells for several days. The supernatant fluid is harvested and frozen. Vaccine stocks are quality and safety tested before they are lyophilized. Measles vaccines may contain sorbitol or gelatin as stabilizers and the antibiotic neomycin, but do not contain thimerosal. Traces of the reverse transcriptase of an avian retrovirus can be found in vaccines cultured in chick embryo fibroblasts but there is no evidence that this is harmful to vaccine recipients. Prior to use, the vaccine must be reconstituted in sterile diluent. Measles vaccines lose about half of their potency after reconstitution if stored at 20°C for 1 h, and lose almost all potency if stored at 37°C for 1 h.

Measles vaccines are recommended for all susceptible children and adults for whom the vaccine is not contraindicated (Table 30.1). Adolescents and young adults may constitute a susceptible population,

| TABLE 30.1 Recommendations for measles vaccination |
|----------------------------------------------------|
| Recommendations of the Advisory Committee on Immunization Practices for the United States |
| • A two-dose schedule with MMR vaccine is recommended. |
| • The first dose is recommended at 12–15 months of age. |
| • The second dose is recommended at 4–6 years of age. |
| • Adults at increased risk should receive special consideration for measles vaccination, including international travelers, students attending colleges and other post-high school educational institutions, and persons who work at health care facilities. |
| • Measles vaccine is not indicated for persons with severe hypersensitivity (anaphylaxis) to neomycin or gelatin, or who are severely immunocompromised. |

Recommendations of the World Health Organization |

• Measles vaccine should be administered at 9 months of age.
• A second opportunity for measles vaccination should be provided through mass measles vaccination campaigns.
• HIV-infected children should receive measles vaccine at 6 and 9 months of age, unless severely immunocompromised, because of their increased risk of severe measles.

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including university students, health care workers, and military recruits. A single dose of measles vaccine provides lifelong immunity in the majority of vaccine recipients. However, a second opportunity for measles vaccination provides protection to those with primary vaccine failure and a chance to reach unvaccinated children. The second opportunity may be delivered through routine health services at school entry or through supplementary immunization activities such as national immunization days.

Measles vaccines are usually injected subcutaneously but can be administered intramuscularly. Each 0.5 mL dose of vaccine contains at least 1000 infective units of measles vaccine virus. The optimal age of measles vaccination is determined by consideration of the age-dependent increase in seroconversion rates following measles vaccination and the average age of infection. In regions of intense measles virus transmission, the average age of infection is low and the optimal strategy is to vaccinate against measles as young as possible. However, both maternally acquired antibodies and immunologic immaturity reduce the protective efficacy of measles vaccination in early infancy (Gans et al., 1998). In many parts of the world, 9 months is considered the optimal age of measles vaccination (Halsey, 1983), and is the age recommended by the Expanded Program on Immunization (EPI). Most countries following the EPI schedule administer measles vaccine alone, although more countries are introducing combined measles and rubella vaccines as rubella control programs expand. Under some circumstances, provision of an early dose of measles vaccine at 6 months of age (e.g., in outbreaks or to HIV-infected children) is appropriate. In regions that have achieved measles control or elimination, where the risk of measles in infants is low, the age of measles vaccination is increased to ensure that a higher proportion of children develop protective immunity. For example, in the United States the first dose of measles vaccine is administered at 12–15 months of age, as the combined MMR vaccine.

Measles vaccine induces both humoral and cellular immune responses. Antibodies first appear between 12 and 15 days after vaccination and peak at 21–28 days. IgM antibodies appear transiently in blood, IgA antibodies are predominant in mucosal secretions, and IgG antibodies persist in blood for years. Vaccination also induces measles virus-specific T-lymphocytes (Ovsyannikova et al., 2003; Wong-Chew et al., 2004). Although both humoral and cellular responses can be induced by measles vaccine, they are of lower magnitude and shorter duration compared to those following wild-type measles virus infection (Ward et al., 1995).

The proportion of children who develop protective antibody titers following measles vaccination depends on the presence of inhibitory maternal antibodies and the immunologic maturity of the vaccine recipient, as well as the dose and strain of vaccine virus. Frequently cited figures are that approximately 85% of children develop protective antibody titers when given measles vaccine at 9 months of age and 90–95% respond when vaccinated at 12 months of age (Cutts et al., 1995). Concurrent acute infections may interfere with the immune response to measles vaccine, although this is probably uncommon (Scott et al., 1999). Polymorphisms in human immune response genes also influence immune responses to measles vaccine (Ovsyannikova et al., 2004).

The duration of immunity following measles vaccination is more variable and shorter than following wild-type measles virus infection, with an estimated 5% of children developing secondary vaccine failure at 10–15 years after vaccination (Anders et al., 1996). Immunologic boosting from repeated exposure to measles virus may play a role in maintaining protective antibody levels in communities with measles virus transmission (Whittle et al., 1999).

