Measles Virus

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Name of Virus: Measles virus

8.1 Brief Introduction

Measles (MV) is an extremely contagious human disease, characterized by fever, exanthema, and inflammation of the eyes and respiratory tract (Neihart and Liu 1989). Measles is typically a disease of children, and it can cause severe pneumonia, diarrhea, encephalitis, and death (Yanagi et al. 2006). Despite the availability of effective live vaccines, measles is still responsible for 4 % of deaths in children younger than 5 years of age worldwide (WHO 2007).
Synonyms: Rubeola

8.2 Classification

Family – *Paramyxoviridae*
Genus – *Morbillivirus*

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8.3 Epidemiology

MV outbreaks usually occur in late winter/early spring, and transmission is via aerosolized droplets (Hayward 1826; Rall 2003). MV is one of the most highly contagious infectious agents, and outbreaks can occur in populations in which less than 10 % of individuals are susceptible. Before the introduction of measles vaccine, over 90 % of persons would become immune by age 15 as a result of naturally acquired infection. The 1933 studies of Hedrich in Baltimore showed that measles epidemics were related to small fluctuations in the susceptible population under the age of 15 years of age. Epidemics occurred when the susceptible population reached 45–50 % and ceased when the levels were reduced to 30–35 %. A level of herd immunity protected the population from epidemics when it reached 65 % of the children under age 15, but it guaranteed a reservoir of susceptible individuals for endemic measles (Schaffner et al. 1968). It is estimated that 90 % of nonimmune people exposed to an infected individual will become infected. Moreover, infected individuals are contagious for 3–4 days before and after the appearance of the characteristic rash, increasing the risk of transmission. The contagiousness of MV is best expressed by the basic reproductive number (Ro), which is the mean number of secondary cases that would arise if an infectious agent were introduced into a completely susceptible population. The estimated Ro for MV is generally assumed to be 12–18,

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in contrast to only 5–7 for smallpox virus and 2–3 for SARS coronavirus (Rima and Duprex 2006; Monto 1998; Moss and Griffin 2006). The high infectivity of MV implies that a high level of population immunity (approximately 95 %) is required to interrupt MV transmission (Monto 1998). The virus remains transmissible in the air or on infected surfaces for up to 2 h, obviating the need for direct person-to-person contact (Monto 1998).

8.4 Ultrastructure

Measles virus most closely resembles the rinderpest virus – a recently eradicated pathogen of cattle – and probably evolved from an ancestral virus as a zoonotic infection in communities in which cattle and humans lived in close proximity (Moss and Griffin 2006). Measles virus is a spherical, enveloped, with a non-segmented, negative-strand RNA genome (Moss and Griffin 2012) (Fig. 8.1). The genome contains six genes that encode eight proteins that can be divided in two main types: envelope-associated and ribonucleoprotein (RNP)-associated proteins.

The major component of the nucleoprotein core is the ribonucleoprotein. The other two parts are the large protein and the phosphoprotein. The large protein is composed of the enzyme RNA polymerase, which catalyzes the transcription and replication of the nucleocapsid template (Yanagi et al. 2006).

The envelope is made up of a matrix protein, a hemagglutinin protein, and a fusion protein. The attachment of the virions to the host cell is mediated by the hemagglutinin protein; following this process, the fusion and hemagglutinin proteins mediate entry into the host cell. The known measles virus receptors on human cells are the signaling lymphocyte activation molecule (SLAM) CD1506 and the membrane cofactor protein CD46, a regulator of complement activation that plays an important part in protecting host cells from spontaneous complement attack (Yanagi et al. 2006). Measles virus has only one serotype and can, therefore, be prevented with a single monovalent vaccine.

