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Review

Emerging diseases: Measles

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High vaccination coverage rates and the administration of a second dose of measles vaccine have resulted in a significant decline in the incidence of measles and neurologic diseases due to measles in many countries. However, intermittent outbreaks of measles still occur even in countries with excellent vaccination coverage, suggesting the existence of high rates of measles virus introduction from endemic regions and/or waning of vaccine-induced immunity. Strategies to sustain high levels of global immunity to measles virus by increasing vaccine coverage with routine and supplementary vaccination campaigns must be supported. *Journal of NeuroVirology* (2005) **11,** 447–454.

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Introduction and epidemiology

Measles is a highly contagious disease caused by measles virus. According to the World Health Organization (WHO), measles remains a major cause of child morbidity and mortality, especially in developing countries, with 30 to 40 million cases and 745,000 deaths estimated in 2001 (Centers for Disease Control and Prevention, 2004a). This represents 50% to 60% of the estimated million deaths attributable to vaccine-preventable diseases of childhood. Measles is also the major cause of preventable blindness in the world (Centers for Disease Control and Prevention, 2004a).

Clinical manifestations

The epidemiological features of measles, including characterization of the incubation period, lifelong immunity, and the duration of infectivity, were first documented in the classic observations of Peter Panum, a Danish physician who investigated a measles epidemic in the Faroe Islands in 1846 (Panum, 1938). The prodrome is characterized by fever, malaise, coryza, conjunctivitis, and cough, lasting 2 to 4 days. Koplik spots, small white punctate lesions believed to be pathognomnic of measles, may be visible on the buccal mucosa during the prodrome (Brem, 1972). The characteristic erythematous and maculopapular rash appears first on the face and behind the ears, then spreads in a centrifugal fashion to the trunk and extremities. The rash lasts for 3 to 4 days and fades in the order of appearance (Griffin *et al*, 1994; Katz, 1995). In uncomplicated measles, clinical recovery begins soon after appearance of the rash.

Virology and pathogenesis

Measles virus was isolated from the blood of David Edmonston in 1954 by Enders and Peebles (Enders and Peebles, 1954). Measles virus is a spherical, nonsegmented, single-stranded, negative-sense RNA virus and is a member of the genus *Morbillivirus* in the family *Paramyxoviridae* (Griffin, 2001). The measles virus genome encodes eight proteins. Two of these, V and C, are nonstructural proteins. Of the six structural proteins, phosphoprotein (P), large protein (L), and nucleoprotein (N) are complexed with viral RNA forming the nucleocapsid; whereas hemagglutinin protein (H), fusion protein (F), and matrix protein (M), together with cellular lipids, form the viral envelope. The P protein regulates transcription and replication, whereas the M protein links ribonucleoproteins with envelope proteins during virion assembly. The H and F proteins mediate attachment

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and penetration of the virus through receptors on permissive cells (Griffin, 2001). Wild-type measles virus enters cells mainly through the signaling lymphocyte activation molecule SLAM (CD150) expressed on T and B lymphocytes (Tatsuo *et al*, 2000), whereas most vaccine strains bind to the ubiquitously expressed regulator of complement activation, CD46 (Naniche *et al,* 1993; Dorig *et al*, 1993). Data suggest that measles virus might use both CD46 and SLAM as receptors during acute infection (Santiago *et al*, 2002; Schneider *et al*, 2002). Additional but yet unidentified receptors for measles virus may exist on human endothelial and epithelial cells (Andres *et al*, 2003).

Humans are the only natural reservoir for measles virus. Monkeys are susceptible to experimental infection, but cannot maintain transmission in the wild because of small colony size. Aerosols from infected people serve as vehicles of transmission by infecting the respiratory epithelium of susceptible hosts. During the 10- to 14-day incubation period, measles virus replicates and spreads within the infected host. Initial viral replication occurs in the epithelial cells at the portal of entry, and spreads to the local lymphatic tissue (Kempe and Fulginiti, 1965). Replication in the local lymph nodes is followed by viremia and dissemination to many organs, including peripheral and central lymph nodes, skin, kidney, gastrointestinal tract, and liver (Moench *et al*, 1988). Further replication and spread of the virus occur in the epithelial and endothelial cells of these organs, as well as in monocytes and macrophages. Measles virus can be isolated from the nasopharynx and blood during the later part of the incubation period and early phase of the rash (Ruckle and Rogers, 1957; Esolen *et al*, 1993).

The rash results from virus-specific cellular immune responses and marks the beginning of viral clearance from the blood and tissue. Infected capillary endothelial cells and a mononuclear infiltrate are observed (Kimura *et al*, 1975). Complete clearance of infectious virus from blood and other tissues generally occurs within the first 1 to 2 weeks after the appearance of the rash, although a more sensitive polymerase chain reaction (PCR)-based assays suggests the continued presence of measles virus RNA in the blood for at least 1 month. Measles in human immunodeficiency virus (HIV)-infected persons may be unusually severe, occur without the characteristic rash, and viral clearance may be prolonged due to defective cellular immunity (Kaplan *et al*, 1992; Palumbo *et al*, 1992; Permar *et al*, 2001).