The WHO encourages measles vaccination of all susceptible children and adults. Because measles can be more severe in HIV-infected persons and the risk of serious adverse events appears to be small, the WHO recommends that asymptomatic HIV-infected persons, and even those who are symptomatic but not severely immunocompromised, receive measles vaccine. The American Academy of Pediatrics recommends that severely immunocompromised children and adults, defined by low CD4+ T-lymphocyte cell counts or percentage, should not receive measles vaccine because of the potential risk of vaccine-related pneumonia. Measles vaccine is contraindicated in persons with a history of anaphylactic reaction to neomycin, gelatin, or other vaccine components.

Fever occurs in approximately 5–15% of recipients 6–12 days following measles vaccination, and a rash occurs in approximately 5% of recipients. These signs and symptoms are a consequence of the host immune response to replicating measles vaccine virus, but do not result in serious morbidity or mortality. Rarely, thrombocytopenia may occur.

Although assumed to be rare, the risk of disease caused by attenuated measles vaccine virus in HIV-infected persons is unknown. The only documented case of disease induced by vaccine virus in an HIV-infected person was in a 20-year-old man who died 15 months after receiving his second dose of measles vaccine (Angel et al., 1998). He had a very low CD4+ T-lymphocyte cell count but no HIV-related symptoms at the time of

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Measles Vaccines in Development

Aerosol administration of measles vaccine was first evaluated in the early 1960s in several countries, including the former Soviet Union and the United States. More recent studies in South Africa (Dilraj et al., 2000) and Mexico (Bennett et al., 2002) have shown that aerosol administration of measles vaccine is highly effective in boosting antibody titers, although the primary immune response to aerosol measles vaccine is lower than following subcutaneous administration (Wong-Chew et al., 2004). Administration of measles vaccine by aerosol has the potential to greatly facilitate measles vaccination during mass campaigns, and the WHO plans to test and bring to licensure an aerosol measles vaccine by 2009.

The ideal measles vaccine would be inexpensive, safe, heat-stable, immunogenic in neonates or very young infants, and administered as a single dose without needle or syringe. The age at vaccination should coincide with the EPI schedule to maximize compliance and share resources. Finally, a new vaccine should not elicit atypical measles upon exposure of immunized individuals to wild-type measles virus and should not be associated with prolonged immunosuppression, adversely affecting immune responses to subsequent infections.

A number of vaccine candidates with some of these characteristics are undergoing preclinical studies (Table 30.2). Naked cDNA vaccines are thermostable, inexpensive, and could theoretically elicit antibody responses in the presence of passively acquired maternal antibody. DNA vaccines encoding either or both the measles H and F proteins are safe, immunogenic, and protective against measles challenge in naïve, juvenile rhesus macaques (Polack et al., 2000). A different

### TABLE 30.2  Measles Vaccine Candidates

| Vaccine type                  | Viral proteins | Model  | Delivery            | References                                             |
|-------------------------------|----------------|--------|---------------------|--------------------------------------------------------|
| DNA                           | H, F, H/F      | Macaques | Intradermal gene-gun | Polack et al. (2000)                                   |
| DNA                           | H/F/N          | Macaques | Intradermal         | Premanenko-Lanier et al. (2003, 2004)                  |
| Sindbis virus replicon particles | H, F, H/F  | Macaques | Intradermal         | Pan et al. (2005)                                     |
| Sindbis virus replicon DNA    | H, F, H/F      | Mice    | Intramuscular       | Song et al. (2005)                                    |
| Chimeric human-bovine parainfluenza virus type 3 | H              | Macaques | Intranasal          | Skiadopoulos et al. (2001)                            |
| Salmonella enterica serovar Typhi CVD 908-htrA | H              | Cotton rat | Intranasal         | Pasetti et al. (2003)                                 |
| *Shigella flexneri* 2a CVD 1208 | H              | Cotton rat | Intranasal          | Pasetti et al. (2003)                                 |
| Transgenic plant protein      | H              | Mice    | Intraperitoneal, oral | Huang et al., (2001); Webster et al. (2002)            |

Vaccination. Ten months later he developed giant cell pneumonitis and measles vaccine virus was identified in his lung. Fatal, disseminated infection with measles vaccine virus has been reported rarely in persons with other impairments of immune function (Monafo et al., 1994), and MIBE due to vaccine virus was reported in a child with an uncharacterized immune deficiency (Bitnun et al., 1999).

