WebLog Journal of Pediatrics

Review Article
Published: 06 Jun, 2026

Measles Virus Infection is Preventable but Potentially Fatal

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WebLog Open Access Publications
Article ID : wjp.2026.f0602
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Abstract

Measles Virus (MV), despite being well controlled with vaccination, is making a resurgence due to the loss of herd immunity from a decreased rate of vaccination. There are many reasons for the decreased vaccination rate, especially in high income countries. This review will discuss the MV epidemiology, pathophysiology, immunologic response of the host and MV dodging of immune host response, risk factors for MV infection, diagnosis, differential diagnosis, complications, treatment, prevention, and promotion of vaccination. It has become an important endeavor for health care workers to improve vaccination efforts and restore herd immunity to prevent the spread of infection especially among the most vulnerable population groups such as children, immunosuppressed individuals, and those with comorbidities.

Keywords: Measles; Epidemiology; Immunology; Diagnosis; Complications; Vaccine; Therapy

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Received Date: *01 May 2026*
Accepted Date: *04 Jun 2026*
Published Date: *06 Jun 2026*

Citation:
Thyyar M Ravindranath. Measles Virus Infection is Preventable but Potentially Fatal. WebLog J Pediatr. wjp.2026.f0602. https://doi.org/10.5281/zenodo.20838447

Introduction

The virus: Measles, also known as rubeola and generally seen in children, is a highly infectious viral disease that is caused by the measles morbillivirus or the measles virus (MV) belonging to the genus morbillivirus, the family of Paramyxoviridae, and the subfamily of Orthoparamyxovirinae [1]. MV consists of an envelope with a diameter of 100-300 nm and possesses a single-stranded, negative sense (complimentary to mRNA and cannot be translated into protein), coiled helix of protein and unsegmented RNA with a genome of approximately 16,000 nucleotides. Eight clades containing 24 genotypes exists [2]. Due to the increase in vaccine coverage and elimination efforts, the number of genotypes has fallen from 13 in 2002 to two in 2022. At present, only B3 and D8 genotypes are identified to be circulating [3]. It appears that the B3 genotype is more efficiently transmitted than the D8 genotype, resulting in vaccine failures, hospitalization, and complications in the recent outbreaks [4]. The number of reported cases of MV oscillated from 2000 to 2019, initially decreasing and then increasing. During the same period, vaccination was successful in preventing mortality by nearly 26 million [5]. During the COVID-19 pandemic, the number of reported MV infections globally fell to 59,619 in 2021. In the US there were only 13 cases of MV reported in 2020 due to travel restrictions, social distancing, and enforcement of personal protection as well as disruption of the scrutiny system [6]. However, there is a resurgence of MV infection stemming from decreased vaccination for various reasons [7]. Measles was certified as eliminated in 2000 in the US [8] as defined by the absence of persistent transmission for more than a year. However, the US is at risk of losing its status as being free from endemic MV transmission.

Epidemiology: The natural hosts of MV are humans. Monkeys are suspected to be infected with MV [9]. In the absence of a vaccine, it is projected that MV epidemics lasting 3-4 months may occur every 2-5 years due to the accumulation of vulnerable people who were overlooked during seasonal occurrences [10]. In temperate climates, the MV epidemic appears in early spring and in late winter due to the gathering of children at school. In the tropics, the measles epidemic occurs in the dry season resulting from high birth rates and swings in population density [11]. With the MV vaccine coverage exceeding 80% and the decreasing the rate of accrual of at-risk persons from each birth unit, the period between epidemics is about 4 to 8 years or longer in the tropics [12]. Respiratory droplets, airway secretions and microparticle aerosols that remain suspended in the air for several hours spread the virus over a short distance. MV can be spread by direct contact with infected secretions but fails to survive on fomites and is inactivated by heat as well as ultraviolet radiation within hours. The incubation period is 10-14 days (95% confidence interval [CI] of 11.8-13.3 days) during which the MV replicates in lymphoid and myeloid cells and launches a systemic infection. Subsequent to the incubation period, MV spreads to the peripheral lymph nodes, leading to the prodromal phase which is followed by a systemic spread after the development of Koplik spots. Symptoms can