Immune responses to measles virus

The first antibody produced after measles virus infection is IgM, followed by a switch to IgG1 and IgG4 isotypes (Graves *et al*, 1984; Isa *et al*, 2002; Mathiesen *et al*, 1990). IgA, IgM, and IgG antibodies are found in secretions. The avidity of the initial measles virus-specific IgG antibody is low but increases with maturation of the humoral response. The most abundant and most rapidly produced antibody is against the nucleoprotein. Consequently, its absence is the most accurate indicator of seronegativity to measles virus (Norrby and Gollmar, 1972). Antibodies to H and F proteins contribute to neutralization and play a major role in the prevention of viral spread. These antibodies appear to be sufficient to provide protection against measles virus infection. The protective efficacy of antibodies is illustrated by the immunity conferred on infants in early infancy by passively acquired maternal antibodies, and protection of exposed, susceptible individuals given anti-measles virus gamma globulin (Black and Yannet, 1960). Indirect evidence of the role of T lymphocytes in immunity to measles is in the ability of children with agammaglobulinemia to recover from measles, whereas those with defects in T lymphocyte function develop severe and fatal forms of the disease (Burnet, 1968).

Recent work using measles virus peptides demonstrated the activation of measles virus-specific T lymphocytes after measles virus infection (Nanan *et al*, 1995). In animal models, measles virus-specific CD8+ T lymphocytes are activated and expanded during the acute phase of measles virus infection, and are important for recovery (Niewiesk *et al*, 1993). CD8+ T lymphocyte–depleted rhesus monkeys challenged with wild-type measles virus had a more extensive rash, higher viral loads, and a longer duration of viremia than control animals (Permar *et al*, 2003a). Vigorous CD8+ T lymphocyte responses to measles virus-specific peptides can be demonstrated *in vitro* (Jaye *et al*, 2003; Nanan *et al*, 1995). CD4+ T lymphocytes are also activated in response to measles virus infection and secrete cytokines capable of affecting both the innate and adaptive immune responses (Nanan *et al*, 2000). Further evidence for the role of CD4+ T lymphocytes is demonstrated by the sustained elevation of soluble (s)CD4 for several weeks following measles virus infection (Ryon *et al*, 2002; Griffin and Ward, 1993). Plasma cytokine profiles show increased levels of interferon-gamma (IFN-γ) in the acute phase, followed by a shift to high levels of interleukin (IL)-4 and IL-10 during convalescence (Moss *et al*, 2002; Tetteh *et al*, 2003; Ward and Griffin, 1993). The initial predominant T-helpher type 1 (Th1) response is assumed to be essential for viral clearance by CD8+ T lymphocytes, whereas the later Th2 response promotes the development of measles virus-specific antibody.

Complications of measles

Complications occur in up to 40% of measles cases, and the risk of complication is increased by extremes of age and malnutrition (Barkin, 1975; Morley, 1969). Complications of measles include pneumonia, otitis media, diarrhea, thrombocytopenia,

laryngotracheobronchitis, keratoconjuctivitis, and pericarditis/myocarditis (Barkin, 1975; Ibrahim *et al*, 2002; D'Souza and D'Souza, 2002; Olowu and Taiwo 1990; Ross, 1952).

Rare but serious complications of measles occur in the central nervous system. Post-measles encephalomyelitis complicates 1 in 1000 cases of measles, mainly in older children and adults (Miller, 1964; Lee *et al*, 2003). Encephalomyelitis occurs within 2 weeks after the onset of the rash and is characterized by fever, seizures, and a variety of neurologic abnormalities. Periventricular demyelination of axons, high cerebrospinal fluid (CSF) beta-2 microglobulin, increased plasma immunoglobulin (IgE) levels, and induction of immune response to myelin basic protein are observed, without evidence of measles virus in the brain, suggestive of an autoimmune disorder (Litvak *et al*, 1943; Griffin *et al*, 1985, 1992). Central nervous system complications occurring months to years after the acute disease are measles inclusion body encephalitis (MIBE) and subacute sclerosing panencephalitis (SSPE). In contrast to postmeasles encephalomyelitis, MIBE and SSPE are caused by a persistent measles virus infection. MIBE or subacute measles encephalitis (SME) is a rare but fatal complication, and affects young individuals with defective cellular immunity (Poon *et al*, 1998). SSPE is a slowly progressive disease characterized by seizures, progressive deterioration of cognitive and motor functions followed by death. It occurs 5 to 15 years after measles virus infection, most often in those infected under the age of 2 years. Pathological studies show inflammatory changes, lymphocytic infiltration, encephalomalacia, and brain atrophy in addition to inclusion bodies (Otzurk *et al*, 2002; Takasu *et al*, 2003; Anlar *et al*, 2001).

