

Measles

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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.

The measles virus (MeV) is a single-stranded, negative-sense RNA virus in the genus *Morbillivirus* of the family Paramyxoviridae¹. MeV is an airborne pathogen that is transmitted by inhalation of respiratory droplets that disperse within minutes and smaller aerosols that can remain suspended for several hours^{2,3}. The virus can also be transmitted through direct contact with infected secretions, but MeV does not survive long on fomites (that is, any object that can carry pathogens, for example, skin, hair, clothing and bedding) as it is inactivated by heat and UV radiation within a few hours. The prodromal phase of measles involves sneezing and coughing, which enhance the transmission of the virus.

The incubation period is approximately 10 days to the onset of fever and 14 days to the onset of rash. The clinical signs of measles are a generalized maculopapular (non-vesicular) skin rash and fever above 38.3°C (101°F) accompanied by cough, coryza (or rhinitis) and/or conjunctivitis. The clustered white lesions that can be seen on the buccal mucosa lining the cheeks — Koplik spots — are considered pathognomonic for measles. People with measles are considered infectious from 4 days before to 4 days after the onset of rash, when the levels of MeV in the respiratory tract are highest¹. The fact that MeV is contagious before the onset of recognizable disease can hinder the effectiveness of quarantine measures, although

isolation of susceptible contacts is recommended. Measles is a vaccine-preventable disease, and a safe, effective and inexpensive vaccine is widely available.

This Primer summarizes the epidemiology of measles, describes the global efforts to control and eliminate the transmission of MeV, contains a description of the pathogenesis of MeV infection and highlights recent research that has redefined our understanding of this important infectious disease.

Epidemiology History of measles

Before the introduction of a measles vaccine in 1963, an estimated 30 million cases of measles with >2 million deaths occurred each year globally⁴ (FIG. 1). Measles mortality started to decline in industrialized countries in the first half of the twentieth century in association with economic development, improved nutritional status and better supportive care, particularly antibiotic therapy for measles-associated bacterial pneumonia⁵. Despite this trend, the most remarkable progress in reducing measles incidence and mortality resulted from increasing coverage with a first dose of a measles-containing vaccine (MCV1) in the first year of life. The addition of a second dose (MCV2) through routine immunization further increased disease protection, as did supplementary

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immunization activities (SIAs) — mass immunization campaigns to capture children missed by routine vaccination or without protective immunity. The reason for the need of two-dose coverage is that maternally acquired IgG antibodies interfere with immune responses to the attenuated measles vaccine by inhibiting the replication of the vaccine virus. In general, maternally acquired antibodies wane over time and are no longer present in the majority of children by 9 months of age, which is the age of routine measles vaccination in many countries. Vitamin A supplementation probably further contributed to the reduction in measles mortality⁶. The exact mechanism by which vitamin A reduces measles morbidity and mortality remains unknown, but most likely involves beneficial effects on epithelial cells and host immune responses.

Vaccination and elimination targets

Established in 2001 by five core partners including the WHO, United Nations Children's Fund (UNICEF), the American Red Cross, the United Nations Foundation and the US Centers for Disease Control and Prevention (CDC), initially with a focus only on measles, the Measles & Rubella Initiative (M&RI) provided a global vision statement for achieving global elimination of measles and rubella: the Global Measles and Rubella Strategic Plan 2012–2020. The estimated coverage with

MCV1 increased globally from 70% to 85% during 2000–2014, and the number of countries with $\geq 90\%$ MCV1 coverage increased from 44% to 63%⁷ (FIG. 2). In addition, the proportion of countries with $\geq 90\%$ MCV1 coverage overall that also had $\geq 80\%$ MCV1 coverage in all districts increased from 1% in 2003 to 40% in 2014. Measles elimination requires high levels of two-dose coverage, and during 2000–2014, the estimated coverage with MCV2 increased from 15% to 56% globally and the number of countries providing MCV2 through routine immunization services increased from 51% to 79%.

In 2010, the World Health Assembly (WHA) established three global targets for measles control by 2015: a routine measles vaccination coverage of $\geq 90\%$ nationally and $\geq 80\%$ in every district; a reported measles incidence of fewer than five cases per 1 million population; and a measles mortality reduction of $\geq 95\%$ compared with mortality in 2000 (REF. 8). Subsequently, the WHA endorsed the Global Vaccine Action Plan for 2012–2020, which established targets for measles and rubella elimination. This plan called for all six WHO regions to establish goals to eliminate measles by 2020 or sooner, with the aim for complete elimination of measles in at least five WHO regions by 2020 (REF. 9). As of September 2013, WHO member states in all six regions have adopted measles elimination goals. Elimination is defined as the absence of endemic MeV transmission in a defined geographical area for ≥ 12 months in the presence of a well-performing surveillance system¹⁰. From 2000 to 2014, the number of deaths attributed to measles declined by 79%^{8,11} (FIG. 3). Although this is a considerable reduction, it did not meet the 2015 global target. Countries with suboptimal MCV2 coverage conduct SIAs every 2–4 years, with SIAs conducted in 28 countries in 2014 estimated to have reached approximately 221 million children⁷. In addition to vaccination, high-quality measles case-based surveillance is essential for elimination efforts. By the end of 2014, 96% of countries implemented case-based surveillance and 98% had access to standardized quality-controlled testing through the WHO Global Measles and Rubella Laboratory Network (GMRLN)^{12,13}.

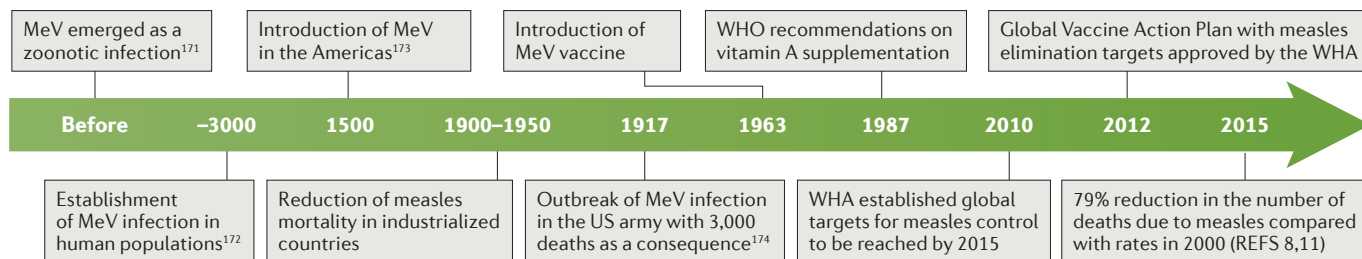


Figure 1 | History of measles virus infection and elimination programmes.

Closely related to the recently eradicated cattle virus rinderpest¹⁷⁰, measles virus (MeV) probably evolved from an ancestral virus and emerged as a zoonotic infection in communities in which cattle and humans lived in close proximity¹⁷¹. MeV most likely became established in humans about 5,000 years ago when human populations achieved sufficient size in Middle Eastern agrarian civilizations to maintain virus transmission¹⁷². Measles did not always have a global distribution and probably first entered the Americas in the fifteenth century with the immigration of Europeans. MeV and

smallpox infections probably facilitated the European conquest of Native American civilizations by causing large numbers of deaths among the fully susceptible Native Americans¹⁷³. The outbreak of measles in the US Army from 1917 to 1918 that resulted in >95,000 cases of measles and 3,000 deaths provided a striking example of the devastating effect of measles and associated bacterial co-infections that occurred before the introduction of antibiotics or measles vaccines¹⁷⁴. Increasing measles vaccine coverage prevented an estimated 17.1 million deaths between 2000 and 2014 (REF. 8). WHA, World Health Assembly.

