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DIAGNOSIS AND TREATMENT OF THE INFECTIOUS DISEASE MEASELS

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ABSTRACT

Measles is an infectious disease in humans caused by the measles virus (MeV). Before the introduction of an effective measles vaccine, virtually everyone experienced measles during childhood. Symptoms of measles include fever and maculopapular skin rash accompanied by cough, coryza and/or conjunctivitis. MeV causes immunosuppression, and severe sequelae of measles include pneumonia, gastroenteritis, blindness, measles inclusion body encephalitis and subacute sclerosing panencephalitis. Case confirmation depends on clinical presentation and results of laboratory tests, including the detection of anti-MeV IgM antibodies and/or viral RNA. All current measles vaccines contain a live attenuated strain of MeV, and great progress has been made to increase global vaccination coverage to drive down the incidence of measles. However, endemic transmission continues in many parts of the world. Measles remains a considerable cause of childhood mortality worldwide, with estimates that >100,000 fatal cases occur each year. Case fatality ratio estimates vary from <0.01% in industrialized countries to >5% in developing countries. All six WHO regions have set goals to eliminate endemic transmission of MeV by achieving and maintaining high levels of vaccination coverage accompanied by a sensitive surveillance system. Because of the availability of a highly effective and relatively inexpensive vaccine, the monotypic nature of the virus and the lack of an animal reservoir, measles is considered a candidate for eradication.

1. INTRODUCTION

The measles virus (MeV) belongs to the family Paramyxoviridae and is a single-stranded, negative-sense RNA virus in the genus Morbillivirus [1]. MeV is an airborne pathogen that can be spread through the inhalation of tiny aerosols that can linger in the air for several hours as well as respiratory droplets that disperse quickly [2.3]. The virus can also spread through direct contact with secretions that are contaminated, however MeV is inactivated and does not last long on fomites (i.e., any object that might harbour pathogens, such as skin, hair, clothing, and bedding). by heat and UV light in a short period of time. Sneezing and coughing, which increase the virus's ability to spread, are a part of the prodromal phase of the measles. The incubation period lasts roughly 10 days before fever sets , and 14 days before rash appears. A generalised maculopapular (non-vesicular) skin rash, temperature exceeding 38.3 °C (101 °F), cough, coryza (or rhinitis), and/or conjunctivitis are the clinical symptoms of measles. Koplik spots, which appear as a cluster of white lesions on the buccal mucosa bordering the cheeks, are thought to be pathognomonic for measles. Patients with measles are considered contagious between 4 days prior to and 4 days following the appearance of the rash, when MeV levels in the respiratory tract are at their highest [1]. Although isolation of susceptible contacts is advised, the efficiency of quarantine measures may be hampered by MeV's contagiousness before the start of recognisable disease. A safe, efficient, and affordable vaccine is widely accessible to prevent the measles, a disease that can be prevented by vaccination. This Primer provides an overview of the epidemiology of measles, details international efforts to prevent the spread of MeV, defines the pathogenesis of MeV infection, and emphasises recent studies that have revolutionised our understanding of this significant infectious disease.

2. EPIDIMOLOGY

History of measles

Before the measles vaccine was developed in 1963, the number of cases and fatalities from the disease was estimated to be 30 million per year worldwide [4] (Fig. 4). In the first half of the 20th century, industrialised nations saw a drop in measles mortality as a result of economic growth, better nutrition, and more supportive care, particularly antibiotic therapy for measles-associated bacterial pneumonia [5]. Despite this pattern, increasing coverage with a first dose of a measles-containing vaccine (MCV1) in the first year of life led to the most notable improvements in lowering measles incidence and death. The majority of the children no longer have maternally acquired antibodies by the time they are 9 months old, which is the age at which standard measles vaccine is offered in many nations. Supplementing with vitamin A most likely made a further contribution to the decline in measles mortality [6]. Although the precise mechanism by which vitamin A lowers measles morbidity and mortality is yet understood, it probably involves favourable effects on epithelial cells and host immunological responses.