Much public attention has focused on a purported association between MMR vaccine and autism following publication of a report in 1998 hypothesizing that MMR vaccine may cause a syndrome of autism and intestinal inflammation (Wakefield et al., 1998). The events that followed, and the public concern over the safety of MMR vaccine, led to diminished vaccine coverage in the United Kingdom and provide important lessons in the misinterpretation of epidemiologic evidence and the communication of scientific results to the public (Offit and Coffin, 2003). The publication that incited the concern was a case series describing 12 children with a regressive developmental disorder and chronic enterocolitis. Nine of the children had autism. Onset of the developmental delay was associated by the parents with MMR vaccination in eight children. This simple temporal association was misinterpreted and misrepresented as a possible causal relationship, first by the lead author of the study and then by the media and public. Subsequently, several comprehensive reviews and additional epidemiological studies rejected evidence of a causal relationship between MMR vaccination and autism (DeStefano and Thompson, 2004). One of the most conclusive studies was a large retrospective cohort study of over half a million Danish children that found the relative risk of MMR vaccine for autistic disorder to be 0.92 (95% confidence interval, 0.68–1.24) (Madsen et al., 2002).
construct, containing H, F, and N genes and an IL-2 molecular adjuvant, provided protection to infant macaques in the presence of neutralizing antibody (Premenko-Lanier et al., 2003, 2004). Alternative techniques for administering measles DNA, such as alphavirus (Pan et al., 2005), parainfluenza virus (Skiadopoulos et al., 2001), or enteric bacterial (Pasetti et al., 2003) vectors, also are under investigation. Immune responses to intranasal administration of measles virus vaccines is enhanced by the use of adjuvants (Chabot et al., 2005). Novel oral immunization strategies have been developed using plant-based expression of the measles virus H protein in tobacco (Webster et al., 2005). These vaccines induced humoral immune responses following both primary immunization and as a booster dose after a DNA prime. In addition, attenuated recombinant measles virus vaccines have been used as vectors for the delivery of genes from other pathogens (Tangy and Naim, 2005).

POSTEXPOSURE IMMUNOPROPHYLAXIS

Immune globulin can be given intramuscularly to susceptible persons within 6 days of exposure to prevent or lessen the severity of disease. Postexposure immunoprophylaxis is indicated for those at high risk of severe disease, including susceptible household contacts between 6 months and 1 year of age, pregnant women, and immunocompromised persons. Where resources are not limited, HIV-infected children, or those exposed to HIV but whose infection status is unknown, should receive postexposure immunoprophylaxis. Persons who are not immunocompromised and who have received at least one dose of measles vaccine at 12 months of age or older should not receive postexposure immunoprophylaxis. If given with 72h of exposure, measles vaccine may provide protection against disease.

PROSPECTS FOR THE FUTURE

The possibility of measles eradication has been discussed for almost 40 years (Sencer et al., 1967). Serious consideration of measles eradication began in the late 1960s as smallpox eradication was nearing completion and the effective, long-term immunity induced by measles vaccine became apparent. Measles virus meets many of the biologic criteria for disease eradication (Moss and Griffin, 2006). Measles virus has no nonhuman reservoir; infection can be accurately diagnosed, and measles vaccination is a highly effective intervention. Although measles virus displays sufficient genetic variability to conduct molecular epidemiologic analyses, the antigenic epitopes against which protective antibodies develop have remained stable. Measles virus differs from smallpox and polio viruses, however, in that it is more highly infectious, necessitating much higher levels of population immunity to interrupt transmission.

 Potential barriers to measles eradication include: (1) lack of political will; (2) difficulties of measles control in densely populated urban environments; (3) the HIV epidemic; (4) waning immunity and the potential transmission from subclinical cases; (5) transmission among susceptible adults; (6) the risk of unsafe injections; and (7) unfounded fears of disease due to measles vaccine (Orenstein et al., 2000). Whether the threat from bioterrorism precludes stopping measles vaccination after eradication is a topic of debate, but, at the least, a single-dose rather than a two-dose measles vaccination strategy could be adopted (Meissner et al., 2004). The elimination of endemic measles virus transmission in large geographic areas, such as the Americas, suggests that global eradication is feasible with current vaccination strategies (de Quadros, 2004). Many believe this to be a realistic and morally imperative goal, but, as polio eradication efforts have shown, the endgame may be full of challenges.

KEY ISSUES

- Measles is highly contagious viral infection.
- Great progress has been made in measles control and elimination through accelerated efforts, including increased routine vaccination coverage rates and supplementary immunization activities.
- Despite the reduction in measles cases and deaths, measles remains a leading cause of vaccine-preventable death worldwide.
- The high infectivity of measles virus is a characteristic suitable to a biothreat agent.
- Increasingly high levels of measles vaccination coverage throughout the world would protect many from the deliberate use of measles virus as a biothreat agent.
- Measles vaccine virus can be used as a vector to deliver genes derived from other pathogens.
- Genetic engineering of a measles virus strain that was not neutralized by antibodies induced by the current attenuated measles vaccines would likely have reduced infectivity, although this is not certain.
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