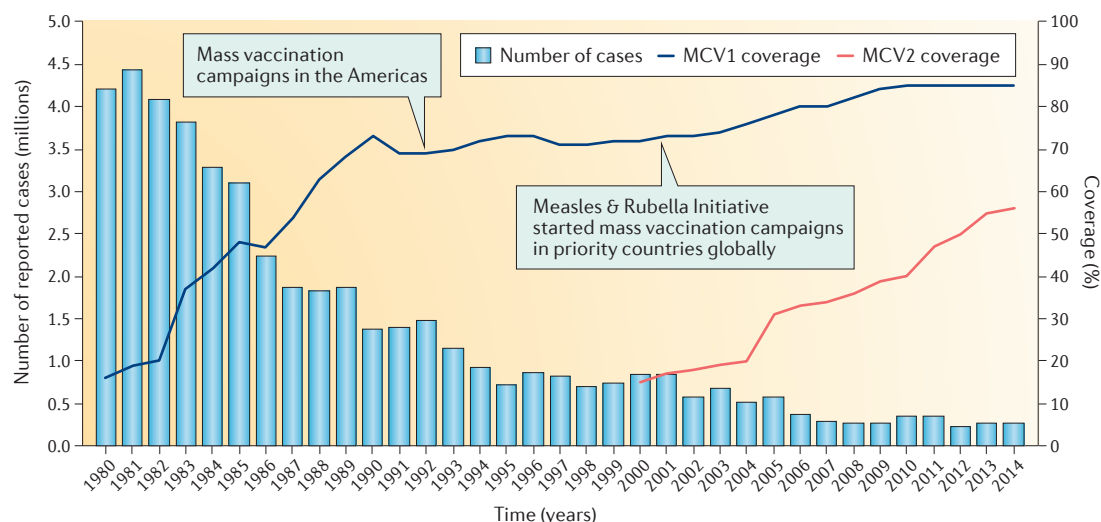


Figure 2 | Global reported measles cases and estimated coverage with the first and second dose of measles-containing vaccine by year (1980–2014). MCV, measles-containing vaccine. Figure adapted from data available from the WHO^{175,176}.

Measles outbreaks

In the pre-vaccine era, measles incidence peaked in yearly seasonal epidemics that were superimposed on longer epidemic cycles, with large outbreaks occurring every few years¹⁴. In temperate climates, annual measles outbreaks typically occur in late winter and early spring and are driven by social interactions that facilitate MeV transmission, such as the congregation of children at school¹⁴. In the tropics, measles outbreaks occur in the dry season, driven by high birth rates and shifts in population density^{15,16}. MeV infection occurs at low incidence during the inter-epidemic period in large populations, thus maintaining continuous chains of transmission in between seasonal outbreaks. Every 2–5 years, a large outbreak develops because of the accumulation of susceptible individuals who were missed during the seasonal outbreaks. Following a large outbreak, the number of susceptible individuals again decreases, which drives the epidemic cycles^{17,18}. The inter-epidemic period can be 4–8 years or longer when measles vaccine coverage exceeds 80%, by reducing the rate of accumulation of susceptible individuals from each new birth cohort¹⁸. In many countries with sustained high but heterogeneous measles vaccine coverage, relatively small but spatially clustered groups of unvaccinated individuals exist¹⁹, and measles outbreaks occur irregularly and less predictably²⁰.

Population immunity

MeV is one of the most highly contagious infectious agents, and outbreaks can occur even in populations in which <10% of individuals are susceptible to measles^{2,21} (BOX 1). Chains of MeV transmission commonly occur among susceptible individuals in closed settings or with high contact rates, including within households, schools and health care facilities.

The high infectivity of MeV implies that a high level of population immunity is required to interrupt MeV transmission. However, interruption of MeV transmission does not require immunity in all individuals within a population. The probability that a susceptible

person will be exposed to an infectious individual decreases below the level required to sustain transmission when a sufficient proportion of the population acquires protective immunity. This reduction in the risk of exposure results in herd immunity; the estimated level of population immunity that is necessary to stop MeV transmission (the herd immunity threshold) is 89–94%²² (BOX 1). The herd immunity threshold does not represent the level of measles vaccination coverage but the overall proportion of the population protected against measles (that is, effectively immunized or recovered from infection). MCV1 delivered to children at 9 months of age will not achieve this level of population immunity. For this reason, the WHO recommends providing MCV2 and targeting ≥95% two-dose coverage for achieving and maintaining measles elimination.

Case fatality ratio

The case fatality ratio (CFR) estimates for measles vary widely from <0.01% to >5% and depend on the average age of infection, nutritional status of the population, vaccine coverage and access to health care²³. Measles is a major cause of death in displaced populations (especially refugee camps), and CFRs in children in major humanitarian crises have been estimated to be as high as 20–30%²⁴. Measles is less severe in vaccinated individuals with waning immunity and mortality rates in this group are lower than for measles cases in unvaccinated individuals. As vaccination coverage increases in a population, the average age of infection increases and shifts the burden of disease away from the age groups that have severe morbidity and the highest CFRs.

Age for acquiring measles

The average age for acquiring measles depends on epidemiological and biological factors, including the rate of decay of protective maternal antibodies¹⁷. Maternally acquired IgG antibodies protect young infants who were born to measles-immune mothers. However, the rate of decay and mean half-life of maternal antibodies

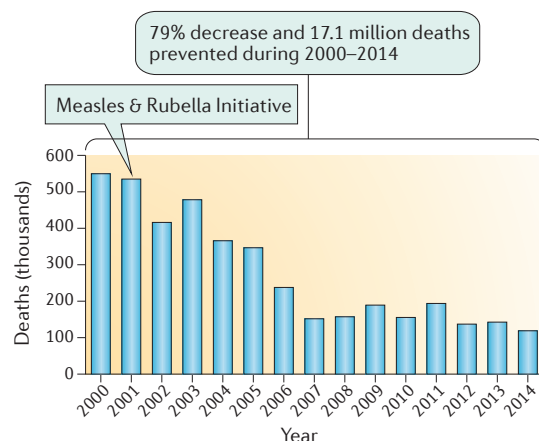


Figure 3 | The number of estimated measles deaths globally by year (2000–2014). The Measles & Rubella Initiative was established in 2001; global estimated measles mortality decreased by 79% during 2000–2014, preventing an estimated 17.1 million deaths⁸. Adapted with permission from REF. 7, CDC MMWR.

to MeV varies, but in general these antibodies are no longer detectable in most children by 9 months of age²⁵. Women with vaccine-induced immunity have lower levels of anti-MeV antibodies than women with naturally acquired immunity, resulting in a shorter duration of protection in their infants^{26,27}. Similarly, children born to women with human immunodeficiency virus (HIV) infection can become susceptible to measles at a younger age, which is independent of their HIV infection status^{28,29}.

The age distribution of measles also reflects the intensity of exposure and patterns of susceptibility. Measles is a disease of infants and young children in densely populated urban settings with low vaccination coverage. The average age of infection increases as measles vaccination coverage increases or birth rates decrease, reflecting the lower probability that susceptible infants and children will encounter an infectious individual. In such settings, measles cases can predominate in school-age children (5–10 years of age), reflecting an increased risk of exposure in settings where susceptible children congregate. The average age of measles can even shift to adolescents and young adults as vaccination coverage increases further, requiring targeted measles vaccination efforts to immunize older age groups²⁹.

Box 1 | Infectivity of measles virus and herd immunity

The basic reproductive number (R_0) represents the mean number of secondary cases that are expected to arise if an infectious individual is introduced into a completely susceptible population and is an important metric to compare the contagiousness of measles virus (MeV) to other viruses. The estimated R_0 for MeV is 9–18 (REF. 22), which is in contrast to only 5–7 for smallpox virus¹⁴⁰ and 4–13 for polioviruses¹⁵².

Analytical models of infectious disease dynamics combined with several simplifying assumptions, including the unrealistic assumption of homogeneous mixing within a closed population, estimate the level of population immunity that is necessary to stop transmission, known as the herd or population immunity threshold, using the standard approximation of $1 - 1/R_0$. For measles, the estimated R_0 values of 9–18 imply that herd immunity thresholds range from 89% to 94%²².