Figure 1: The Measles virus genome.
N: Nucleocapsid protein, P: Phosphoprotein, C & V: Non-structural proteins, M: Matrix protein, F: Fusion protein, H: Hemagglutinin protein, L: Large protein.

persist for up to 3 weeks. The infectious period starts 4 days prior to the onset of rash and lasts 4 days following the appearance of rash [13]. MV is extremely infectious, and the reproduction number (Ro) is 12-18 i.e., one infected person can transmit infection to 12-18 other individuals. Because of the high infectivity of MV, vaccine coverage for 95% of the population is needed to achieve herd immunity. The mean case fatality ration between 1990-2015 was estimated to be 2.2% [14]. MV, as alluded to earlier, is one of the most highly transmittable illnesses and infection occurs even in populations where less than 10% is vulnerable to MV. Infection takes place in close settings due to high contact rates such as what is observed within households, schools, and health care facilities. Although MV is a disease of infants and children, the age of onset of MV infection rises as the MV vaccination coverage increases or as birth rate contracts, resulting in MV infection predominating in children between 5-10 years of age. As the rate of vaccination rises, the age of onset of MV infection can further increase to involve adolescents and young adults, requiring MV vaccinations in these age groups [15].

Pathophysiology: The single-stranded genome of the MV consists of six structural proteins that include nucleocapsid protein N, phosphoprotein P, matrix protein M, fusion protein F, hemagglutinin protein H, and large protein L as well as V and C (Figure 1 & 2). The N, P, and L proteins are complexed with RNA. These proteins are separated from each other by non-coding intergenic regions. V and C are involved in inhibition of the innate immune response as well as in the regulation of viral transcription and replication [16]. The H protein is implicated in the attachment of MV to the host cell whereas F protein is involved in the spread of the virus from cell to cell. The measles virus infects cells *via* the receptor signaling lymphocyte activation molecule (SLAM; CD 150) (Figure 3) found on immature thymocytes, T cells (activated and memory), B cells (naïve and activated), macrophages, and dendritic cells (DCs) as well as nectin-4 receptor, also called Poliovirus Receptor-Like-4 (PVRL4), which is a second cell receptor for MV and is present on the basal surface of epithelial cells of the respiratory tract and the adherent junction; thereby facilitating the aerosolization of the MV [17, 18]. The involvement of the SLAM receptor explains the lymphotropic effect of the MV and its immunosuppressive effect [19]. Intercellular adhesion molecule 3-grabbing non-integrin (DC-sign or CD209) and C-type lectin domain family 4 member K (Langerin) encourages the MV infection of DC's and Langerhans cells respectively, resulting in the high transmission of MV [20, 21]. Neuronal cells lack cellular receptors for MV. Following infection, the MV in the respiratory tract is carried to thymocytes, T and B cells, and hemopoietic stem cells by tissue resident DCs which are targeted initially, and macrophages [22] facilitated by SLAM and DC-SIGN. MV can also infect alveolar macrophages directly via SLAM present on alveolar macrophages [23]. Epithelial cells are not the initial target of MV infection since nectin-4 is not present on the apical surface of the epithelial cells. However, lymphocytes and DCs infected by MV can migrate into respiratory tract subepithelial layers and infect epithelial cells *via* nectin-4 [24]. MV is easily transmitted between epithelial cells via intercellular membrane pores [25] by using adherens junction protein nectin-4/afadin complex. This helps MV in the cells lining the airway detach, triggering sneezing as well as coughing leading to aerosolization of MV. The entry and dissemination of the MV to the epithelial cells and endothelial cells is facilitated by the infected mononuclear cells where replication occurs. The spread to lymph nodes ensues via DCs followed by systemic spread. The initial stage of infection involves the respiratory tract followed by the replication stage in lymphoid organs and tissues. The infectious period is at its peak when the virus multiplies in the upper respiratory tract (nasopharyngeal) rather than in the lower respiratory tract (tracheobronchial) [26]. This is followed by an incubation period of 7-14 days when individuals are asymptomatic. The prodromal phase which follows the incubation period is characterized by fever over 40°C, cough or coryza or conjunctivitis from damage to the epithelium secondary to viral replication [27]. A keratoconjunctivitis from infection of keratocytes facilitated by the presence of nectin-4 can be complicated by blindness. A maculopapular rash that is seen universally in all infected individuals is due to infiltrated immune cells that are involved in clearing infected myeloid and lymphoid cells. Secondary bacterial infection leads to pneumonia, diarrhea, and otitis media [28]. The onset of rash coincides with the appearance of measles specific IgM antibodies and lasts 2 months which is flowed by the appearance of IgG antibodies which may persists for life [13]. CD 147 enables MV entry into epithelial and neuronal cells explaining Central Nervous System (CNS) involvement in MV infection [29]. Immune related issues include transient immune suppression that is responsible for secondary infections [30] which may last as long as 2-3 years [31] as well as immune amnesia due to the altered composition of lymphocyte population (depletion of $CD150^{+}$) in some [22]. However, MV induces significant cellular and humoral response that provide lifelong protection in most cases. The mechanism of life-long immunity to MV infection is unknown.

