Review Article

The Reemergence of Measles: Epidemiology, pathogenesis, Laboratory diagnosis and Management.

ABSTRACT

Measles is the leading cause of vaccine-preventable childhood disease in developing countries, with the highest incidence among children under 5 years of age. The emergence and recurrence of measles as an infectious disease affects high-risk groups and the number of cases and deaths increases rapidly. Before the idea of vaccination was introduced, more than 2 million people died each year. Measles is most common in areas where there is little or no vaccination coverage, especially areas with limited resources such as Africa and Nigeria. Although measles is a vaccine-preventable disease, it is endemic in Nigeria and exhibits a seasonal pattern with high incidence during the dry season, with most occurring between February and April. every year, which is associated with the dry season. In 2016, an estimated 39.9 million measles cases and 777,000 deaths were recorded worldwide. Africa and East Asia account for 70% and 84% of measles and measles-related diseases reported worldwide. Nigeria is Africa's largest country and the burden of measles remains high. Measles is endemic in most of the northern states of Nigeria, including Sokoto state. In this review study, we discuss the reemergence of measles: epidemiology, pathogenesis, laboratory diagnosis and management.

Key words: Measles; Vaccine; Diagnosis; Epidemiology; Reemergence.

1.INTRODUCTION

The emergence and recurrence of measles as an infectious disease affects high-risk groups and the number of cases and deaths increases rapidly. In a world where it is easy and frequent to move from one hemisphere to another, emerging infectious diseases (EID) are spreading rapidly between countries and across countries. when control efforts are ineffective and EID is not recognized, epidemics of infectious diseases that are not recognized by the community can easily spread locally, nationally, and internationally (1).

Epidemics and epidemics affect human history. When a new pathogen enters the human body, its ability to spread becomes a key factor in its emergence. Introduction and spread of vectors into host populations are not isolated but occur simultaneously. The return of "old" pathogens that successfully controlled the spread is often the result of failed public health efforts (2). The emergence of organisms that pose a serious threat to individuals and communities is a major concern and concern for public health systems in developed and developing countries.

Emerging infectious diseases (EIDs) are infectious diseases that have recently emerged in a community, or are rapidly increasing in prevalence or geography, and threaten to increase in the short term. Reemerging Infectious Diseases (RIDs) are diseases that were once controllable but are now threatening public health (3).

2. THE REEMERGENCE OF MEASLES

In recent years, measles has re-emerged in areas where the disease was once thought to be rare. This measles infection is a cause for concern and should be carefully evaluated. In fact, when vaccination rates fall below a certain threshold, outbreaks of vaccine-preventable diseases can occur and the community will die. This threshold theorem (2) is the basis for the theory of the restricted B group. Herd immunity can be thought of as the threshold level of infection in a population that prevents the disease from spreading. For measles, the level of immunity required to prevent transmission is higher than the threshold for other vaccine-preventable diseases. To prevent continued transmission of measles, 92% to 94% of the population should be protected (3).

Vaccination coverage has declined in some groups in the United States and Europe in recent years. Parental concerns about vaccine safety issues, such as the link between vaccines and autism, although not supported by reliable scientific evidence, have increased the number of parents who do not, or to delay vaccination for their children (4). This is a concern because children who receive unmedicated positions are at increased risk (5). Globally, 2006 was the first year since WHO conducted surveillance and fewer than 500,000 cases were reported. The period 2017–2019 saw the highest increase in measles cases since 2006 (Figure 1) (6).