Risk factors

Undernutrition is an important risk factor for developing more-severe measles complications. Some studies have suggested that the intensity of exposure (for example, transmission within households) is another important determinant of mortality. In addition, the period in which a person infected with MeV remains infectious may be prolonged in individuals who are immunocompromised by severe undernutrition or HIV infection^{30,31}. The nutritional status of children with measles is, in turn, worsened by decreased food intake (particularly in children with mouth ulcers), increased metabolic demands of infection and gastrointestinal loss of nutrients. Malnutrition and vitamin A deficiency may be exacerbated by measles and can lead to keratitis, corneal scarring and blindness in children with severe vitamin A deficiency.

Some studies suggest a 5% higher measles mortality in girls than in boys in some settings³², whereas others do not support this conclusion³³. Geographical differences in measles morbidity and mortality reflect variability in nutritional factors and access to high-quality health care, although host genetic factors, such as genes regulating cytokine production, might explain some differences in response to MeV infection and vaccination. Studies of immune responses to measles vaccine suggest that polymorphisms in human leukocyte antigen (HLA) genes are associated with different antibody responses³³.

Mechanisms/pathophysiology

Measles virus

MeV has a non-segmented, negative-sense, single-stranded RNA genome of approximately 16,000 nucleotides in length (FIG. 4a). The genome contains six genes, each encoding a single structural protein: the nucleocapsid (N) protein, phosphoprotein (P), matrix (M) protein, fusion (F) protein, haemagglutinin (H) protein and large (L) protein. The P gene encodes two additional, non-structural proteins: V protein and C protein¹.

Viral life cycle

Both the H and the F transmembrane glycoproteins are exposed at the virus surface. Binding of the H protein to a host receptor triggers conformational changes in the F protein, which induces fusion of the viral envelope with the plasma membrane and the release of ribonucleoprotein (RNP) complexes in the cytoplasm of target cells. Following replication and transcription of the viral genome in the 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)). During these processes, the virus assembles and is released from the infected cells (FIG. 4b). Although progeny virions are assembled at and bud from the plasma membrane, the budding of MeV is inefficient and a large amount of the infectious progeny viruses remains associated with the cell³⁴. Virus dissemination within the host is primarily mediated by direct cell-to-cell transmission of the virus via infectious synapses.

Host receptors

Signalling lymphocyte activation molecule (SLAM; also known as SLAMF1 and CD150) has been identified as a cellular receptor for MeV³⁵. Thymocytes, macrophages, mature dendritic cells (DCs), Langerhans cells (LCs), lymphocytes and platelets express SLAM; its expression further increases following immune activation^{36,37}. Nectin 4 (also known as PVRL4), which is expressed at adherens junctions of epithelia, was identified as a second major cellular receptor for MeV through studies in human epithelial cells *in vitro* and in non-human primates *in vivo*^{38,39}. 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) promote MeV infection of DCs and LCs, respectively, possibly contributing to the high transmissibility of MeV^{40,41}. Although MeV shows neurovirulence, no cellular receptor for MeV has yet been identified in neural cells. However, studies have suggested that the substance P receptor supports trans-synaptic transmission of MeV by interacting with the F protein. Vaccine strains and certain laboratory strains of MeV also use human membrane cofactor protein (MCP;

also known as CD46)⁴², via specific amino acid substitutions, N481Y or S546G, in the H protein⁴³. The ability to use CD46 as a receptor is essential for haemagglutination by MeV.

MeV infection

SLAM-positive lymphocytes and DCs are the main targets of MeV *in vivo*^{44–46}. Tissue-resident DCs in the respiratory tract are possible initial targets of MeV (FIG. 5). The infection of immune cells with MeV is mediated by SLAM, but DC-SIGN also supports the attachment of MeV to DCs, promoting SLAM-mediated MeV infection and the transmission of MeV to T lymphocytes⁴⁷. MeV can also directly infect alveolar macrophages in the lungs, which express SLAM^{46,47}. Epithelial cells are unlikely to be the initial targets of infection because MeV antigens are not detected in epithelial tissues early after infection and nectin 4 is not expressed on the apical surface of these cells. MeV infection is amplified in draining lymphoid tissues and subsequently causes viraemia mediated by circulating MeV-infected lymphocytes⁴⁸. Analyses in non-human primates using recombinant MeVs lacking SLAM-binding or nectin 4-binding ability

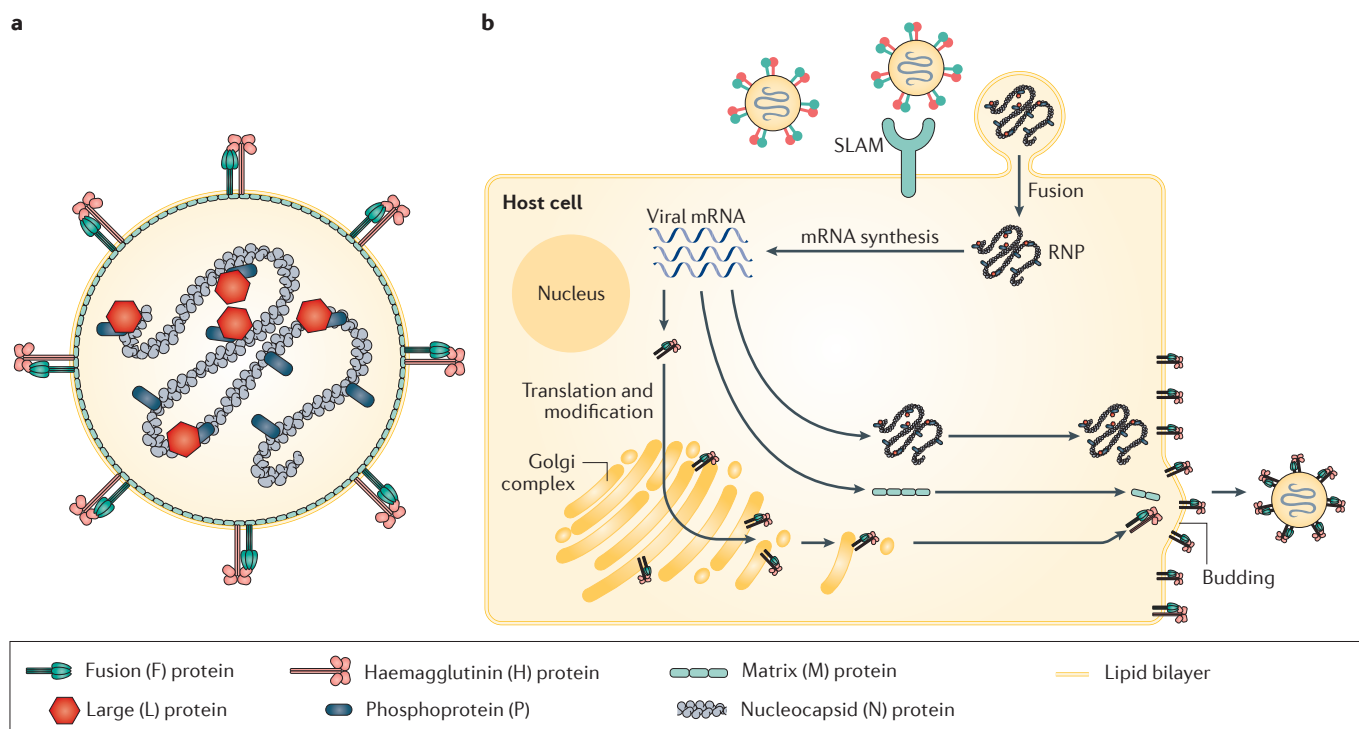


Figure 4 | Measles virus and the viral life cycle. **a** | Structure of measles virus (MeV). The RNA genome of MeV is encapsulated by the N protein, forming a helical ribonucleoprotein (RNP) complex that is associated with viral RNA-dependent RNA polymerase (L protein) and polymerase cofactor (P). Two types of transmembrane glycoproteins, the H protein and the F protein, are incorporated into the lipid envelope that is derived from the host cell membrane. The H protein is responsible for receptor binding with the host cell, whereas the F protein mediates membrane fusion¹⁷⁷. The M protein interacts with both the RNP complex and the cytoplasmic tails of the glycoprotein spikes, and promotes virion assembly. The non-structural V protein and C protein are involved in the evasion of host innate immune responses in infected cells.

b | MeV infection. Following the binding of the H protein to the host receptor, membrane fusion occurs, which releases the viral RNA into the host cytoplasm. Replication and transcription of the viral genome takes place entirely in the cytoplasm. *De novo*-synthesized RNP complexes are transported by RAS-related protein RAB11a-positive recycling endosomes that move along microtubules¹⁷⁸. The H protein and the F protein are transported to the plasma membrane using a different secretory pathway. The M protein interacts with RNP complexes, the cytoplasmic tails of the H protein and the F protein, the cell membrane and actin filaments in the host cells¹⁷⁹. These interactions promote virus assembly and regulate cell-to-cell fusion of MeV¹⁸⁰. SLAM, signalling lymphocyte activation molecule.