The role of immunity in MV infection: Even though RNA viruses possess high mutation rates, the surface protein of MV that is responsible for generating protective immunity retain their antigenic stability for decades; thereby enabling the use of live attenuated vaccine that is developed from old strains of the MV. Anti-viral response is initiated by the MV virus when it is encountered by the Pathogen-Associated Molecular patterns (PAMs) that include Retinoic acid-Inducible Gene 1 protein (RIG-1), Melanoma Differentiation Associated protein 5 (MDA5), and Laboratory of Genetics and Physiology 2 (LPG 2) all of which sense viral RNAs. RIG-1 like receptor activate kinases that phosphorylate interferon (IFN) regulatory factors, leading to the formation of INFs. The INFs activate Janus Kinase (JAK) which is a Signal Transducer and Activator of Transcription (STAT) signaling pathway in neighboring cells leading to the formation of many antiviral genes [32].

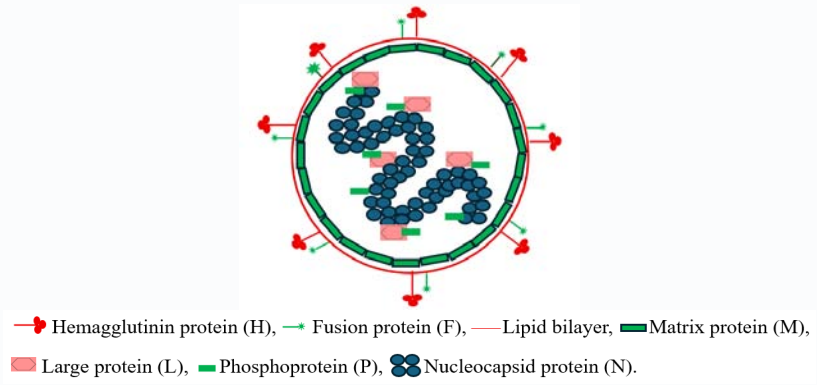

Figure 2: Structure of MV.

The cell-mediated adaptive immunity plays an important role in MV clearance and development of memory to prevent reinfection [33]. Therefore, individuals with defective cellular immunity fare poorly compared to those with hypogammaglobulinemia i.e., humoral immunity [34]. The role of $CD8^+$ T cells in MV infection is better clarified than $CD4^+$ T cells. MV prodrome is characterized by an elevation in Th1 cytokines interferon gamma (IFN-ɣ) and Interleukin 2 (IL-2) in the blood [35], however, during recovery from MV infection, elevation in the Th2 cytokines IL-4 and IL-5 follows. Severe lymphopenia follows in acute MV infection involving CD4 (helper T cells) and $CD8^+$ T cells (cytotoxic T cells) [36]. Suppression of T cell proliferative response has been documented due to the effect of the MV-H protein as well as the F protein on the virus or viral infected cells [37]. Although, the secretion of IL-2, IL-6, IL-10, and IFN-ɣ alteration is not significant, IL-4 is decreased. There is also a reduction of IL-2Ra (interleukin-2 receptor antagonist) [38]. DC that are infected with MV upregulate Major Histocompatibility Complex-1 and 2 (MHC) and chemokine generation help in the migration of DCs into the lymph node, helping in the spread of MV virus [39]. The MV glycoprotein HA and F suppress interaction between DCs and T cells helping to suppress T cell proliferation [40]. Maternally acquired IgG antibodies shield infants, which lasts until about 9 months of age [41]. However, a shorter duration of protection of their infants is found in women with vaccine induced immunity owing to their lower levels of anti-MV antibodies versus women with naturally acquired immunity [42]. When infected with MV, DC's poorly mature and lose the ability to stimulate proliferative response in lymphocytes and undergo cell death [43]. MV infection also suppresses delayed type of immune response and cellular and humoral responses to new antigens are lost [44]. Measles also impairs memory immune responses to other pathogens. Adaptive immune response is important for viral clearance and antibody response protects from reinfection.