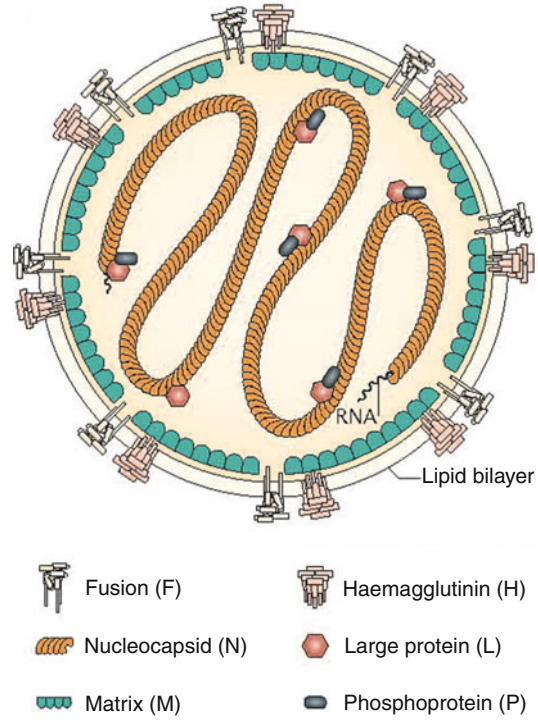


Fig. 8.1 Ultrastructure of the measles virus showing a spherical, enveloped virion with a non-segmented negative-stranded RNA genome (With permission from Lancet [Reproduced with permission of Exp. Rev. Mol. Med 30, 1–18. © Cambridge University Press])

8.5 Pathogenesis

Infected persons transmit MV via respiratory droplets delivering infectious virus to epithelial cells of the respiratory tract of susceptible hosts. During the incubation period MV replicates and spreads in the infected host. Type 1 pneumocytes, alveolar macrophages, and respiratory epithelial cells become infected but is yet unknown which is the initial site of viral replication. The virus then spreads to local lymphatic tissue, and this replication is followed by viremia and dissemination to many organs, including the lymph nodes, skin, kidney, gastrointestinal tract, and liver, in which the virus replicates in the epithelial and endothelial cells and in lymphocytes, monocytes, and macrophages (Griffin 2010). Measles immunity involves humoral, cellular, and mucosal responses. Cell-mediated immunity is required for recovery from measles, and humoral immunity

is associated with protection from infection or reinfection (Moss and Griffin 2012).

MV infection results in immunosuppression with depressed responses to non-MV antigens. This effect lasts for several weeks to months after resolution of the acute illness. Patients with measles showed suppressed delayed-type hypersensitivity (DTH) responses to recall antigens, such as tuberculin, and impaired cellular and humoral responses to new antigens. This MV-induced immune suppression renders individuals more susceptible to secondary bacterial and viral infections that can cause pneumonia and diarrhea and is responsible for much of the measles-related morbidity and mortality (Moss and Griffin 2006). Pneumonia, the most common fatal complication of measles, occurs in 56–86 % of measles-related deaths (Duke and Mgone 2003). The production of IL-12 is reduced while the production of IL-10, which inhibits DTH responses and downregulates the synthesis of cytokines and suppresses macrophage activation and T-cell proliferation, is elevated for several weeks in the plasma of children with measles (Yanagi et al. 2006). The measles skin rash is thought to be caused by the T-cell response to MV-infected cells in capillary vessels because it does not appear in children with T-cell immunodeficiency (Yanagi et al. 2006).

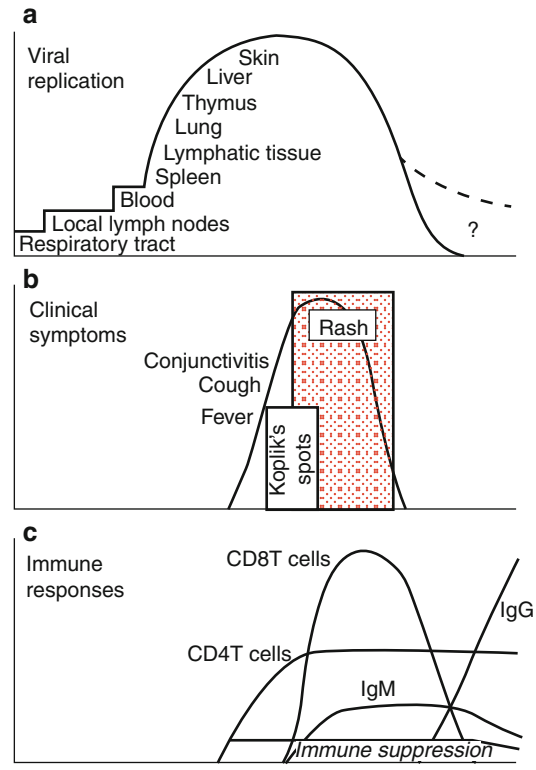


Fig. 8.2 Schematic reproduction of the pathogenesis of measles from virus infection to recovery (With permission from Lancet [Reproduced with permission of Griffin, D.E. Measles virus-induced suppression of immune responses. (**a**) viral replication. (**b**) clinical symptoms. (**c**) immune responses. Immunological Reviews June 15, 2010, pp 176–189. © John Wiley & Sons])