(SLAM-blind MeV and nectin 4-blind MeV, respectively) further clarified the individual roles of SLAM and nectin 4 (REFS 49,50). Nectin 4-blind MeV efficiently infected non-human primates, caused a systemic infection and replicated in immune cells to similar levels as wild-type MeV, even when administered intranasally⁵⁰. Conversely, infection by SLAM-blind MeV was highly attenuated and this virus induced strong adaptive immune responses and hardly caused viraemia in non-human primate models⁴⁹. Conversely, infection by SLAM-blind MeV was highly attenuated and this virus induced strong adaptive immune responses and hardly caused viraemia in non-human primate models⁴⁹, suggesting that SLAM is primarily important for MeV pathogenesis.

MeV-infected lymphocytes and DCs can migrate into subepithelial cell layers of the respiratory tract where they can transmit MeV to epithelial cells using nectin 4 as a receptor^{46,51,52} (FIG. 5). Experiments using polarized airway epithelial cells *in vitro* demonstrated that MeV can enter cells from the basolateral side and buds exclusively from the apical membrane⁵⁰, replicating

directional entry and budding of MeV *in vivo*. The virus is efficiently transmitted between epithelial cells through intercellular membrane pores^{53–55}. Nectin 4-blind MeV is not shed into the respiratory tract in infected non-human primates, but different experimental conditions were used for wild-type MeV, prohibiting definitive conclusions^{46,50}. Other mechanisms of transmission have also been proposed. For example, damage to the epithelium of lymphoid tissues in the upper respiratory tract may allow shedding of the virus produced by MeV-infected immune cells or epithelial cell debris by coughing and sneezing⁵⁶.

Immune response

Host response. After viral entry into host cells, anti-viral responses are initiated by the host triggered by the detection of pathogen-associated molecular patterns, such as cytoplasmic single-stranded RNA bearing 5'-triphosphate and double-stranded RNA. The retinoic acid-inducible gene I protein (RIG-I; also known as DDX58)-like receptors, melanoma differentiation-associated protein 5 (MDA5; also known as IFIH1) and laboratory of genetics and physiology 2 (LGP2; also known as DHX58) function as intracellular sensors for virus-specific RNAs. MeV RNAs are mainly detected by RIG-I and to a lesser extent by MDA5 (REFS 57,58). RIG-I-like receptors activate specific kinases, which phosphorylate interferon (IFN)-regulatory factors, leading to the production of IFNs. Secreted IFNs activate the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signalling pathway in adjacent cells, stimulating the transcription of various antiviral genes⁵⁹.

Immune evasion by MeV. The viral V protein, C protein and P protein have roles in evading the host innate immune response to infection. For example, the V protein directly binds to MDA5 and LGP2 and effectively inhibits IFN synthesis⁶⁰. The C protein interferes with IFN induction at the transcriptional level⁶¹ and might also indirectly inhibit IFN induction via its regulatory role in viral RNA synthesis. Viral RNAs are accumulated in cells infected with C protein-deficient MeV, possibly stimulating host innate immune responses^{61,62}. In addition to blocking IFN induction, the V protein actively blocks the JAK–STAT signalling pathway by interacting with STAT1 and STAT2 (REF. 63). The P protein, which shares its amino-terminal domain with the V protein, shows similar IFN-antagonizing activities⁶⁴. Although some studies have demonstrated that the C protein can directly interfere with the IFN-stimulated signalling pathway⁶⁵, the results are controversial^{66,67}. Nonetheless, both the C protein and the V protein are necessary to completely circumvent the host IFN responses and to exhibit high virulence of MeV *in vivo*⁶⁸.

Measles involves suppression of the adaptive immune response that can lead to increased susceptibility to opportunistic infections and that occurs through various mechanisms. Lymphopaenia is noticeable during the acute phase of measles, and the numbers of circulating CD4⁺ and CD8⁺ T cells and B cells are decreased⁶⁹.

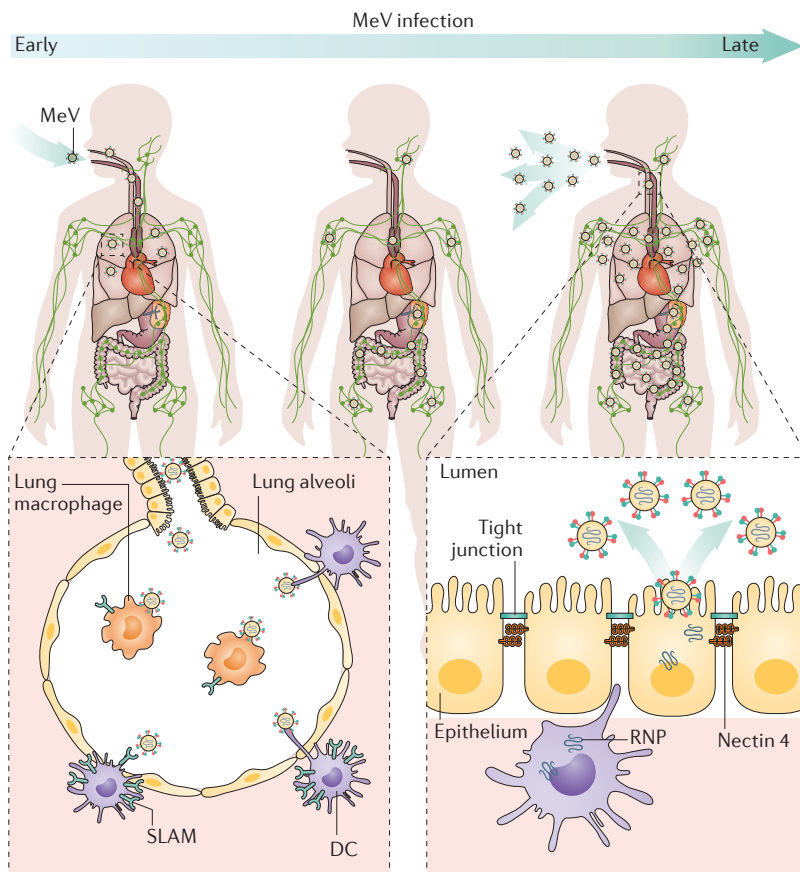


Figure 5 | Measles virus infection and transmission. Measles virus (MeV) is an airborne pathogen. MeV aspirated into the respiratory tract infects alveolar macrophages or dendritic cells (DCs) using signalling lymphocytic activation molecule (SLAM; also known as CD150) as a receptor. MeV infection is amplified in regional lymphoid tissues followed by a systemic infection throughout the body. MeV-infected lymphocytes and DCs migrate into the subepithelial cell layer and transmit MeV to epithelial cells of various organs or tissues using nectin 4 as a receptor. MeV infection is amplified in the epithelia, and a large amount of progeny viruses are released into the respiratory tract. RNP, ribonucleoprotein.