Measles virus–associated immune suppression

The intense immune responses induced by measles virus infection are paradoxically associated with depressed responses to unrelated antigens, which lasts for several weeks beyond the resolution of the acute illness. This state of immune suppression increases susceptibility to secondary infectious pathogens responsible for most measles-related morbidity and mortality (Miller, 1964; 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). Cellular and humoral responses to new antigens are impaired during the acute and convalescent stages of measles (Coovadia *et al*, 1978). Reactivation of tuberculous lesions and remission of autoimmune diseases occur after measles virus infection, and are attributed to immunosuppression (Starr and Berkovich, 1965; Lin *et al*, 1988).

Abnormalities in different compartments of both the innate and adaptive immune system could be responsible for immune suppression. Transient lymphopenia, with a reduction in CD4+ and CD8+ T lymphocytes, occurs in children following measles virus infection (Ryon *et al*, 2002). Increased surface expression of CD95(Fas) and annexin V staining on both CD4+ and CD8+ T lymphocytes during acute measles suggest that apoptosis of uninfected lymphocytes may account for some of the lymphopenia (Ryon *et al*, 2002). However, the rate of decline and repopulation of the peripheral lymphocyte pool is so rapid that redistribution of lymphocytes within the lymphoid tissue may account for much of the peripheral lymphopenia. Impaired thymic output does not appear to be a cause of lymphopenia as an increase in the lymphocyte content of T-cell receptor rearrangement circle (TREC) was observed in children with measles, suggesting a compensatory increase in thymic output (Permar *et al*, 2003b).

Functional abnormalities of immune cells have also been detected, including decreased lymphocyte proliferative response to mitogens, and limited natural killer (NK) cell and neutrophil activities (Hirsch *et al*, 1984). Dendritic cells infected with measles virus *in vitro* mature poorly, lose the ability to stimulate proliferative responses of lymphocytes, and undergo apoptosis (Servet-Delprat *et al*, 2000). Antigen presentation by such immature and defective dendritic cells could bias the differentiation of effector T lymphocytes to either Th2 or regulatory phenotype (Ridge *et al*, 1996; Roncarolo *et al*, 2001). The dominant Th2 response is characterized by eosinophilia, and high IgE and IL-4 levels in the blood of children recovering from measles (Griffin *et al*, 1985; Griffin and Ward, 1993). Decreased production of IL-12, a key cytokine for the development of Th1 responses, was observed for several weeks after measles (Atabani *et al*, 2001), consistent with the observation that IL-12 production decreases following engagement of the monocyte surface receptor for measles virus (CD46) with antibody (Karp *et al*, 1996). A limited Th1 response leads to increased susceptibility to infectious pathogens for which Th1 responses are required. Engagement of CD46 and CD3 on monocytes induced 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). This finding is supported by *in vivo* data showing sustained elevated levels of IL-10 levels in plasma of children after measles virus infection (Moss *et al*, 2002).

Prevention and control

The first attenuated Edmonston B vaccine licensed in 1963 was effective but reactogenic, producing fever and rash in a large proportion of vaccinees. An alternative, formalin-inactivated vaccine required several doses, provided short-lived protection, and recipients exposed to measles virus often developed

atypical measles, a severe illness characterized by hemorrhagic rash and pneumonitis (Carter *et al*, 1962; Rauh and Schmidt, 1965). For these reasons the formalin-inactivated vaccine was withdrawn in 1967 without an understanding of the pathogenesis of atypical measles. In monkeys, atypical measles is associated with the formation of antibodies capable of fixing complement but with low avidity for measles virus. The vasculitis of atypical measles is associated with deposition of IgG, complement and immune complexes in dermal tissues (Polack *et al*, 2003a).

The currently used live-attenuated measles vaccines were derived from further passaging of the original Edmonston strain through chick embryo fibroblasts. The Moraten vaccine and the Schwarz vaccine, both produced by additional passaging of Edmonston virus in chick cells, are used for immunization in much of the world. Despite the differences in their passage history, these vaccine strains appear to be identical (Parks *et al*, 1994).

The standard dose measles vaccine contains between 10^3 and 10^4 plaque-forming units. The immunogenicity of measles vaccine in early infancy is limited by the relative immaturity of the immune system as well as interference of transplacentally transferred maternal measles-specific antibodies (Gans *et al*, 1998). These factors together with regional variation in the prevalence of measles determine the optimal age of vaccination, which varies from 6 to 15 months. A second dose of measles vaccine, administered through routine immunization services or mass campaigns, is critical to the control of measles virus transmission.