8.6 Clinical Features

After an incubation period of 10–14 days, prodromal measles begins with fever of 39–40 C, cough, coryza, and conjunctivitis (Fig. 8.2). The initial presentation resembles a cold except that fever is an early sign. These symptoms worsen over a 2- to 4-day period; sneezing, rhinitis, and congestion are common. The cough is frequently troublesome and often has a brassy quality, suggesting laryngeal and tracheal involvement. If the mucous membranes lining the cheeks opposite the molar teeth are examined, there will be found in the majority of patients a few white to bluish-gray spots the size of a pinhead with red margins. These are known as Koplik's spots and are a pathognomonic exanthem of measles.

The rash starts behind the ears and spreads to the face and trunk within 24 h. The rash is deep pink or red in color, appeared in blotches scattered as little islands with unaffected skin between, and is pruritic. The rash then spreads to cover the entire body in about 3 days (Kilbourne 1967). It is unusual for the rash to persist more than 5–7 days, and when it fades the skin appears dry while the superficial layers scale off. The fever usually lasts 5–7 days. Within 5 days of the appearance of the rash, most children are up and about (Towsley 1947).

Complications of measles are largely attributable to the pathogenic effects of the virus on the respiratory tract and immune system (Axton 1979). Acute otitis media is the most common complication, and pneumonia is the most common cause of death in measles. Croup, tracheitis,

and bronchiolitis are common complications in infants and toddlers with measles (Moss and Griffin 2012; Duke and Mgone 2003; Perry and Halsey 2004). Pneumonia is a severe complication of measles and as noted accounts for most measles-associated deaths. In studies of unselected hospitalized children with measles, 55 % had radiographic changes of bronchopneumonia, consolidation, or other infiltrates; 77 % of children with severe disease and 41 % of children with mild disease had radiographic changes. In recent years, pneumonia was present in 9 % of children <5 years old with measles in the United States, in 0–8 % of cases during outbreaks, and in 49–57 % of adults.

Pneumonia may be caused by the measles virus alone, secondary viral infection with adenovirus or HSV, or secondary bacterial infection. Measles is one cause of Hecht's giant cell pneumonia, which usually occurs in immunocompromised persons but can occur in otherwise normal adults and children. Studies that included culture of blood, lung punctures, or tracheal aspirations revealed bacteria as the cause of 25–35 % of measles-associated pneumonia. *S. pneumoniae*, *S. aureus*, and *H. influenzae* were the most commonly isolated organisms. Other bacteria (e.g., Pseudomonas species, *Klebsiella pneumoniae*, and *E. coli*) are less common causes of severe pneumonia associated with measles. In studies of young adult military recruits with pneumonia associated with measles, *Neisseria meningitidis* was a probable cause in some cases (Perry and Halsey 2004; Enders et al. 1959; Mitus et al. 1959; Ellison 1931). Diarrhea and vomiting are common symptoms associated with acute measles; appendicitis may occur from obstruction of the appendiceal lumen by lymphoid hyperplasia. Febrile seizures occur in <3 % of children with measles (Moss and Griffin 2012; Duke and Mgone 2003).

Measles infection is known to suppress skin test responsiveness to purified tuberculin antigen. There may be a higher rate of activation of pulmonary tuberculosis in populations of individuals infected with Mycobacterium tuberculosis who are then exposed to measles (Griffin 2010). The three most serious complications of measles occur in the CNS. These are acute demyelinating encephalomyelitis (ADEM), measles inclusion body encephalitis (MIBE), and subacute sclerosing panencephalitis (SSPE); the last two are invariably fatal. ADEM develops a week after the appearance of the rash and is seen in 1:100 infected children. Approximately 15 % of patients with ADEM die, and 20–40 % suffer long-term sequelae, including mental retardation, motor disabilities, and deafness. MIBE is seen in immunocompromised patients between 2 and 6 months after acute infection or vaccination. SSPE is caused by a persistent measles virus infection and develops years after the initial infection (Rima and Duprex 2006; Perry and Halsey 2004). Findings in cerebrospinal fluid (CSF) include lymphocytic pleocytosis in 85 % of cases and elevated protein concentration.