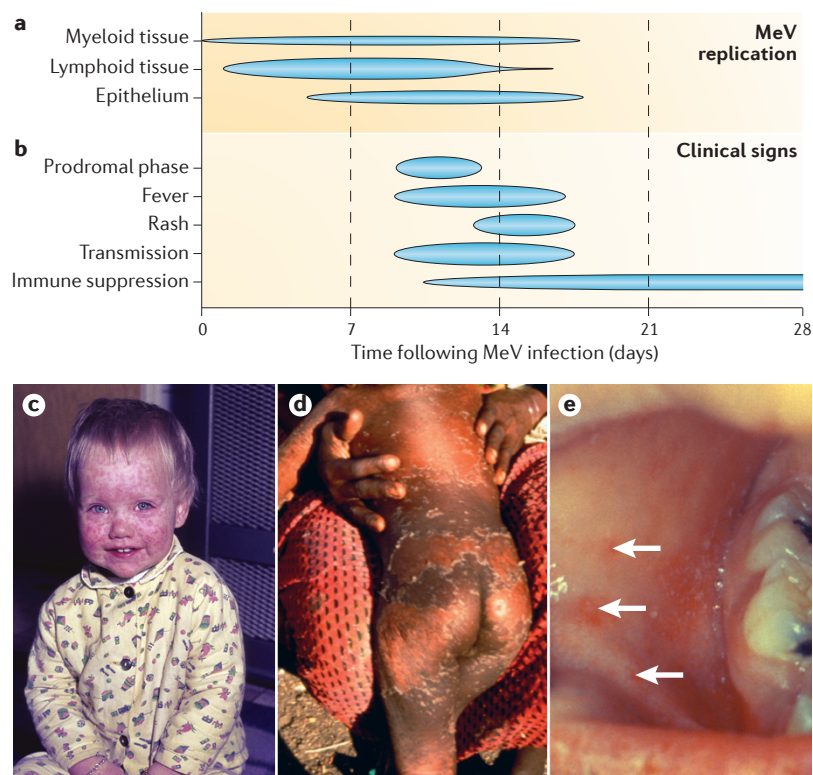


Figure 6 | Pathogenesis of measles. A schematic representation of the kinetics of measles virus (MeV) replication (part **a**) and measles-associated clinical signs (part **b**). The maculopapular skin rash (part **c**) can lead to severe desquamation (part **d**). Koplik spots (part **e**; white arrows) are pathognomonic for measles. Image in part **d** courtesy of S. A. Ibrahim, Khartoum, Sudan.

Both MeV-infected and uninfected lymphocytes from patients with measles are vulnerable to cell death⁶⁹. MeV infection of cultured human T cells revealed that considerable portions of uninfected T cells undergo apoptosis^{70,71}. Altered lymphocyte trafficking and suppression of haematopoiesis are also proposed as causes of lymphopaenia in MeV infection^{69,72}. Although the lymphopaenia resolves soon after patient recovery from rash and fever, the immunological abnormalities last for at least several weeks, months or even years⁵. In patients who have recovered from measles, the delayed-type hypersensitivity responses are suppressed⁷³ and susceptibility to secondary infections is increased for at least several weeks. A cytokine imbalance (for example, increased levels of IL-4, IL-10 and IL-13 and suppressed levels of IL-12) associated with a prolonged T helper 2 (T_H2)-biased immunity results in the suppression of cellular immunity and probably contributes to the immunosuppression⁷⁴.

DCs are primary targets of MeV *in vivo*^{48,75}, and DCs infected with MeV have an important role in MeV-induced immunosuppression⁷⁶. MeV infection impairs functional DC maturation and compromises the ability of DCs to stimulate T cell proliferation⁷⁷. CD40 (also known as TNFRSF5) signalling is affected by MeV infection; IL-12 production is suppressed, whereas IL-10 expression is increased^{71,78}. Toll-like receptor 4 (TLR4)-mediated IL-12 synthesis in DCs is also suppressed by MeV infection⁷⁹. Furthermore, when MeV-infected DCs

are co-cultured with T cells, both the DCs and the T cells undergo apoptosis⁷¹.

MeV infection also suppresses the proliferation of lymphocytes. For example, one study showed that lymphocytes isolated from patients or animals infected with MeV proliferated poorly upon *ex vivo* stimulation by mitogens⁸⁰. This unresponsiveness can be caused by contact of lymphocytes with the viral H protein and the F protein on MeV virions or MeV-infected cells, independently of virus replication in lymphocytes and the H protein interaction with SLAM on lymphocytes⁸¹.

Although MeV infection leads to general immune suppression, a robust primary immune response to MeV that results in lifelong immunity is induced⁸². This apparent contradiction is known as the 'measles paradox' and might be explained by preferential infection and depletion of CD150⁺ memory lymphocytes, a process referred to as 'immune amnesia' (REFS 45,83). Thus, immune suppression associated with infection can lead to opportunistic infections for a period of several weeks to months after MeV infection, and a recent analysis of population-level data suggested that measles may cause delayed mortality for 2–3 years after infection⁵.

Genetic and antigenic variation of MeV

Although MeV is considered a monotypic virus, genetic and antigenic variation has been described among wild-type viruses. Sequencing studies have shown that the genome of MeV is quite stable, although genomes with insertions and deletions have been detected⁸⁴. Sequence variations have been used to assign wild-type MeV into one of 24 genotypes⁸⁵. Antigenic differences between different wild-type strains have also been detected based on the binding of monoclonal antibodies to viral proteins (especially the H protein) and neutralization assays with polyclonal antiserum^{86–90}. In addition, the genomes of all of the measles vaccine strains have been sequenced. Although some sequence variation was detected based on the origin and derivation of the strain, all of the vaccine strains were derived from members of genotype A, which are no longer circulating³⁶. These findings suggest that antibodies induced by vaccination might not recognize all wild-type strains. However, some of the epitopes recognized by neutralizing antibodies that are induced by vaccination target-conserved regions of the H protein, including the regions involved in receptor binding or the interaction between the H protein and the F protein, which limits the possibility for antigenic variation^{91–93}. In support of this observation, sequencing studies have not produced evidence for the action of selective pressure on the H protein of MeV^{94,95}. In addition, measles vaccine is highly effective in all countries regardless of the prevailing endemic genotype of MeV⁹⁶.

Diagnosis, screening and prevention

Clinical signs

The clinical signs of measles and their onset and duration can be mapped according to the pathophysiology of the disease (FIG. 6). MeV infection starts with an incubation period, during which the virus replicates primarily

in myeloid and lymphoid cells and establishes a systemic infection. After 7–14 days, when MeV has spread to the peripheral lymphoid tissues, a prodromal phase starts with malaise, fever and cough. One or two days later, clustered white lesions — known as Koplik spots — can be seen on the buccal mucosa, and these are considered pathognomonic for measles. At that point, infected lymphocytes have disseminated the virus to peripheral tissues, including the skin and the submucosa of the respiratory tract, and have transmitted MeV to epithelial cells and keratinocytes. The maculopapular skin rash appears 3–5 days after the prodromal phase and coincides with the appearance of MeV-specific humoral and cellular immune responses. The rash usually starts behind the ears or on the face and spreads to the trunk and extremities. Conjunctivitis appears around the same time and often results in photophobia. Both rash and conjunctivitis are caused by immune-mediated clearance of MeV-infected cells and may be absent in immunodeficient patients, making the disease difficult to recognize in this patient group^{53,97,98}. As many of the typical clinical signs of measles can also be caused by other infectious agents, including rubella virus, parvovirus B19, human herpes virus type 6 and dengue virus, adequate laboratory diagnosis is crucial⁹⁹. In uncomplicated measles cases, clinical signs usually start to fade a few days after the onset of rash and patients recover in approximately 1 week. By contrast, measles-associated immune suppression, which coincides with widespread epithelial damage, increases susceptibility to secondary bacterial infections that can result in complications, such as diarrhoea, pneumonia or otitis media⁸³. In addition, severe central nervous system complications can occur, including acute post-infection measles encephalitis, measles inclusion body encephalitis and subacute sclerosing panencephalitis (SSPE)¹⁰⁰. In industrialized countries, the frequency of these complications is 10–20%, but this may be much higher in developing countries^{101,102}. SSPE occurs in approximately 1–2 in 10,000 reported measles cases, with a higher rate in children <5 years of age, and generally presents 5–10 years after recovery from the initial primary MeV infection. The late and progressive presentation of SSPE may not appear causally associated with measles and may be misdiagnosed. Presentation of SSPE depends on the stage of detection of symptoms, from symptoms of psychological or neurological deterioration (for example, changes in personality, seizures, and photosensitivity) through to death with detection on autopsy. MeV infection during pregnancy increases the risk of maternal, fetal and neonatal complications; it can damage the placenta and/or fetus and lead to spontaneous termination, stillborn birth or live birth of infants with congenital measles^{103–105}.