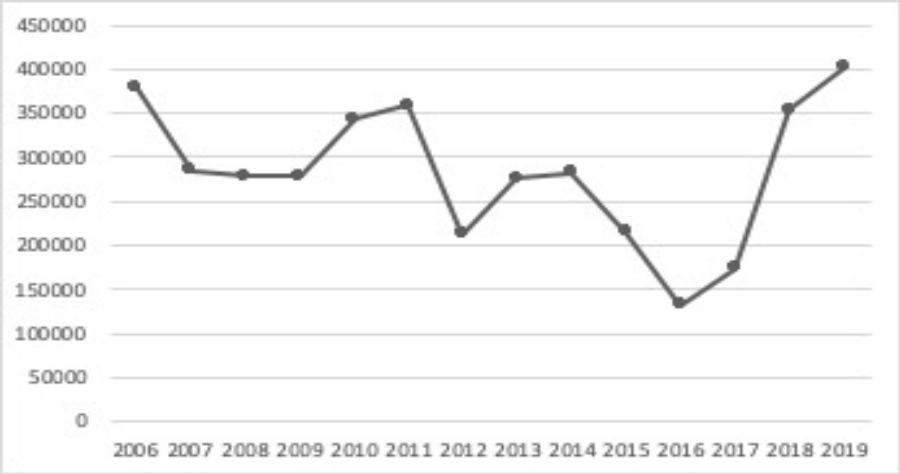

Figure 1: Global incidence of measles reported by WHO 2006-2019.

*Data sourced from WHO measles reports, 2019 data based on monthly data reported to WHO as of August 2019 (6).

Total measles cases reported by WHO were: 2006 – 377 576, 2007 – 285 031, 2008 – 278 751, 2009 – 278 637, 2010 – 343 806, 2011 – 359 332, 2012 – 212 376, 2013 – 275 307, 2014 – 282 078, 2015 – 214 816, 2016 – 132 413, 2017 – 173 457, 2018 – 353 236, 2019 (reported as of Aug 9th) – 401 024.

The decline in global mortality began in 2006 due to efforts to implement 2 vaccination programs in wealthy countries. Developing countries implement and finance single immunization programs through the EPI program.

As of 2006, three types of measles are associated with epidemics and long-term outbreaks: D4, D6, and B3. D4 and B3 are imported from famous countries in Asia and Africa. Nine types of measles have been identified in the European region: D4, D6, B3, B2, D5, D8, D9, G2, and H1 (7). The same subtype B3, proven to have originated in Kenya, has been documented in the United States, Canada, and Mexico (8). The main strains that cause measles are D8 and B3. From August 2018 to July 2019, the D8 strain was found to be responsible for the majority of measles cases in the United States and Europe; Cases in Canada were reported from Pakistan, Thailand and Cambodia. B3 and D8 are imported tapes that cause dead transmission. B3 and D8 occur in Southeast Asia and are recorded throughout the region. D8 is widespread in India, Bangladesh, Nepal, Morocco, and Oman and, along with B3, has been the main genotype in outbreaks in Romania since 2016. Currently B3 is the It is the most Currently B3 is the mostcommon type of measles in the world and has been found to be more transferable than others. other strains in previous outbreaks and show resistance to vaccines (10).

Morbillivirus (MV) belongs to the genus Morbillivirus in the family Paramyxoviridae. It is an enveloped, nonsplicing, single-stranded RNA virus whose genome encodes at least six structural proteins (11). MV (also known as German morbilli virus) causes measles, an acute and highly contagious disease seen in children. Recovery from measles is common, but serious complications can occur in some cases (12).

Severe forms and non-specific clinical features can occur, especially in people with compromised or weakened immune systems, such as those receiving treatment for serious illnesses, transplants, and immunodeficiencies. syndrome (AIDS), or a form of those born with an immunodeficiency (13).

The MV virion consists of a ribonucleoprotein, protein and RNA coil, and an envelope with two short surface extensions: the hemagglutinin (H) and the fusion protein (F). The wild type measles virus can be different from the vaccine type. Gene sequences for nucleoprotein (N) and H are among the most common variants in measles, and are the sequences most commonly used to distinguish between different types of measles (14). There are six MV structural proteins (F, H, L-matrix, M-matrix, N, P). Among them, N, protein phosphate polymerase (P) and large protein (L) are complexed with RNA. C and V are not structural proteins, they interact with cellular proteins and are involved in the regulation of viral transmission and replication (13). Glycoprotein H is involved in the attachment of the virus to the host cell, while glycoprotein F is involved in the spread of the virus from one cell to another. Unlike other paramyxoviruses, neuraminidase was not detected in the morbillivirus envelope (15).

The primary MV receptor is the lymphocyte activation molecule (SLAM; CDw150): wild-type viruses use this receptor for entry, and this element accounts for lymphocyte tropism and immunity. Among the receptors through which the virus travels through the airways and then spreads through aerosols, an important role has been attributed to nectin-4, an epithelial cell protein (16).