A severe form of measles rarely seen now is hemorrhagic measles or "black measles." It manifested as a hemorrhagic skin eruption and is often fatal. Keratitis, appearing as multiple punctate epithelial foci, resolved with recovery from the infection. Thrombocytopenia sometimes occurred following measles (Kilbourne 1967). Myocarditis is a rare complication of measles. Miscellaneous bacterial infections have been reported, including bacteremia, cellulitis, and toxic shock syndrome. Measles during pregnancy has been associated with high maternal morbidity, fetal wastage, stillbirths, and congenital malformations in 3 % of live born infants (Moss and Griffin 2012).

8.7 Pathologic Features

Extrapulmonary pathologic manifestations of measles particularly those in the skin and lymph nodes are well known. Here we turn attention to the pneumonitis caused by the measles virus. Changes in the lung include peribronchial and interstitial mononuclear cell infiltrates, squamous metaplasia of bronchial epithelium, proliferation of Type II pneumocytes, and formation of hyaline membranes, the latter changes indicative of diffuse alveolar damage. Complicated cases may evolve into abscess formation and empy-

ema. The prototypical pulmonary change however is the development of multinucleated giant cells with characteristic nuclear and cytoplasmic inclusions (Fig. 8.3). These cells, which have also been reported in various lymphoreticular tissues throughout the body, are typically large and contain from a few nuclei to too numerous to count. Absence of such multinucleated giant cells in the lung may occur and should not be regarded as exclusionary evidence of measles pneumonia. Conversely, the presence of such multinucleated giant cells is not diagnostic of measles pneumonia. A giant cell pneumonia-like picture may be seen in a variety of granulomatous disorders, but more importantly giant cell pneumonia can be a manifestation of other viral pneumonias. These include cases of giant cell pneumonia secondary to respiratory syncytial virus, parainfluenza, and the Nipah viruses, the latter less likely since it is not known to occur in Europe or the United States. Viral inclusions are also found in pneumonia due to herpes simplex,

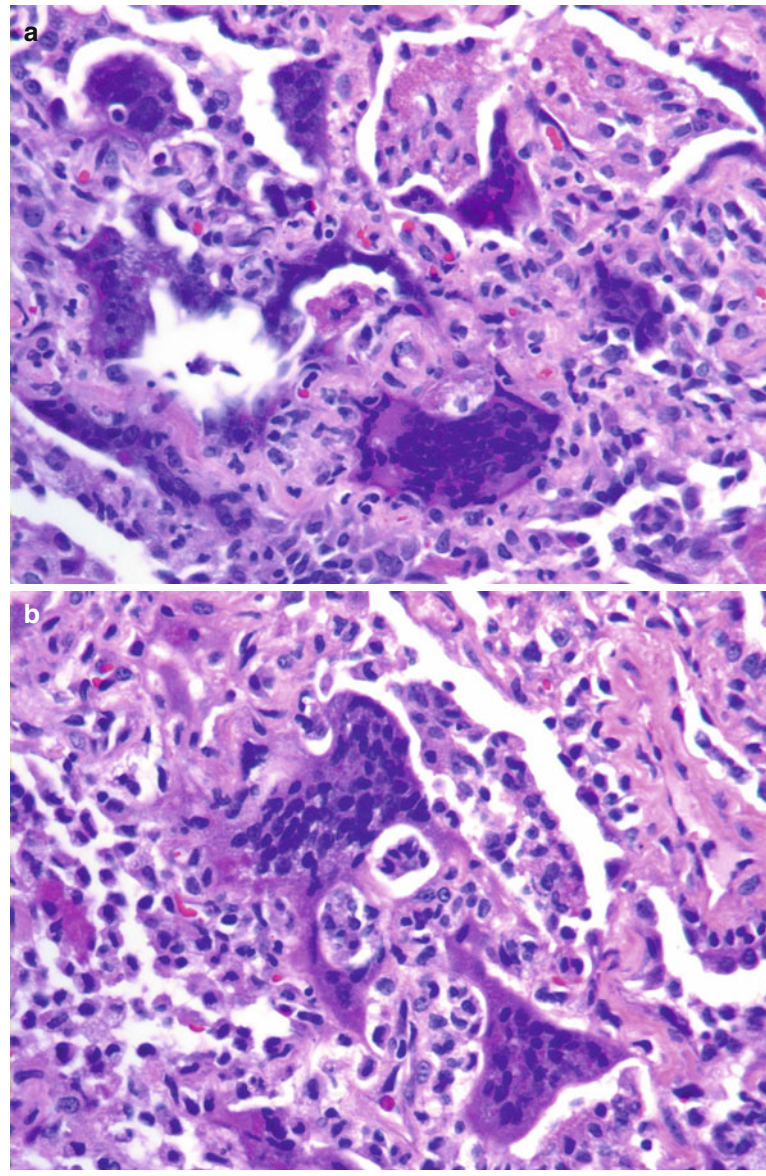
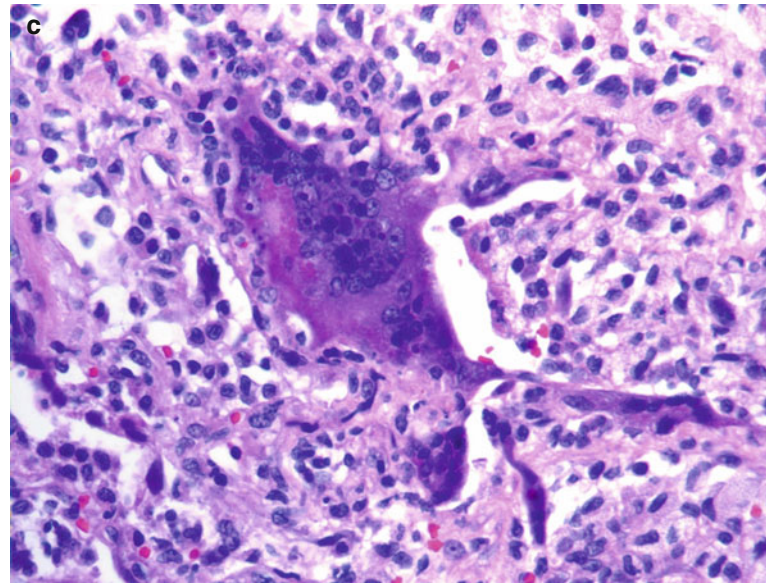