Immune dodging by MV: V protein binding to MDA 5 and LPG 2 inhibits IFN synthesis [45]. The C protein hinders IFN induction at the transcription level [46] as well as indirectly deters IFN induction via its controlling role in viral RNA production. The V protein, on the other hand, actively inhibits the JAK-STAT signaling by working together with STAT 1 and STAT 2 [47]. The P protein shows IFN inhibiting properties similar to V protein [48]. Both C and V proteins are essential to bypass the host IFN responses [49]. Lymphopenia results from altered lymphocyte trafficking and the inhibition of hematopoiesis [50].

Risk factors for MV infection: Risk factors for MV infection include deficient nutritional status such as undernutrition, malnutrition, vitamin A deficiency; the intensity of exposure to MV; an immune compromised state; gender status as suggested by higher mortality in girls [51]; host genetic factors such as gene variable cytokine generation as well as polymorphism in Human Leukocyte Antigen (HLA) genes that leads to differences in antibody responses [52].

Diagnosis

Clinical manifestation: MV is an acute illness. Prodromal period lasts two to four days consisting of fever, cough, coryza, conjunctivitis [13] preceded by Koplik's spot which are tiny bluish-white spots seen in 70% of the subjects. These spots are slightly raised, 2-3 mm in size, present on a reddened base on the buccal mucosa at the level of 1st molar and may be seen over the soft palate as well as vaginal mucosa. It occurs the day before the onset of rash and lasts for 2-3 days, clinching the diagnosis. A maculopapular rash appears two to four days before the onset of fever. However, in those that are vaccinated against MV and in immunocompromised patients, typical symptoms and signs may be absent making the diagnosis difficult. The symptoms become severe over the next 24-48 hours and the rash lasts 3-7 days with involvement of face, head, trunk, palms and soles followed by scaling. The rash may become confluent on the face and upper part of the body. Malnourished children manifest a severe desquamation of the skin. Initially rash involves the face followed by lower part of the skull. Cough can last 10 days and other manifestation include iridocyclitis, pharyngodynia, headache, abdominal pain, and generalized lymph node enlargement. In uncomplicated cases, clinical manifestations subside a few days after the onset of rash and recovery takes place in about a week. Measles hepatitis is secondary to hepatocellular involvement due to direct MV effect [53]. Mortality in developing countries from MV is as high as 1-15% due to malnutrition, overcrowding, and the lack of access to health care [54].

Clinical Presentation in Unique Groups

Hypersensitivity: Inactivated killed MV vaccine which fails to provide protection sensitizes individuals to the MV antigen and, when exposed to MV, causes polyserositis which presents with high fever, rash over extremities with petechiae and pneumonia [55].

In cases of malnutrition, particularly associated with vitamin A deficiency, encephalitis and ocular complications are more common [56].