Measles vaccine induces both cellular and humoral immune responses. However, immunity acquired through vaccination is of lower magnitude and shorter duration, than that following wild-type virus infection. Antibodies first appear between 12 and 15 days, and peak at 21 to 28 days, after vaccination. IgM appears transiently in serum, IgA is predominant in nasal secretions, and IgG persists in serum for several years. A level of 120 mIU/ml of neutralizing antibody is considered protective (Chen *et al*, 1990). This level is achieved in about 85% of children vaccinated at the age of 9 months, and in 90% to 95% of children vaccinated at 12 months of age (Cutts *et al*, 1995). Vaccination also induces measles virus-specific T-lymphocyte proliferative responses and predominantly Th1 memory cells (Wong-Chew *et al*, 2004; Ovsyannikova *et al*, 2003). Malnutrition and HIV infection influence the magnitude and quality of the immune response to measles vaccine (Waibale *et al*, 1999; Brunell *et al*, 1995).

Adverse events associated with receipt of live-attenuated measles vaccine include fever, rash, thrombocytopenia, and febrile seizures. Significant decreases in leukocyte counts and percentages of both CD4+ and CD8+ T lymphocytes occur after reimmunization (Rager-Zisman *et al*, 2003). Lymphocyte proliferation and DTH responses to various antigens are suppressed following measles vaccination (Zweiman *et al*, 1971). However, none of these effects appear to be clinically significant. The role of measles vaccine in the development of childhood autism has generated considerable debate. However, there is no evidence that the measles-mumps-rubella vaccine causes autism or subtypes of autistic spectrum disorder (DeStefano and Thompson, 2004).

Problems and projections

High vaccination coverage rates and the administration of a second dose of measles vaccine have resulted in a significant decline in the incidence of measles in many countries and the elimination of measles in large geographical regions. Nevertheless, the currently used attenuated measles vaccine has limitations. Effective immunization of infants below the age of 9 months remains a challenge due to the limitations caused by immaturity of the immune system and the presence of interfering maternal antibodies. Administration of high-titer measles vaccines, a strategy to overcome the inhibitory effect of maternal antibodies, induced seroconversion in 4- to 6-month-old vaccinees comparable to that of routine vaccine in children aged 9 to 12 months. However, the high-titer strategy was abandoned because of increased mortality in immunized girls (Aaby *et al*, 1993). Even in the absence of detectable maternal antibodies, 6-month-old vaccinees produce significantly lower measles virus antibody titers following vaccination compared to 9- to 15-month-old vaccinees (Gans *et al*, 2003; Kumar *et al*, 1998). The duration of vaccine-induced immunity may be short-lived in developed countries due to the absence of subclinical infections important for boosting protection (Whittle *et al*, 1999). Improved international travel could enable reimportation of measles into such a population with waning vaccine-induced immunity by travelers or immigrants. Thus, until measles virus is eradicated, countries with high vaccine coverage rates are at a substantial risk of reemergence of measles epidemics (Rota *et al*, 2002). Indeed, recent outbreaks of measles in the United States were reported among children adopted from China and some secondarily infected subjects (Centers for Disease Control, 2004b, 2004c).

Several vaccine candidates and formulations with the potential for circumventing these problems are currently undergoing preclinical studies. Aerosol delivery of the current measles vaccine could minimize the interference of maternal antibodies and the ease of administration would facilitate mass vaccination campaigns (Cutts *et al*, 1997). DNA vaccines encoding different measles virus proteins and immune-modulating cytokines have the potential to be immunogenic, minimize the side effects of the current live measles vaccine, and escape the inhibitory effect of maternal antibodies when given in early infancy.

Rhesus macaques vaccinated with a recombinant measles vaccine expressing IL-12 induced high IFN-γ and low IL-4 production by CD4+ T lymphocytes, but lower levels of measles virus–specific IgG4 and neutralizing antibody (Hoffman *et al*, 2003). DNA vaccines encoding either or both the measles virus H and F glycoproteins were safe, immunogenic, and protective against measles virus challenge in rhesus macaques (Polack *et al*, 2000, 2003b). Recombinant modified vaccinia virus Ankara vaccine encoding the measles virus F and H glycoproteins was immunogenic in the presence of maternal antibodies, and the monkeys were effectively protected from challenge (Stittelaar *et al*, 2000). These data suggest that DNA vaccines could be an alternative to the current attenuated vaccine for infants with maternally acquired measles virus-neutralizing antibodies. However, the safety and cost of new measles vaccines are important considerations for their widespread use and must be carefully evaluated given the detrimental and unintended immunological consequences of previous measles vaccine formulations. In the interim, strategies to sustain high levels of global immunity to measles virus by increasing vaccine coverage with routine and supplementary vaccination campaigns must be supported.

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