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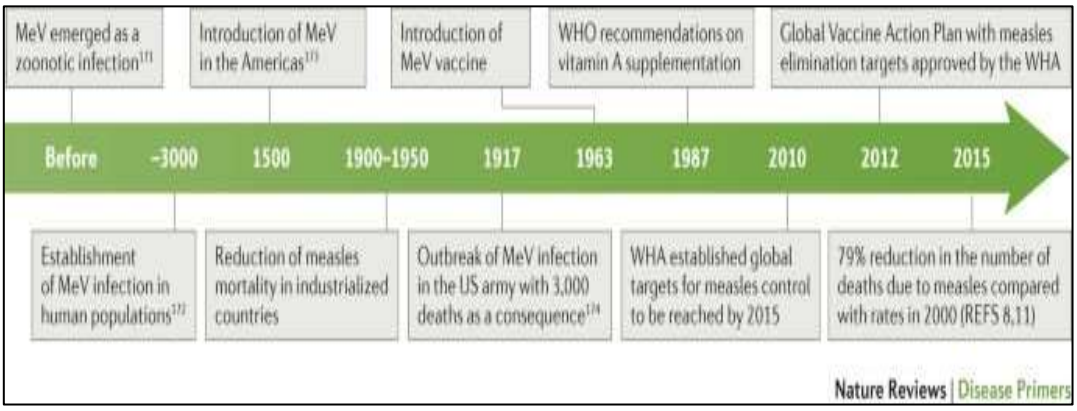

Figure 1: shows the progression of measles virus infections and eradication efforts

objectives for immunisation and eradication

The measles virus (MeV), which is closely linked to the recently eradicated cow virus rinderpest [170], likely originated from an ancestral virus and first appeared as a zoonotic infection in areas where cattle and humans coexisted [171]. MeV most likely first appeared in humans some 5,000 years ago, when populations in Middle Eastern agrarian societies grew large enough to sustain virus transmission [172]. An eye-catching illustration of the devastation caused by measles and accompanying bacterial co-infections that happened before to the introduction of antibiotics or measles vaccines was the outbreak of measles in the US Army from 1917 to 1918, which resulted in more than 95,000 cases of measles and 3,000 fatalities. Between 2000 and 2014, an increase in [174] measles vaccination rates is thought to have avoided 17.1 million deaths (Ref. 8). World Health Assembly, or WHA. The Measles & Rubella Initiative (M&RI), which was founded in 2001 by five core partners, including the WHO and the United Nations Children's Fund (UNICEF), initially focused only on measles, provided a global vision statement for achieving the elimination of measles and rubella worldwide: the Global Measles and Rubella Strategic Plan 2012-2020. Between 2000 and 2014, the estimated MCV1 coverage increased globally from 70% to 85%, and the proportion of nations with an MCV1 coverage of at least 90% rose from 44% to 63% [7] (Fig. 2). In addition, the fraction of nations with 80% coverage of MCV1 and 90% coverage overall. From 1% in all districts in 2003 to 40% in 2014, MCV1 coverage rose. High levels of two-dose coverage are necessary for the eradication of the measles, and between 2000 and 2014, both the estimated global coverage with MCV2 and the number of countries offering it as part of routine immunisation programmes grew.

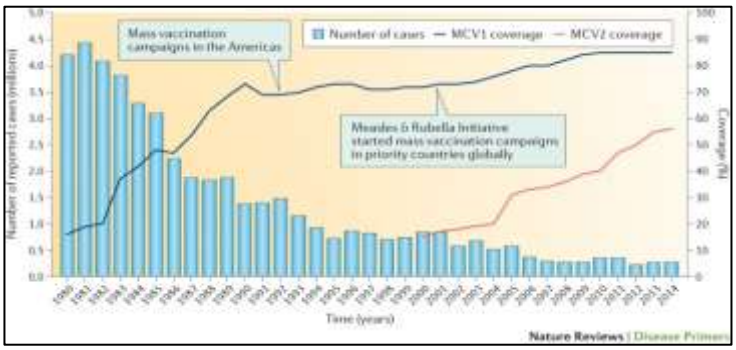

Figure 2: estimated coverage with the first and second doses of the measles-containing vaccine by year (1980-2014) and the number of reported cases of measles worldwide.