Diagnosis

Laboratory confirmation of measles is based on the detection of anti-MeV IgM antibodies or the detection of MeV RNA by reverse transcription PCR (RT-PCR) in clinical samples. The most commonly used method for laboratory confirmation is detection of IgM, usually

by enzyme immunoassay, in serum samples collected at first contact with a suspected case¹⁰⁶. RT-PCR, which is having an increasing role in case confirmation, has the highest sensitivity if samples are collected as early as possible after the onset of rash. In addition to throat or nasal swabs, other clinical specimens that can be used for RT-PCR include oral fluid, urine and peripheral blood mononuclear cells^{107,108}. Detection of the viral RNA has the additional advantage of enabling genotyping, which can be used for molecular epidemiology.

The use of highly susceptible and permissive SLAM-positive B95a cells¹⁰⁹, later replaced by Vero cells modified to express human SLAM (Vero/hSLAM cells)¹¹⁰, allow for efficient isolation of MeV in culture. Viral isolation can take several days to several weeks to complete and is rarely used for diagnostic purposes.

Clinical specimens that can be used for both IgM detection and RT-PCR in diagnosis and surveillance^{111,112} include dried blood spots collected on filter paper, which facilitate storage and transport^{112,113}, and oral fluid samples, which allow for non-invasive sample collection^{114,115}. Although molecular and serological assays performed on dried blood samples and oral fluid samples are highly specific, their sensitivity can be slightly lower than assays performed on serum or throat swabs.

Prevention

The high transmissibility of MeV can be explained by the high viral loads in the upper respiratory tract during the prodromal and early phases of rash, in combination with the epithelial damage that induces a cough reflex. This combination results in the generation of aerosols that contain MeV, facilitating respiratory transmission^{116,117}. Health care facilities can serve as amplification points for measles outbreaks. In addition, mass gatherings and travel hubs, such as airplanes and airports, have often been identified as hotspots of MeV transmission, making international travel a major determinant in global MeV transmission pathways. In post-elimination settings, measles importations occur from areas with measles outbreaks or endemic MeV transmission¹¹⁸.

All current measles vaccines contain a live attenuated strain of MeV. Most of the vaccine strains derive from the prototype Edmonston strain (that is, Moraten, Schwarz and Edmonston-Zagreb strains), although some vaccines derive from other wild-type viruses (for example, CAM-70 and Leningrad-16). According to the WHO requirements, a dose of measles vaccine must contain at least 1,000 TCID₅₀ (the virus titre required to infect 50% of host cells in culture) delivered by subcutaneous injection. Measles vaccine is often delivered in combination with live attenuated vaccines for rubella (MR vaccine) and mumps (MMR vaccine). After a single vaccine dose, 85% of 9-month-old children and 95% of 12-month-old children are presumed immune to measles, and, in most cases, the duration of protection is several decades and probably lifelong. Adverse reactions following measles vaccination are usually mild. Approximately 5–15% of individuals who have had a

Box 2 | Attempts to improve the live attenuated measles vaccine

In parallel with the development of live attenuated measles virus (MeV) vaccines, formalin-inactivated MeV vaccines were developed. Unfortunately, these vaccines were associated with enhanced disease upon subsequent natural MeV infection — referred to as atypical measles — mediated by an immunopathological mechanism¹⁵³. In the 1980s, live attenuated MeV vaccines of increased titre ($>10^5$ TCID₅₀ (that is, the virus titre required to infect 50% of host cells in culture) per dose) were tested as an approach to overcome the presence of maternal antibodies, but this was discontinued after reports of excess and delayed mortality of girls who had received these high titre vaccines as compared with those immunized with standard titre vaccines. In the 1990s, the availability of novel adjuvants and vaccination platforms led to several new vaccines, which showed promising results in non-human primates^{154,155}. None of these vaccines have reached the clinic owing to high costs of clinical trials and the limited possibilities to achieve returns on investment. More recently, several studies have evaluated alternative methods of administration of the existing live attenuated MeV vaccines, which would have the potential to reduce cold-chain dependency and problems associated with injection safety. The most promising routes seemed to be aerosol inhalation, either as a liquid or a dry powder aerosol, or microneedle vaccination^{147,156,157}. However, in a large-scale clinical trial, the aerosolized vaccine proved to be inferior to the subcutaneous vaccine with respect to immunogenicity¹⁵⁸. Whether alternative routes of measles vaccination will be licensed in the near future remains uncertain. In the future, live attenuated MeV vaccines might be modified to express immunogenic proteins of other pathogens to protect against emerging infections^{159–161}.

vaccine experience fever of $>39^{\circ}\text{C}$ between day 7 and day 12 post-vaccination. Rash lasting 1–3 days occurs in approximately 5% of vaccine recipients approximately 7–10 days after vaccination. Although vaccine virus can be detected in respiratory secretions from vaccinated people¹¹⁸, there is no evidence of person-to-person transmission of vaccine viruses¹¹⁹. Although currently available measles vaccines are very safe and effective, the disadvantages for elimination efforts include susceptibility to interference by maternal antibodies in young infants, strict cold-chain dependence and the requirement of hypodermic needles for administration. Despite many attempts to develop new vaccination delivery methods (BOX 2), measles containing vaccines are still being delivered by subcutaneous injection.

Surveillance

Case-based surveillance. Case-based surveillance for measles is required as all the WHO regions have moved to implementation of measles elimination strategies, and surveillance must be sensitive enough to rapidly detect and confirm measles cases and all chains of MeV transmission. Case-based surveillance requires that all suspected cases (BOX 3) have a timely and adequate case investigation, including the collection of clinical samples for laboratory confirmation.

In countries moving toward elimination, cases are further classified based on the source of the infection as endemic, imported, import-related or unknown. A chain of MeV transmission that is continuous for ≥ 12 months is defined as endemic transmission. An internationally imported case had an exposure during international travel occurring 7–21 days before the onset of rash. In the United States, an imported virus case is a case without an identified epidemiological link to an imported case, but with the viral genotype indicative

of imported measles. For unknown source cases, the epidemiological or virological link to importation or endemic transmission cannot be established¹²⁰.

WHO GMRLN. As measles incidence falls, medical personnel become less experienced in recognizing the clinical presentation of measles. Thus, laboratory confirmation of infection is a crucial component of surveillance. Laboratory support for global measles surveillance is provided by the GMRLN¹³ (BOX 4). The GMRLN confirms suspected cases of measles by the detection of anti-MeV IgM antibodies or viral RNA.

Virological surveillance. MeV genetic heterogeneity forms the basis for molecular epidemiological studies of the transmission pathways of MeV¹¹⁸. The WHO currently recognizes 24 genotypes of MeV based on the sequence variation of the 450 nucleotides that code for the carboxyl terminal of 150 amino acids of the N protein (N-450) and the complete coding sequences of the H gene. Of these 24 genotypes, only seven have been detected since 2011: B2, B3, D4, D8, D9, G3 and H1. The GMRLN has been responsible for standardization of the nomenclature and laboratory procedures that are used for viral genotyping^{118,121} and tracking the global distribution of MeV genotypes (FIG. 7).