3. EPIDEMIOLOGY

Measles is a worldwide disease and is the leading cause of death, particularly in children under 5 years of age. Accurate estimates of global mortality are difficult to obtain due to the large number of surveillance systems and limited reporting. Before the idea of Before the idea of vaccination, more than 2 million people died each year. Measles is most common in areas where there is little or no vaccination coverage, especially areas with limited resources such as Africa and Nigeria. Although measles is a vaccine-preventable disease (17), it is endemic in Nigeria and shows a seasonal pattern, with a higher incidence during the dry season (18). Most outbreaks occur between February and April each year, which coincides with the dry season. In 2016, an estimated 39.9 million measles cases and 777,000 deaths were recorded worldwide. Africa and East Asia account for 70% and 84% of measles and measles-related diseases reported worldwide. Nigeria is Africa's largest country and the burden of measles remains high. Measles is endemic in most states in northern Nigeria (17). There was a 79 percent increase in measles cases worldwide in the first two months of 2022 compared to the same period last year. This is an alarming sign of the increased risk of transmission of this infectious disease and other preventable diseases. There is concern about increasing reports of measles worldwide (6).

The groups most at risk of getting measles are babies who are too young to have been vaccinated, people who haven't been vaccinated for other reasons, and people who haven't received a second dose of vaccination, and people who have failed orrefused to receive measles vaccines to trigger immune response (19). refused to receive it. measles vaccine. vaccines to trigger an immune response (19).

Although vaccination has significantly reduced the incidence of measles by 73% worldwide between 2000 and 2018, the burden and prevalence of measles in Nigeria remains high. More than three-quarters of measles cases occur in poor countries with low per capita income and weak health systems due to poor health management. Malnutrition, poor management, lack of vaccination and large numbers of people are exposed to measles. These trends are common in low-income countries such as Nigeria (17).

4. PATHOGENESIS

MV infection begins in the luminal surface of the upper respiratory epithelium, involving many other cell types besides epithelial cells, such as immune system cells, and from here it reaches the regional lymph nodes. Virus particles can spread systemically after infecting other lymphocytes.

MVs bind to a number of receptors on host cells. In influenza, MVs attach to epithelial cells through the interaction of the glycoprotein hemagglutinin (MV-H) with cellular receptors. From *in vitro*in vitrostudies, wild-type MVs (vaccine and laboratory strains) can infect cells using CD46 (a protein present in all human nucleated cells) and CD150 (representing lymphocyte activation molecule) has not been confirmed in wild-type strains which has not been confirmed in wild-type strains (20). Dendritic cell (DC)-SIGN and Langerin are two C-type lectins that act as complementary receptors for MVs (15). Furthermore, in the inflammatory phase, the connexin nectin-4 has been identified as an additional receptor used by MVs to transfect inflammatory cells without causing direct cytopathic effects (21).

4.1 The first phase of the disease

The initial cell death of influenza involves dendritic cells, and most likely a CD150-dependent event that does not involve epithelial cells, which are the primary targets of disease initiation. Therefore, exposure of aerosolized viruses to the tonsils or adenoids is not sufficient, and these areas become infected after the development of MV viremia (13). After capturing the virus from the airways, dendritic cells migrate to regional lymph nodes and deliver MV to lymphocytes, initiating infection (22).

4.2 Copy Section

Measles has a very long incubation period, about 10 days before fever and 14 days before the rash appears. The period of high viremia is similar to the prodromal phase, but the symptoms are similar to the decline of viremia. Lymphoid organs and tissues are the primary sites of viral replication, and multinucleated giant cells are seen in lymphoid tissues before the onset of the rash (23).

After this initial stage of replication, MV can spread to other tissues such as submucosal tissue, tongue, buccal mucosa, trachea, nose, and skin. Persistence of the virus in the body is recorded in epithelial cells, not in lymphocytes which leads to increased circulation. Lymphocyte turnover increases during infection, but it is not clear whether this is due to increased cytotoxicity of the scratch to lymphocytes or their increased vulnerability to attack by the immune system. Measles RNA can be detected in clinical samples (blood, urine, and nasopharyngeal samples) for at least 3 months after the onset of the rash (21).