Three global targets for measles control by 2015 were set by the World Health Assembly (WHA) in 2010: a routine measles vaccination coverage of 90% nationally and 80% in every district; a reported measles incidence of less than five cases per 1 million people; and a measles mortality reduction of 95% compared to mortality in 2000 (Ref. 8). The Global Vaccine Action Plan for 2012-2020, which established goals for the eradication of measles and rubella, was subsequently approved by the WHA. In accordance with this strategy, measles was to be completely eradicated in at least five WHO regions by 2020, with all six WHO regions setting aims to do so by 2020 or earlier (Ref. 9). All six regions' WHO member nations have approved measles eradication targets as of September 2013. In the presence of an effective surveillance system, elimination is defined as the absence of endemic MeV transmission for at least 12 months in a specific geographic area [10]. Measles-related mortality decreased by 79% between 2000 and 2014 [8.11] (Fig. 3) Despite the fact that this is a sizable reduction, the global objective for 2015 was not met. Every two to four years, SIAs are carried out in nations with inadequate MCV2 coverage; in 2014, SIAs were carried out in 28 nations,

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reaching an estimated 221 million children [7]. For measles elimination initiatives, case-based surveillance of the highest calibre is just as important as vaccination. The WHO Global Measles and Rubella Laboratory Network (GMRLN) reported that at the end of 2014, 96% of countries had established case-based surveillance and 98% had access to standardised, quality-controlled testing [12.13].

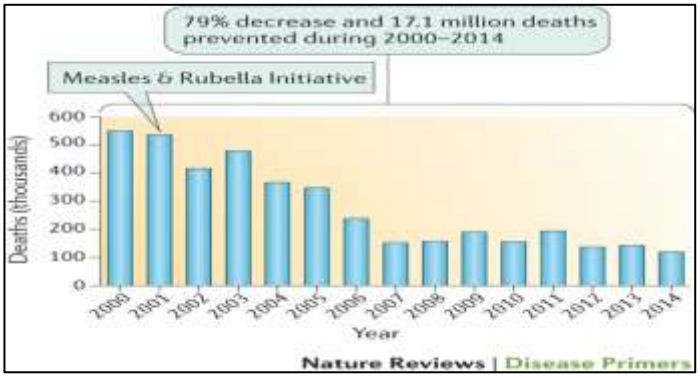

Figure 3 shows the expected global measles mortality toll by year (2000-2014).

The Measles & Rubella Initiative was founded in 2001, and between 2000 and 2014, it is projected that global measles mortality reduced by 79%, averting an estimated 17.1 million deaths [8]. Adapted with permission from CDC MMWR and Reference [7].

3. PATHOPHYSIOLOGY AND MECHANISM

Measles virus- MeV possesses a single-stranded RNA genome that is non-segmented, negative-sense, and roughly 16,000 nucleotides long (Fig. 4a). The nucleocapsid (N) protein, phosphoprotein (P), matrix (M) protein, fusion (F) protein, haemagglutinin (H) protein, and large (L) protein are the six structural proteins that are encoded by the genome's six genes. V protein and C protein are two additional, non-structural proteins that are encoded by the P gene [1].

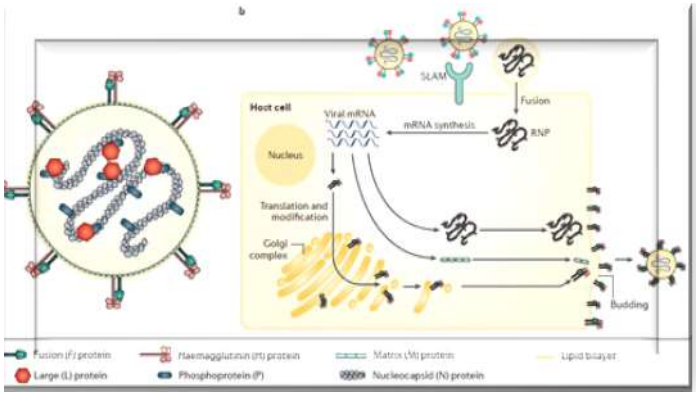

Figure 4: measles virus life cycle.

A) Measles virus (MeV) structure. The viral RNA-dependent RNA polymerase (L protein) and polymerase cofactor (P) are linked to the helical ribonucleoprotein (RNP) complex that the N protein forms by encasing the RNA genome of MeV. The H protein and the F protein are two varieties of transmembrane glycoproteins that are integrated into the lipid envelope, which is produced from the host cell membrane. While the F protein facilitates membrane fusion, the H protein is in charge of binding the receptor to the host cell [177]. The M protein facilitates virion assembly by interacting with the RNP complex and the cytoplasmic tails of the glycoprotein spikes. Infected cells can avoid host innate immune responses thanks to the non-structural V protein and C protein.