The recognized genotypes contain multiple lineages; each lineage presumably represents a single chain of transmission. The GMRLN has recently developed an improved protocol to monitor MeV transmission, which involves naming lineages within a genotype. Viruses belonging to a named lineage have identical N-450 sequences, but are designated based on epidemiological and virological criteria¹²¹. The ability to track named lineages has been especially useful for mapping MeV transmission in regions with multiple, ongoing chains of transmission, such as in Europe^{122–124}. Named lineages can also be used for documenting the rapid global spread of genotypes associated with large outbreaks, such as the transmission of genotype B3 viruses following a large outbreak in the Philippines in 2014 (REF. 125). In addition to using named strains based on the N gene, larger regions of the viral genome, including the H gene, the

Box 3 | Case definitions

- A clinical case of measles is any person with fever and maculopapular skin rash and cough, coryza or conjunctivitis, or any person in whom a clinician suspects measles¹⁶²
- Clinically confirmed cases are those that meet the clinical case definition, but ones in which adequate samples for laboratory confirmation were not obtained
- Laboratory-confirmed cases are those that meet the clinical case definition and are confirmed by positive laboratory test results
- Epidemiologically confirmed cases are those that meet the clinical case definition and are linked to a laboratory-confirmed case
- A suspected case that does not meet the clinical or the laboratory definition should be discarded

P gene and the non-coding regions between the M gene and the F gene, are now being sequenced^{126,127}. More recently, whole-genome sequencing has provided additional insights into the variability of the MeV genomes and supported mapping of MeV transmission during outbreaks^{127,128}.

Analysis of molecular epidemiological data in conjunction with epidemiological data from standard case classification and reporting facilitates accurate mapping of transmission pathways of MeV and are thus a valuable tool for measuring the effectiveness of measles control programmes¹¹⁸. In countries approaching elimination, it will be necessary to obtain sequence information from as many chains of MeV transmission as possible. However, baseline virological surveillance needs to be established or improved in many countries.

Management

Treatment of uncomplicated measles cases typically involves supportive care, including antipyretics, anti-tussives, hydration and/or environmental controls (for example, humidification)¹²⁹. Currently, no antiviral therapies with demonstrated clinical effectiveness exist for treating measles, although limited case reports suggest that intravenous or aerosolized ribavirin might provide some benefit in severe disease^{130,131}.

Proper nutrition and vitamin A supplementation protect against developing more-severe symptoms associated with measles¹³². Owing to its effectiveness in reducing measles-related morbidity and mortality, the WHO recommends that children who are infected with MeV should receive vitamin A treatment¹³². Although less frequent in developed countries, clinicians should consider the administration of vitamin A to individuals with measles who present with impaired intestinal absorption, malnutrition and ophthalmological

evidence that is suggestive of vitamin A deficiency, as well as immunocompromised patients and those who require hospitalization for complications. The immunomodulatory effects of vitamin A may account for the protection from severe measles¹³³.

Secondary bacterial infections (for example, pneumonia or otitis media) can occur in some cases and require efficient and effective antibiotic treatment, with potential hospitalization for severe infections¹³⁴. Pneumonia remains one of the leading causes of morbidity and mortality associated with MeV infections¹³⁴. Children who have been immunized against *Haemophilus influenzae* type b and *Streptococcus pneumoniae* can experience less-severe sequelae of measles owing to their protection from these common causes of bacterial pneumonia secondary to measles¹³⁵.

Severe measles complications can occur and include life-threatening outcomes that are associated with pneumonia, thrombocytopaenia and encephalitis in all individuals and severe malnutrition, including kwashiorkor and marasmus, in undernourished children^{134,136}. Measles can also lead to permanent disabilities, for example, blindness in vitamin A-deficient children or deafness, and intellectual disabilities associated with encephalitis^{134,136} and central nervous system complication, including SSPE 5–10 years after infection. SSPE leads to premature mortality preceded by deterioration of the central nervous system and degeneration to a vegetative state, with death generally occurring 1–3 years after diagnosis of SSPE. Early diagnosis of SSPE and supportive care, including anticonvulsant and antispasmodic drugs, may prolong life, although premature mortality will occur owing to the lack of a cure. As long as MeV continues to circulate and cause infections, SSPE mortality will occur. However, patients with SSPE do not shed MeV into the respiratory tract and are therefore not infectious.

Quality of life

Before the introduction of a measles vaccine, measles was considered an inevitable, one-time malady that led to short-term disability and disruption for most individuals, and permanent disability or death for individuals with severe complications. Widespread global adoption of measles immunization dramatically improved quality of life and prevented millions of deaths^{8,11}. National efforts to eliminate MeV transmission by achieving and maintaining high population immunity using vaccines and the apparent absence of cases can lead to the misperception that measles no longer poses a serious threat to health and quality of life. However, the importation of MeV remains a real and constant threat as long as MeV circulates anywhere in the world, and the absence of cases reflects the continued high coverage with measles vaccine in the population. Given the threat of importation, countries should maintain a capacity for aggressive public health efforts to trace contacts, provide immunization and/or guidance for self-quarantine and symptom identification, communication and preventive immunization campaigns that target susceptible individuals when even a single case occurs in a country that previously

Box 4 | Structure of the WHO Global Measles and Rubella Laboratory Network

As of June 2016, the Global Measles and Rubella Laboratory Network (GMRLN) consists of 703 laboratories, all of which follow a standardized set of testing protocols and reporting procedures with a strong focus on quality assurance. The multi-tiered structure of the GMRLN was based on the model of the Global Polio Laboratory Network (GPLN)¹³ and includes subnational, national, regional reference and global specialized laboratories. National laboratories perform most of the diagnostic laboratory testing and are closely linked with the national vaccination and disease control programmes. The regional reference laboratories support genetic characterization of circulating wild-type viruses and support capacity building of the national laboratories. An annual accreditation and proficiency testing programme ensures high-quality serological and molecular testing within the GMRLN. The global specialized laboratories located in Japan, the United Kingdom and the United States develop and standardize laboratory procedures and protocols and support capacity building through training¹³. As all the WHO regions now have elimination or enhanced control goals for rubella and congenital rubella syndrome, the GMRLN provides integrated surveillance for rubella.

Public Health England and the WHO jointly developed a global sequence database for measles, known as the Measles Nucleotide Surveillance (MeaNS (<http://www.who-measles.org>))¹⁰⁷. Members of the GMRLN submit most of the sequence information, but sequences are also downloaded from GenBank. As of 1 July 2015, MeaNS contained 24,571 N-450 sequences (that is, the 450 nucleotides that encode the carboxy-terminal region of the nucleocapsid protein), reflecting submissions from 56 laboratories in all six WHO regions¹²¹.