Fig. 8.3 *Panels A*, *B*, and *C* close-up view of lung measles infection showing morphological variations of multinucleated giant cells. Note numerous mononuclear inflammatory cells in the vicinity of the giant cells

Fig. 8.3 (continued)



herpes zoster and adenovirus, and other viral infections but are morphologically different and generally do not represent a diagnostic problem (Zaki and Paddock 2008; Radoycich et al. 1992).

8.8 Diagnosis

Detection of measles-specific immunoglobulin M (IgM) in serum is the standard test for the rapid laboratory diagnosis of measles. IgM testing is most commonly performed using commercial enzyme immunoassay (EIA) kits (WHO 2007). A number of commercially available IgM assays for measles use the indirect format. This format requires the blockage of IgG antibodies and rheumatoid factor through a pretreatment step to ensure optimal performance. IgM assays based on the capture format have been developed for measles (WHO 2007; Moss and Griffin 2012). These assays do not require the removal of IgG antibodies and are considered to be slightly more specific and technically easier to perform than the indirect EIAs for detection of IgM antibodies.

Although no longer routinely used for diagnosis of acute measles infection, detection of a rise in specific IgG in serum samples collected during the acute and convalescent phases can be used to confirm infection. IgG assays rely on the collection of two samples about 10–30 days apart and can also be used for confirmation of sporadic cases when the IgM result is equivocal.

Systems for the direct detection of measles and rubella through RT-PCR are becoming more common, and although standard methods are becoming established, no single standard method has yet been developed. Well-established and widely used methods for RT-PCR detection of measles, developed by the Centers for Disease Control and Prevention, Atlanta, USA (CDC), and the Health Protection Agency, London, UK (HPA), are available from WHO or other relevant laboratories upon request. Although not recommended for routine laboratory diagnosis, culture of measles and rubella virus from clinical specimens is an important component of measles control strategies (WHO 2007).

8.9 Differential Diagnosis

Most often, the diagnosis of measles can be made without difficulty on clinical grounds. Viral infections and other conditions causing cutaneous rash (rubella, dengue fever, drug reactions) should be considered in cases with atypical symptomatology. Histologically, giant cells with

multinucleation in the setting of an interstitial pneumonitis are a helpful indicator, but other viral pathogens (respiratory syncytial virus, human metapneumovirus, parainfluenza, and the henipah viruses) may also be associated with multinucleated giant cells. Immunohistochemical studies in these cases are useful in highlighting viral antigens and pointing to specific etiologies. Laboratory tests as outlined above (see diagnosis) are helpful diagnostic tools.