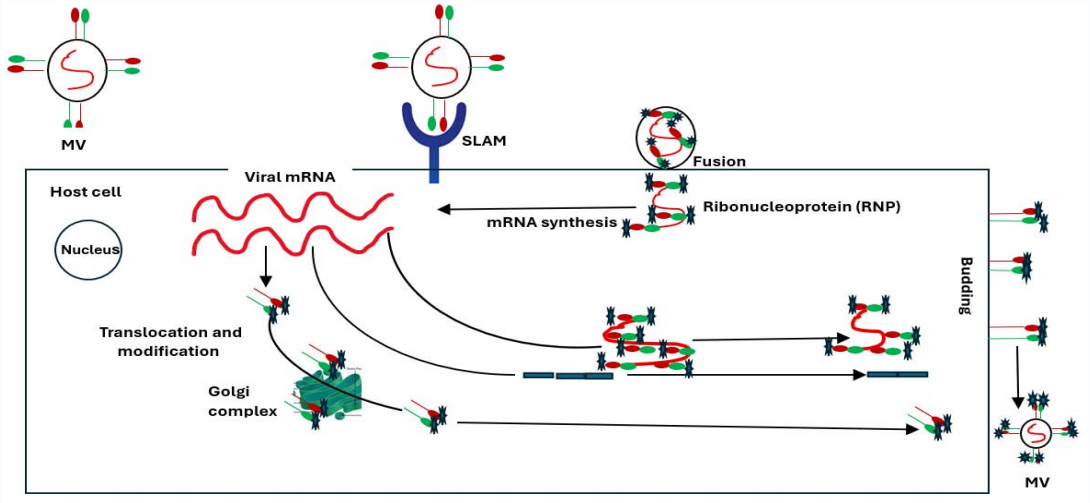

Figure 3: MV life cycle.
Signaling Lymphocyte Activation Molecule (SLAM). The steps involved in MV infection comprises the binding of H protein to host receptor followed by membrane fusion resulting in the release of the viral mRNA into the infected cell cytoplasm. Replication and transcription takes place subsequently in the cytoplasm resulting in assembly of RNP complexes that are moved along microtubules by endosomes. The H and F protein are transported to the plasma membrane by a secretory pathway. The virus assembly and cell to cell fusion occurs by the interaction of M protein with RNP, H protein, F protein, the cell membrane, and actin filaments in the host cells.

Diagnosis: Clinical diagnosis is based on the presence of fever, cough, coryza, conjunctivitis, maculopapular rash that is observed over the face first, and Koplik spots. The presence of MV infection is often confirmed by laboratory diagnosis especially in those with atypical presentation.

One such diagnostic tool is the detection of specific anti-measles IgM antibodies in the serum (sensitivity of 83-89% and specificity of 95-99%), which are constantly present from four days after the onset of rash [57]. ELISA and RT-PCR (real-time polymerase chain reaction) detection of MV RNA in throat and nasopharyngeal swabs, urine, oral fluid and blood (sensitivity of 94% and specificity of 99%) [58] are used commonly for diagnosis [13]. RT-PCR turns positive prior to the detection of IgM antibodies and is useful for genotyping. Sensitivity is highest when samples are collected as early as possible after the onset of rash. IgM may be low or undetectable in individuals who are vaccinated. False positivity is seen in other infections characterized by fever or rash as well as interference by rheumatoid factor. Viral culture is time consuming and not cost effective.

Differential diagnosis: Differential diagnosis includes rubella, dengue, parvovirus B19 infection, human herpesvirus 6, and a reaction to the measles vaccine. Case definition for MV infection includes maculopapular rash, fever greater than 38.3°C, cough, coryza, or conjunctivitis or a combination of these symptoms and signs. Although these differential diagnostic criteria have a sensitivity of 75-90%, they have a low positive predictive value in settings where the incidence of MV infection is low. Therefore, laboratory diagnosis is essential to confirm the diagnosis of MV infection [59].

Complications

Infectious: The majority of complications are due to interruption of epithelial surfaces and/or immunosuppression. Complications from the MV include otitis media in 7-9%, laryngotracheobronchitis with a purulent exudate, bacterial tracheitis, and pneumonia in 1-6% [60] [Hecht's giant cell pneumonia] either from the virus itself or secondary to bacterial infection within the first two weeks of the observance of MV infection inception. Pneumonia can also be complicated by infection from adeno or herpes simplex virus. Bacterial pneumonia is caused by *Streptococcus pneumoniae, Staphylococcus aureus, Hemophilus influenzae*, and *Neisseria meningitidis* [61]. Pneumomediastinum and mediastinal emphysema has been reported [62]. In those who have vitamin A deficiency, a more severe infection ensues resulting in higher complications.