B) MeV contamination. The viral RNA is released into the host cytoplasm as a result of membrane fusion after the H protein binds to the host receptor. The viral genome is fully replicated and translated within the cytoplasm. RAS-related protein RAB11a-positive recycling endosomes that travel along microtubules carry newly synthesised RNP complexes [178]. A separate secretory pathway is utilised for the transportation of the H protein and the F protein to the plasma membrane. RNP complexes, the cytoplasmic tails of the H protein and the F protein, the cell membrane, and actin filaments in the host cells are all interacted with by the M protein [179]. These interactions aid in the formation of the virus and control MeV cell-to-cell fusion [180]. Signalling lymphocytic activation molecule, or SLAM.

viral life cycle

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At the virus surface, both the H and the F transmembrane glycoproteins are visible. When the H protein binds to a host receptor, the F protein undergoes conformational changes that cause the viral envelope to fuse with the plasma membrane and release ribonucleoprotein (RNP) complexes into the target cells' cytoplasm. The H protein and the F protein expressed on the cell surface of MeV-infected cells induce fusion between infected cells and neighbouring cells, producing multinucleated giant cells or syncytia (see Supplementary information S1, S2 (videos)). This occurs after replication and transcription of the viral genome in the cytoplasm. The virus assembles and is discharged from the infected cells throughout these activities (Fig. 4b). Despite of the fact that progeny virions are built at and bud from the plasma membrane, MeV's budding process is ineffective, and a sizable portion of the infectious offspring viruses remain bound to the cell [34]. Direct cell-to-cell transmission of the virus through infectious synapses is the primary mechanism by which the virus spreads within the host.

The host receptor

Cellular receptor for MeV has been identified as signalling lymphocyte activation molecule (SLAM; also known as SLAMF1 and CD150) [35]. SLAM is expressed by lymphocytes, platelets, mature dendritic cells (DCs), mature thymocytes, mature Langerhans cells (LCs), and mature dendritic cells (DCs) [36–37]. Studies in human epithelial cells in vitro and in non-human primates in vivo revealed nectin 4 (also known as PVRL4), which is expressed at adherens junctions of epithelia, to be a second important cellular receptor for MeV [38–39]. The promotion of MeV infection of DCs and LCs by DC-specific intercellular adhesion molecule 3-grabbing non-integrin 1 (DC-SIGN; also known as CD209) and C-type lectin domain family 4 member K (also known as Langerin) respectively may be a factor in the high transmissibility of MeV [40–41]. MeV exhibits neurovirulence, but no MeV cellular receptor has been found in neural cells yet. However, research indicates that through interacting with the F protein, the substance P receptor promotes MeV transsynaptic transmission. Human membrane cofactor protein (MCP; also known as CD46) is used by vaccine strains and some laboratory strains of MeV [42, 43]. This is achieved by particular of amino acid changes, N481Y or S546G, in the H protein. Haemagglutination by MeV is dependent on the ability of CD46 to function as a receptor.

MeV contamination

The primary targets of MeV in vivo are lymphocytes and DCs that express the SLAM protein [44–46]. MeV's potential initial targets in the respiratory tract include tissue-resident DCs (Fig. 5). SLAM mediates MeV infection of immune cells, although DC-SIGN also aids in MeV attachment to DCs, facilitating MeV infection of immune cells through SLAM and transmission of MeV to T lymphocytes [47]. Alveolar macrophages in the lungs that express SLAM can also be directly infected by MeV [46–47]. Because MeV antigens are not found in epithelial tissues until after infection and because nectin 4 is not expressed on the apical surface of these cells, epithelial cells are not anticipated to be the initial targets of infection. As a result of MeV infection being amplified in draining lymphoid tissues, circulating MeV-infected lymphocytes mediate viraemia [48]. The distinct roles of SLAM and nectin 4 were further elucidated by analyses in non-human primates employing recombinant MeVs lacking SLAM-binding or nectin 4-binding capability (Refs 49, 50). Even when given intranasally, nectin 4-blind MeV effectively infected non-human primates, led to a systemic infection, and replicated in immune cells to levels comparable to wild-type MeV [50]. In contrast, SLAM-blind MeV infection was significantly suppressed in non-human primate models, and this virus strongly elicited adaptive immune responses and hardly ever generated viraemia [49].