4.3 Complications

Scratching can affect almost every organ and system. Disease risk varies with age and health status. Most of the complications arise from epithelial surface breakdown and/or immune suppression.

Scratching kills the epithelium and facilitates bacterial infection. Most otitis media are caused by the structure of the eardrum, and are therefore susceptible to ear infections. The same is true for laryngotracheobronchitis, with purulent exudate and symptoms of secondary bacterial tracheitis, pneumonia, or both. Pneumonia is the most common cause of measles and the cause of most measles-related illnesses (24). This can occur with measles alone, secondary to adenovirus or HSV viral infection (a clinical example in some children of viral-mediated bronchiolitis), or secondary to bacterial infection (24). Measles is the cause of severe Hecht's disease, which occurs most often in people with weakened immune systems but can also affect adults and children. About 30% of pneumonia cases are caused by bacteria, the most common pathogen being Staphylococcus aureus. Streptococcus pneumoniae, Staphylococcus aureus, and Haemophilus influenzae. Neisseria meningitidis was also occasionally found. In rare cases, severe emphysema and mediastinal emphysema occur (25). MV infects the intestines of most people with measles. Cases of appendicitis have been reported before and during the shooting. In this case, large cells of measles are found in the intestinal epithelium (22). In the United States, 8% of cases result from cancer. Especially in the two age groups under 5 years and over 30 years, the etiology of these cases is similar to diarrhea in children who have not been infected

with measles (24). Cases of gangrenous stomatitis associated with measles have also been reported in developing countries.

In the United States and the United Kingdom, 0.1–2.3% of children with measles develop a febrile rash, which usually does not last long. The pathophysiology is fever and metabolic changes rather than physical changes in the brain.

There are three rare but serious complications of measles that may involve the central nervous system (CNS). Acute Disseminated Encephalomyelitis (ADEM) is an autoimmune disease usually caused by a virus that occurs within days to weeks in 1 in 1,000 measles cases. Myocardial infarction (MIBE) occurs more frequently in immunocompromised hosts (20). Subacute sclerosing panencephalitis (SSPE) is a chronic, degenerative neurological disease that develops on average 7 years after measles, with most children affected before 2 years of age. It is almost always caused by a wild-type virus. Genotyping indicated that this SSPE case was caused by wild-type measles circulating last year. Thus, vaccination may prevent many more cases of SSPE than previously thought (26).

Patients with SSPE have high levels of measles antibodies in serum and cerebrospinal fluid. It is thought that the measles virus spreads to the brain during menopause and infects other endothelial cells. Trans synaptic spread of the virus has also been suspected.

However, in contrast to measles virus infection in non-neuronal cells, in this setting there is no direct cytopathic effect other than viral resistance. In this process, they are responsible for the modification of the M-H-F viral protein. In fact, it has been described how gene expression patterns are altered in the presence of certain measles antibodies. This may explain the high incidence of SSPE in children less than one year old who were infected when maternal antibodies are still circulating (20). In addition, host factors, such as immune deficiency and low ability of specific antibodies to reduce intracellular virus growth, are considered to be involved in the pathogenesis of SSPE.

For the eye, the main problem is conjunctivitis, sometimes with keratitis, secondary to a bacterial or viral infection (such as HSV or adenovirus), which rarely causes scarring and permanent blindness (27).

4.3.1 Clinical manifestations

Measles is considered a systemic disease. After exposure, the incubation period before the first symptoms appear is usually 10-12 days. Prodromal symptoms of measles, rhinitis, and conjunctivitis, known as B3Cs^, B3CSoccur before the rash appears. Fever may occur during the prodromal phase, reaching a high temperature of 105°F. Koplik areas, which are small areas with a white or bluish-white center, appear at the base of buccal erythema around the second molars. These episodes are transient and occur in 50% to 70% of patients, but are highly specific (23). The rash usually appears 14 days after exposure (range 7 - 18 days) (Morbillivirus-Structure, Pathogenesis, Laboratory Diagnosis - Microbiology Online, n.d.). The appearance of the rash in people with measles is a red, lumpy, maculopapular rash with a centrifugal craniocaudal distribution, which starts on the face and spreads, lasting 4 to 7 days (28). Once the rash appears, the fever will stop. Influenza patients are considered contagious from 4 days before to 4 days

after the onset of rash (29) and if admitted to hospital, isolation measures should be taken at this time. Measles should be suspected in patients who have a fever, chills, or other epidemiological risk factors (such as travel to an area where measles is endemic or where new transmission is known).