Cardiac: MV associated myocarditis can rarely arise [63].

Gastrointestinal tract: Appendicitis occurring with rash was reported with detection of giant cells in the intestinal epithelium [64]. Diarrhea is also noted in 8% of patients [63]. Severe malnutrition is seen in those that are already undernourished.

Pregnancy: Spontaneous abortion, preterm labor, and low birth weight are some complications of MV infection. Infection in late pregnancy leads to perinatal infection in neonates and respiratory issues [65]. Although MV can infect the placenta, no fetal malformations have been reported [66]. Maternal death has been reported [67]. No treatment is available for MV infection in pregnancy other than prophylaxis with immunoglobulin and prevention with vaccine administered prior to pregnancy [68]. While MV vaccination currently is not recommended, incidental vaccination during pregnancy has not resulted in danger to mother, fetus, or to infants [69].

Neurological: Febrile seizures occur in less than 1 per 3000 cases. Acute Disseminated Encephalomyelitis (ADEM) was seen in 0.5 to 1 in 1000 cases and is an immune mediated demyelinating disease characterized by fever, fatigue, headache, nausea, vomiting, seizures, and coma leading to mortality occurring within two weeks of MV infection. IgG antibodies in the serum, PCR from respiratory secretions, and MRI help to make a diagnosis [70].

In those who are immunocompromised, inclusion body encephalitis is seen between 6-12 months after MV infection and clinically presents as cognitive decline, hearing, and vision loss leading to coma and death [71]. The virus is detectable in brain tissue

following biopsy.

Another mortal condition that is observed includes Subacute Sclerosing Panencephalitis (SSPE) due to persistent MV infection in 6-11/10,000 individuals infected with the virus and is seen 5-10 years after acute measles with an observed mortality of 1 per 1000. Defective cellular immunity may play a role in precipitating SSPE [72]. It occurs years after infection, consisting of cognitive decline, personality and behavior changes followed by myoclonus, seizures, coma, and death [73]. Patients with SSPE are not infective since they do not shed MV. The MV is hypothesized to spread to the brain during acute onset of rash when endothelial cells are infected. Increased levels of IgG antibodies in CSF, EEG, and MRI helps to make the diagnosis.

Eye: Eye complications include conjunctivitis with or without keratitis secondary to bacterial or viral infection such as adeno and Herpes simplex virus leading to blindness [74].

Ear: Otitis media occurs in 7-9% of MV infected individuals.

Other issues: MV infection results in decreased life expectancy, added disability, loss of productivity as well as missed school time, lost work time from caring for sick or disabled individuals, and increased use of health care resources.

Mortality: Death from MV occurs 1per 1000 in developed countries and 1 to 15 per 100 in developing countries (100,000-200,000 total deaths annually). Despite implementation of MV vaccination, measles remain a leading cause of mortality in children under the age of 5 years.

Table 1: Complications: MV *vs.* Vaccine.

Complications	MV	Vaccine
Febrile seizures	1/3000	5%-15%
Rash	Always present	5%
Pain	Yes	25% at the injected site
Koplik spots	Pathognomonic	No
Otitis media	7%-9%	No
Low platelets	Yes	1/3000
Parotitis	Rare	<1%
Lymphadenopathy	Yes	5% in children & 20% in adults
Pneumonia	1%-6%	No
Meningitis	Yes	1-10/million
Encephalitis	1-3/1000	<1/million
Anaphylaxis	No	2-14/million
ADEM	0.5/million	No
SSPE	6-11/10,000	No
Mortality	1-10,000 to 1-15/100	No

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Treatment

Prophylaxis following MV exposure: Contacts of an infected individual are administered passive immunization with immunoglobulin especially in those who are younger than 6 months, pregnant women, and immunocompromised hosts within six days after exposure (95% effective) [75]. The dose recommended is 0.5 ml/kg administered Intramuscularly (IM) for those with a body weight of up to 30 kg and 400 mg/kg for those who weigh greater than 30 kg [76]. MMR vaccine is administered after 6 months for those who received IM immunoglobulin or 8 months after Intravenous (IV) dose. Vaccine can also be administered within seventy-two hours after MV exposure (90% effective).