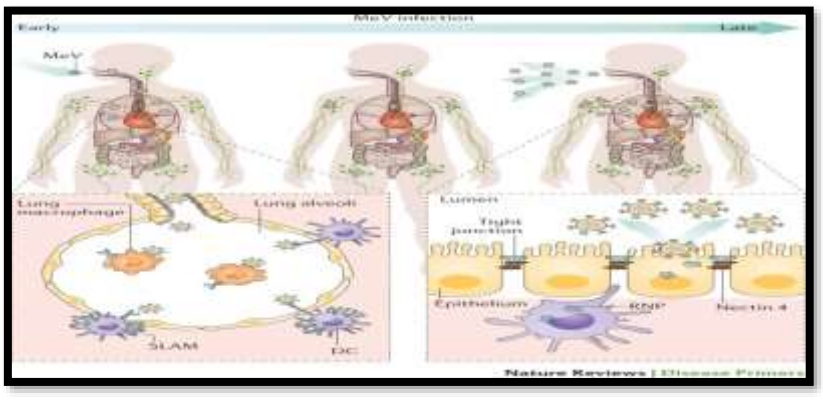

Figure 5 shows the spread of the measles virus.

The measles virus (MeV) can spread through the air. MeV inhaled into the respiratory system infects dendritic cells (DCs) or alveolar macrophages through the receptor signalling lymphocytic activation molecule (SLAM; also known as CD150). The MeV infection first intensifies in local lymphoid tissues, then spreads systemically throughout the

body. Utilising nectin 4 as a receptor, MeV-infected lymphocytes and DCs penetrate the subepithelial cell layer and spread MeV to epithelial cells of numerous organs or tissues. The offspring viruses produced by the MeV infection are greatly increased in the epithelia and discharged into the respiratory tract. Ribonucleoprotein, or RNP. [.

Immune response host reaction After the virus has entered the host cell, the host starts to mount an antiviral defence after spotting pathogen-associated molecular patterns including cytoplasmic single-stranded RNA carrying 5′-triphosphate and double-stranded RNA. The melanoma differentiation-associated protein 5 (MDA5; also known as IFIH1), laboratory of genetics and physiology 2 (LGP2; also known as DHX58), and retinoic acid-inducible gene I protein (RIG-I; also known as DDX58)-like receptors serve as intracellular sensors for virus-specific RNAs. RIG-I and MDA5 are primarily used to detect MeV RNAs, respectively (Refs 57, 58). IFNs are produced when certain kinases, which are activated by RIG-I-like receptors, phosphorylate interferon (IFN)-regulatory factors. Various antiviral genes are stimulated to transcribe during the activation of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signalling pathway in neighbouring cells by secreted IFNs [59].

MeV's antigenic and genetic variation Although MeV is regarded as a monotypic virus, wild-type viruses have been found to differ genetically and antigenically. Despite genomes with insertions and deletions being found, sequencing studies have demonstrated that the MeV genome is very stable [84]. To categorise wild-type MeV into one of 24 genotypes, sequence variants have been employed [85]. Based on the binding of monoclonal antibodies to viral proteins (particularly the H protein) and neutralisation experiments using polyclonal antiserum, antigenic variations between several wild-type strains have also been discovered [86–90]. Additionally, the genomes of every strain used in the measles vaccination have been sequenced. These results imply that not all wild-type strains may be recognised by the antibodies produced by vaccination. However, some of the target-conserved regions of the H protein that are recognised by neutralising antibodies that are induced by vaccination—such as the regions involved in receptor binding or the interaction between the H protein and the F protein—have not yet produced evidence for the action of selective pressure on the H protein of MeV [94, 95].