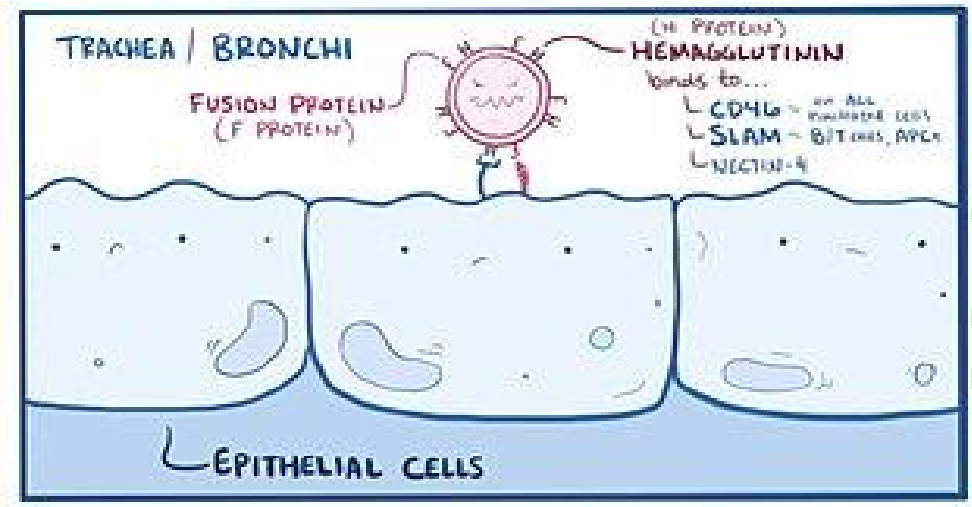

Figure 2: A sketch of the measles virus attaching to the lining of the trachea (23)

5. LABORATORY DIAGNOSIS

Measle -specific immunoglobulin M (IgM) and immunoglobulin G (IgG) are both produced during the primary immune response and can be detected in the serum within days of the onset of the rash using immunotherapy. enzyme-linked immunosorbent assay (ELISA). About 70% of measles cases are IgM positive 0-2 days after the rash appears, and 90% are IgM positive 3 to 5 days after the rash appears. IgM antibody levels peak after 7-10 days, then decline and become undetectable after 6-8 weeks. Repeated exposure to the scratch stimulates the immune response, rapidly increasing IgG antibodies, thereby preventing clinical disease. Measles can be isolated from daily clinical samples (nasopharyngeal swabs, urine or peripheral blood mononuclear cells) within 5 days from the onset of the rash and using molecular methods such as polymerase chain reaction (PCR)testing after the rash appears (28). testing. after the rash appears. Separation of measles from urine); up to 5 to 7 days); detection of measles virus antigen in clinical samples by direct immunofluorescence using specific monoclonal antibodies. showed aantibodywhich showedmore than four-fold increase in antiviral antibody titers between the acute and subacute episodes or the detection of measles-specific IgM (30). Other serological tests include: a hemagglutination inhibitor test; symptom reduction test;

6. PREVENTION AND CONTROL

Mothers who don't have measles can pass the vaccine on to their babies while they're in the womb, especially if the mother gets the vaccine through an infection rather than a vaccination (21). These antibodies usually protect against measles in newborns, but they usually disappear during the first nine months of life. Infants under one year of age who have lost the maternal

antibodies to rabies are susceptible to measles. Infants under one year of age who have lost the mother's anti-rabies antibodies are susceptible to measles (25).