Supportive care: Infected patients that are hospitalized are isolated to prevent airborne transmission. Supportive care includes correcting underlying dehydration, antipyretics, antitussives, environmental control such as humidification, treating nutritional deficiencies including that of vitamin A, and pain control [77] since there are no specific drugs that can be used against the MV. It is recommended by WHO to administer one dose of vitamin A to children in less than 5 years and a second dose a day later. If there is evidence of vitamin deficiency, a third dose is given 4-6 weeks later followed by supplementation. The dosage of vitamin A is as follows, 200, 000 International Units (IU) over the age of 12 months; 100,000 IU for infants between 6-12 months; and 50,000 IU for infants younger than 6 months [78]. In addition, vitamin A is indicated in children who are immunosuppressed and those who recently immigrated from places with a high mortality from MV infection. Vitamin A exerts beneficial effects on epithelial cells and host immune response. An antibiotic is administered to treat secondary bacterial infections such as bacterial pneumonia and otitis media, and prophylactic use is discouraged. ADEM is treated with corticosteroids or IV immunoglobulins or plasmapheresis [70]. SSPE is managed with the administration of Isoprinosine, an immunomodulatory and an anti-viral agent with or without ribavirin at a dose of 50 mg/kg [79]. IV immunoglobulin, intrathecal interferon α, and amantadine were also used in SSPE management [73]. The use of steroid is reported in case reports in MV pneumonia [80]. Children immunized against Hemophilus influenzae and streptococcus pneumoniae experience less severe infection following MV due to their protective effect. The cost of treating MV infection in 2013 was estimated to be $1000-2000 in high-income countries and lower in low-income countries [81].

Preventive health care: Isolation of infected individuals in Airborne Infection Isolation Room (AIIR) with doors closed and directing exhaust of air to the outside. After the patient leaves the room, it should remain vacant for the appropriate time (up to 2 hours) to allow for 99.9% of airborne-contaminant removal. Health Care Personnel (HCP) must use respiratory protection (i.e., a respirator) that is at least as protective as a fit-tested, National Institute for Occupational Safety and Health (NIOSH) certified disposable N95 filtering facepiece respirator, regardless of presumptive evidence of immunity, upon entry to the room or care area of a patient with known or suspected measles. Appropriate quarantine, and vaccination of susceptible contacts [82] are important considerations in the preventive aspects of MV. Most MV virus belong to the B3 or D8 genotypes.

MV vaccines: Prior to the introduction of MV vaccine in 1963, it was assessed that there were 30 million MV cases with over 2 million deaths occurred yearly around the world [83]. MV vaccines are live attenuated vaccines which are not only effective, but also inexpensive. These vaccines are available as monovalent, bivalent consisting of MV and rubella, trivalent comprising MV, mumps, and rubella, or tetra valent that includes MV, mumps, rubella, and varicella [84]. MV vaccine is exceedingly effective in all countries irrespective of the prevailing ubiquitous genotype [85]. Response to MV vaccine is less effective than response to wild-type infection with similar cellular response, but with lower and less sustained antibody levels [86].

Side effects of MV vaccine: Fever > 39°C is observed between

7-12 days post-vaccination (5-15%), pain at the injected site, joint pain (25%), rash (5%) 7 to 12 days after vaccination, febrile seizures (1 per 3000), transient low platelets (1 per 30,000), anaphylaxis (2-14 per million), parotitis, lymphadenopathy, and encephalitis [<1 per million] [87], transient lymphadenopathy (5% of children and 20% of adults), parotitis (<1%), and aseptic meningitis (1 to 10/million). No cases of otitis media, diarrhea, pneumonia, SSPE, or death were reported following MV vaccination [88]. The rubella constituent of MMR vaccine can cause transient arthralgia or arthritis especially in susceptible post pubertal female patients. There is no evidence of person to person transmission of vaccine virus.

Table 1 shows complications from MV vs. MV vaccine.