4. PREVENTION, SCREENING, AND DIGNOSIS

Clinical symptoms

According to the pathophysiology of the illness, the clinical indications of measles can be mapped along with their onset and persistence (Fig. 6). An incubation period precedes MeV infection, during which the virus largely replicates in myeloid and lymphoid cells and creates a systemic infection. When MeV has reached the peripheral lymphoid tissues after 7–14 days, a prodromal phase with malaise, fever, and cough begins. Kolpik dots, which are clustered white lesions that appear on the buccal mucosa one or two days later and are thought to be pathognomonic for measles, can be detected. At that time, the virus has spread to peripheral tissues like the skin and the submucosa of the respiratory system and has been transmitted to epithelial cells and keratinocytes by infected lymphocytes. 3-5 days following the prodromal phase, the maculopapular skin rash develops along with humoral and cellular immune reactions that are unique to the MeV. The rash typically develops on the face or behind the ears before moving to the trunk and extremities. A common side effect of conjunctivitis, which arises at the same time, is photophobia. It can be difficult to diagnose the condition in individuals who are immunodeficient since both rash and conjunctivitis are brought on by immune-mediated clearance of MeV-infected cells [53, 97, 98]. A proper laboratory diagnosis is essential since many of the usual clinical indications of measles can also be brought on by other infectious agents, such as dengue virus, rubella virus, parvovirus B19, human herpes type 6 and parvovirus [99]. Clinical symptoms often start to disappear a few days after the rash appears in cases with simple measles, and patients recover in about a week.

Diagnosis

The discovery of anti-MeV IgM antibodies or the detection of MeV RNA by reverse transcription PCR (RT-PCR) in clinical samples is the basis for laboratory confirmation of the measles. The most popular technique for laboratory confirmation is IgM detection in serum samples taken at the first sign of a suspected illness, typically by enzyme immunoassay [106]. The highest sensitivity is achieved with RT-PCR, which is playing an increasing role in case confirmation, if samples are taken as soon as possible after the rash starts. Oral fluid, urine, and peripheral blood mononuclear cells are additional clinical specimens that can be used for RT-PCR in addition to throat or nose swabs [107, 108]. A further benefit of viral RNA detection is that it makes genotyping possible, which is useful for molecular epidemiology. The successful isolation of MeV in culture is made possible using extremely susceptible and permissive SLAM-positive B95a cells [109], which were later replaced by Vero cells engineered to express human SLAM (Vero/hSLAM cells) [110]. Viral isolation is rarely used for diagnostic purposes and can take several days to many weeks to complete. Clinical specimens such as dried blood spots collected on filter paper, which enable storage

and transport [112, 113], and oral fluid samples, which permit non-invasive sample collection [114, 115] are clinical specimens that can be utilised for both IgM detection and RT-PCR in diagnosis and surveillance [111, 112]. Though highly specific, molecular, and serological assays run on dried blood and oral fluid samples can have a little lower sensitivity than those run on serum or throat swabs. Prevention - The high viral loads in the upper respiratory tract during the prodromal and early periods of rash, together with the epithelial destruction that triggers a cough reflex, can be used to explain the high transmissibility of MeV. As a result of this interaction, MeV-containing aerosols are produced, aiding in respiratory transmission [116,117]. Facilities that provide healthcare can act as hubs for measles outbreaks. Additionally, large crowds and transportation hubs like airports and aeroplanes have frequently been identified as hotspots of MeV transmission, making global MeV transmission pathways a significant factor in determining where people travel internationally. Measles importations from regions with outbreaks or persistent MeV transmission happen in post-elimination contexts [118]. A live, attenuated strain of MeV is present in each modern measles vaccine. Although some vaccinations come from different wild-type viruses (such CAM-70 and Leningrad-16), majority of the vaccine strains come from the prototype Edmonston strain (i.e., the Moraten, Schwarz, and Edmonston-Zagreb strains). A dosage of the measles vaccination must, by subcutaneous injection, contain at least 1,000 TCID50 (the viral titre necessary to infect 50% of host cells in culture). The live attenuated vaccinations for rubella (MR vaccine) and mumps (MMR vaccine) are frequently administered alongside the measles vaccine. 85% of 9-month-old children and 95% of 12-month-old children are thought to be immune to measles after receiving a single dose of the vaccine, and in most cases, the period of protection is many decades and perhaps lifelong. Following measles immunisation, adverse effects are frequently modest. A fever of >39 C occurs in 5–15% of vaccine recipients between days 7 and 12 after receiving the shot. Around 5% of vaccine recipients experience a rash that lasts 1-3 days 7–10 days following their inoculation.

5. CONCLUSION

There is no proof of person-to-person transmission of vaccine viruses, despite of the fact that vaccine virus can be found in the respiratory secretions of those who have had vaccinations [118]. The disadvantages for measles elimination attempts include vulnerability to interference by maternal antibodies in young infants, stringent cold-chain reliance, and the need for hypodermic needles for delivery, despite of the fact that currently available measles vaccines are very safe and effective.

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