8.10 Treatment

There is no specific antiviral treatment for measles. Treatment with vitamin A has resulted in a reduction in morbidity and mortality in children with measles. The WHO recommends administration of once daily doses of 200,000 IU of vitamin A for 2 consecutive days to all children aged 12 months or older who have measles. Lower doses are recommended for younger children: 100,000 IU per day for children aged 6–12 months and 50,000 IU per day for children younger than 6 months. In children with clinical evidence of vitamin A deficiency, a third dose is recommended 2–4 weeks later (Moss and Griffin 2012; Griffin 2010; Duke and Mgone 2003). Treatment with antibiotics is indicated when patient with measles developed a secondary bacterial infections.

Antibiotics are indicated for individuals with measles who have clinical evidence of pneumonia and otitis media. Streptococcus pneumoniae and Haemophilus influenzae type b are common causes of bacterial pneumonia after measles, and vaccines against these pathogens will probably lower the incidence of secondary bacterial infections after measles (Moss and Griffin 2012).

8.11 Vaccine

Measles, like polio and smallpox, has no host except man; therefore, eradication of measles is possible if all those who are susceptible to measles are immunized (Zaki and Paddock 2008). Measles virus was first isolated in tissue culture in 1954 (Edmonston strain). Since 1963 a killed virus vaccine (Edmonston A) and a live attenuated vaccine (Edmonston B) were introduced for use globally (Markowitz et al. 1990). The killed vaccine was not used after 1967 because of its incomplete protection (MMWR 2008). Before the introduction of measles vaccine in 1963, there were approximately three to four million US cases annually, and an estimated 90 % of the population had the disease by age 15. Measles vaccination is one of the most cost-effective health interventions ever developed (Perry and Halsey 2004). Thanks to the use of measles vaccine, measles was declared eliminated in the United States in 2000, although sporadic cases continue to occur owing to importation (Enders et al. 1959). The current live, further attenuated vaccines in use in the United States have shown protection for properly immunized children between 91 % and 99 %.

To prevent measles, mumps, rubella, and varicella (MMRV), the Advisory Committee on Immunization Practices (ACIP) recommends a 2-dose vaccine schedule in childhood, with the first dose administered at age 12–15 months and the second dose at age 4–6 years (Am Acad of Ped 2009). The MMRV vaccine may be administered simultaneously with other vaccines recommended for children aged 12–15 months and 4–6 years. If simultaneous administration is not possible, MMRV vaccine may be administered at any time before or after an inactivated vaccine but at least 28 days before or after another live, attenuated vaccine, except varicella vaccine, for which a minimum interval of 3 months is recommended. Live attenuated virus vaccines are contraindicated in patients with altered immunity (i.e., blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system); primary or acquired immunodeficiency including HIV infections/AIDS, cellular immune deficiencies, hypogammaglobulinemia, and dysgammaglobulinemia; family history of congenital or hereditary immunodeficiencies, unless the immune competence of the potential vaccine recipient has been demonstrated; systemic immunosuppressive therapy, including oral steroids ≥2 mg/kg of body

weight or ≥20 mg/day of prednisone or equivalent for persons who weigh >10 kg, when administered for ≥2 weeks; and pregnancy (MMWR 2008). Measles immunization is not contraindicated in children with HIV infection who are not severely immunocompromised (Am Acad of Ped 2009).

8.12 Clinicopathologic Capsule

A highly contagious disease, measles is typically a disease of children. Despite the availability of effective live vaccines, the disease is still responsible for 4 % of diseases in children younger than 5 years of age worldwide. The virus is transmitted via respiratory droplets delivering infectious particles to epithelial cells of the respiratory tract of susceptible nests. Pneumonia is a major complication, characterized in part by the presence of multinucleated giant cells. The differential diagnosis includes giant cell pneumonia due to parainfluenza and respiratory syncytial virus among others. An effective vaccine is available and was helpful to declare measles elimination in the United States in 2000. However, sporadic cases continue to occur owing to failure to seek vaccination in selected population groups.

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