Contraindications: Previous allergic reaction to MV vaccine, immunosuppression, and pregnancy [89] are contraindications for MV vaccination.

Immunogenicity of MV vaccine: The live attenuated vaccine is given by injection induces cellular and humoral immunity which develops over months. Those who receive the vaccine are protected from measles induced illness but not from MV infection. MV vaccine also protects from all-cause mortality. Although not definitively known, it may be due to the prevention of immunosuppression that follows MV infection and thus prevents secondary infections [90].

Vaccine schedule: Two doses of MV vaccine 4 weeks apart are recommended as per WHO for routine immunization to ensure the development of immunity. In high-risk settings, such as in endemic areas, the 1st dose is recommended at the age of 9 months. During outbreaks of measles, for displaced population, and children with HIV the first dose is given at 6 months of age [91]. In low-risk setting, the vaccination is advocated at the age of 12 months. The former schedule at 9 months results in 85%-90% seroconversion and the latter at 12 months results in 90%-95% seroconversion [90]. Vaccine efficacy (84%) and higher antibody titers are observed when vaccine is administered at the age of 12 months or greater [92] with a median effectiveness of 93% with a range of 39 to 100 and after two doses the median effectiveness is 97% with a range of 67 to 100 [78]. The second dosage is recommended at 15 to 18 months of age [91]. As per CDC recommendation in the USA, the 1st dose is administered between 12-15 months of age, and the second dose is administered between 4-6 years of age [93]. A third dose of MV vaccine is suggested in adolescents and young adults in order to prevent secondary vaccine failure due to waning immunity [94]. Secondary vaccine failure rates are projected to be 5% at 10-15 years after vaccination. Antigenic activation of plasma cells and not memory B cells in the bone marrow are responsible for prompt humoral response after contact with wild type MV [95]. Two doses of MV vaccine are required to reach herd-immunity and interrupt the spread of MV infection. CDC recommends that MMR and varicella vaccine be given separately but can be given together for the second dose [76]. The reason for two dosage schedule for MV vaccine is that maternally acquired IgG antibodies interfere with immune response to the attenuated measles vaccine by inhibiting the replication of the vaccine virus. However, maternally acquired antibodies decline over time and are absent by 9 months of age in most children. The immunity from MV vaccine is lifelong.

Promotion of vaccination: Checking vaccination status at school entry, when starting employment, vaccinating individuals who may have not completed vaccine schedule, will help to maintain herd immunity level of at least 95%. Serological survey in high risk groups help to confirm the immune status. In addition, to overcome vaccine hesitation, it is suggested to promote positive media coverage that attests to the benefits, efficacy, and safety of MV vaccine as well as its effect on reducing all-cause mortality [96] and negative consequences of not getting vaccine. Phone messages, reminder letters may help to increase vaccine uptake [97]. In resource constrained locations, a different method of vaccine administration such as microneedle patches may help to overcome limitations. Previously, the anti-vaccine movement was focused on religious beliefs, in the late 1990s vaccination was linked to autism and further exacerbated by prominent people and politicians supporting anti-vaccine movement. Several epidemiological studies have documented that there is no link between autism and measles vaccination [98] nor to that of inflammatory bowel disease. The spread of many websites and forums aided the anti-vaccine movement. Therefore, it is required to intervene at many levels to overcome the lack of accurate information and the spread of misinformation [99].

Overcoming other issues: Other issues that need attention are overcoming insufficient resources, lack of political commitment, deficiency of leadership, poor surveillance, and a dearth of immunization services [73]. These issues are becoming more pervasive and possess a challenge to healthcare workers.

Conclusion

MV is a highly infectious viral disease affecting multiple organ systems with severe complications, especially in children. However, it is a preventable infection with an effective and available vaccine. The lower vaccination rate has made the disease resurgent due to decreased levels of herd immunity. The diagnosis is made using clinical criteria and confirmed by laboratory tests especially in atypical cases. In order to increase the uptake of the MV vaccine, health care personnel must educate the public about the safety and the necessity of the vaccine and counteract vaccine hesitancy and misinformation.

Acknowledgement

The author would like to thank Malini Ravindranath, PhD, for reading and editing the article.

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