In developing countries, children are recommended to receive the measles vaccine at 12 months of age, usually as part of the three-dose MMR (measles, mumps, rubella) vaccine. Vaccines are often not given before this age because babies don't respond well to vaccines because of their immune systems. Children four to five years old are usually given a second dose of the vaccine to boost immunity. More than 1 billion people have been vaccinated (17). Vaccination rates are high and measles is rare. Adverse reactions to the vaccine are rare, and the most common are fever and pain at the injection site. Life-threatening adverse reactions occur in less than 1 in 1,000,000 patients (<0.0001%) (19).

In endemic countries, the World Health Organization (WHO) recommends two doses of the vaccine at 6 and 9 months of age. age. Children should be vaccinated even if they are infected with HIV (20). Vaccination is less effective in HIV-infected infants than in the general population, but early treatment with antiretroviral drugs can be more effective. Vaccination programs are often used to implement other child health interventions, such as mosquito nets to prevent malaria, antiparasitic drugs and vitamin A supplements, which help reduce disease. of children in other cases.

False claims that there is a link between vaccines and autism; These false concerns reduce vaccination rates and increase the number of measles cases so that herd immunity is kept at a minimum. Additionally, there are false claims that measles protects against cancer (23). Getting the MMR vaccine provides post-exposure prophylaxis, which provides protection against measles after exposure to the virus. Post-exposure prophylaxis guidelines are jurisdictional and population specific (31). Intravenous vaccination may be effective as early as seven days after exposure to measles. Compared to no treatment, the risk of measles is reduced by 83%, and the risk of measles is reduced by 83%. However, the effectiveness of the vaccine against the active vaccine remains unclear (32). The MMR vaccine is 95% effective in preventing measles after a single dose given to children 12 months of age or older, and a second dose of the MMR vaccine kills 99 % of children (33).

There is no evidence that the vaccine can be given to other people except children(32).

7. MANAGEMENT

If measles does occur, there is no specific antiviral treatment. Instead, these medications are designed to treat chronic infected children'sconditions, keep you hydrated and well hydrated, and relieve pain. Some groups, such as young children and people with serious illnesses, also take vitamin A, which works as an immune modifier, increasing the antibody response to measles and reducing the risk of serious complications (34; 35).

7.1 Vaccination

There are several types of measles vaccine, and most African countries and other countries (including Russia) use at least one version (31). The mumps, measles, rubella (MMR) vaccine is also used in other parts of Europe and North America. The measles, mumps, rubella, and

varicella vaccine (MMRV) is available in the United States and is as safe and effective as the MMR vaccine, but carries a higher risk ofmeasles than the trivalent vaccine.measles. than the trivalent vaccine.

All of these vaccines are antibodies that replicate in the host to induce immunity. The World Health Organization recommends administering the first dose at 12 months of age, and the second dose at 15 to 18 months of age (6); The US CDC recommends a series of first doses at 12 to 15 months of age and administered at 4 to 6 years (36).

In some special cases, the World Health Organization recommends administering the first dose of measles vaccine (MCV1) at 9 months of age when measles is fatal. In special circumstances, such as during an outbreak, the first dose of the vaccine is given after 6 months, to refugees and HIV-infected children (6). However, several studies show that on a two-vaccine schedule, susceptibility to measles is 2 to 4 times higher if the first dose is given before 15 months. Accordingly, there is evidence that antibody titers are lower if the first dose is given before or after 9 months of age, but the effect of the vaccine is not low, because the T cell response is not timely vaccine (33a). Although, the World Health Organization recommends two doses of the vaccine and the first dose is given before 9 months of age (5).

To achieve effective protection (herd immunity), the entire population needs a certain level of immunity. In fact, the vaccination coverage required for two doses of the vaccine ranges from 93% to 95% (31; 32).

8. CONCLUSION

Although vaccination is very effective, measles remains the leading cause of death in children worldwide. It is highly contagious, and early identification of febrile illnesses with typical symptoms of cough, rhinitis, and conjunctivitis can prevent spread. The number of outbreaks that have occurred in areas where measles is endemic is a cause for concern, possibly due to low vaccination rates. Urgent action is needed to address the low vaccination coverage and the lack of vaccination coverage. Efforts should be made to increase awareness of this disease and strengthen vaccination promotion to prevent this disease from becoming a fatal disease.

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