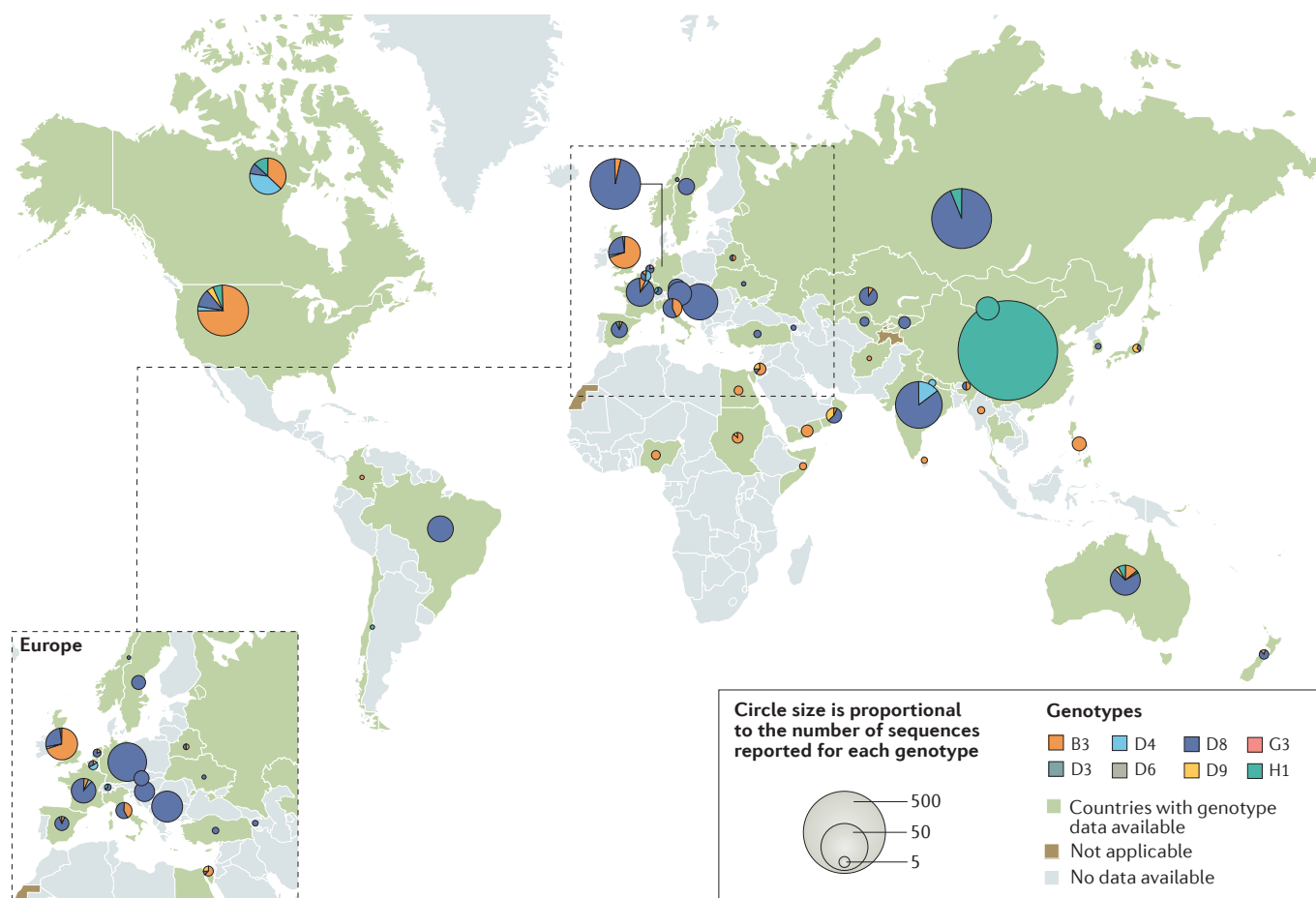


Figure 7 | Detection of the global distribution of measles virus genotypes and incidence in 2015. During 2014–2015, the most frequently reported measles virus (MeV) genotype was genotype H1, which is endemic in China, a country with a high reporting efficiency for molecular surveillance. The most widely distributed MeV genotypes globally were genotypes B3 and D8. In the past, genotype B3 viruses were only endemic in sub-Saharan Africa countries; but recently, genotype B3 viruses were associated with cases and outbreaks in all six WHO regions, including a large measles outbreak in the Philippines in 2014–2015 (REF. 125). Likewise, genotype D8 had been primarily detected historically in South-East Asia, but more recently genotype D8 has caused reported outbreaks in all the WHO regions except the African region. The size of the pie sectors reflect the number of sequences reported for each genotype¹³. Adapted with permission from REF. 13, WHO/CDC.

eliminated indigenous measles. Despite global implementation of vaccination, measles remains a leading cause of mortality for children <5 years of age¹³⁷. However, the considerable reductions in measles mortality associated with the increased use of measles vaccines have contributed to the Millennium Development Goal 4, which aimed to reduce child mortality¹³⁷.

Measles immunization saves profound costs for the individuals affected, their families and the national health care system. A recent study estimated expected treatment cost per MeV infection of US\$1,000–\$2,000 in 2013 in high-income countries, with lower values estimated for relatively lower-income countries¹³⁶. The expected treatment costs reflect a high probability of low costs for most cases (that is, mild or moderate cases) and the remaining probability of high costs for more-severe cases. Measles also leads to lower average life expectancy, increased disability and considerable productivity losses. Prevention of measles means fewer

days of school missed, fewer days of lost work time spent caring for sick or disabled individuals, increased worker productivity and less utilization of health care system resources for treatment. Compared to MeV infection, the expected sequelae and treatment costs of receiving a dose of measles vaccine are much less severe and significantly less costly (\$1–2 in 2013 in expected treatment costs per dose of measles vaccine received in high-income countries), with very small expected productivity losses¹³⁶. Although not currently recommended during pregnancy, measles vaccination incidentally received during pregnancy does not seem to adversely affect the pregnancy, fetus or infant¹³⁸.

Outlook

Eradication as a goal

MeV has caused human devastation and death, infecting nearly everyone for more than a millennium. Measles is an eradicable disease¹³⁹ and could join smallpox

Table 1 | Parameters to consider for virus eradication

Parameters	Smallpox	Polio	Measles
Eradication status	Eradicated	Wild polio virus type 2 eradicated, type 3 potentially eradicated as of publication of this paper and type 1 nearly eradicated	Candidate for eradication
Clinical presentation	Fever and rash	Acute flaccid paralysis	Fever and rash
Asymptomatic infections or carriers	No	Yes	No
Primary mode of transmission	Respiratory droplets	Fecal–oral route or oral–oral route	Aerosolized respiratory secretions
Period of contagiousness	25 days	4–6 weeks	9 days
Basic reproductive number (R_0)	5–7	4–13	9–18
Herd or population immunity threshold	80–85%	75–92%	89–94%
Serotypes	1	3	1
Vaccine delivery	Intradermal injection	Oral drops (oral polio vaccine) or intradermal or intramuscular injection (inactivated polio vaccine)	Subcutaneous injection
Number of vaccine doses needed to stop transmission	1	≥ 3	1–2
Vaccine-derived virus transmission	No	Yes	No

and, soon, polio on the list of eradicated human viral diseases (TABLE 1). The success of the smallpox eradication programme, which resulted in global eradication of smallpox in 1977, energized global vaccination efforts and led to the establishment of the global Expanded Program on Immunization (EPI) in 1974 (REF. 140). In 1988, the WHA officially adopted the polio eradication goal, and the WHO and partners established the Global Polio Eradication Initiative (GPEI). In July 2010, an expert advisory panel convened by the WHO concluded that measles can and should be eradicated^{141,142}, conclusions that were endorsed by the WHO Strategic Advisory Group of Experts and the WHA¹⁴³.

Challenges

There has been tremendous progress towards measles elimination globally; however, MeV continues to cause infections, severe morbidity and mortality. Even though the WHO recommended two doses of a measles-containing vaccine for all children in 2009, nearly 40 countries continue to use a one-dose immunization schedule, and other missed opportunities to vaccinate have not been addressed¹⁴⁴. As MCV1 coverage improves, establishing a visit during the second year of life to integrate MCV2, if recommended, as well as other child health interventions can help to further reduce the measles burden. In countries that do not routinely provide MCV2, measles SIAs are an essential component of the elimination strategy. Implementation of high-quality SIAs can be logistically challenging; however, they are a proven strategy for achieving high ($\geq 95\%$) and homogeneous two-dose coverage that is needed to interrupt MeV transmission. To maximize impact, SIA-target age groups should be determined based on surveillance and immunization data.

Competing priorities among key global partners and funding shortfalls have hampered global efforts to fully implement elimination strategies and develop innovations. Long-term stable financial investments and commitments are needed to galvanize partnerships and accelerate progress. Funding and leadership from the M&RI and partners, including Gavi, are needed to support the implementation of elimination strategies. To complement the funding from global partners to achieve measles elimination goals, country ownership and investments are encouraged to mobilize adequate additional resources. High-level advocacy is ongoing to strengthen national immunization programmes and to ensure effective programme management and strategy implementation.

Opportunities

A small number of human infectious diseases currently are considered to be eradicable, including polio, measles, mumps, rubella, lymphatic filariasis, cysticercosis, yaws and dracunculiasis. The historical window of opportunity to eradicate these diseases and the value of having a globally focused eradication programme should not be taken for granted or underestimated. Previous vaccination programmes have fostered public health partnerships and instilled a data-driven approach within the EPI that uses vaccination coverage and disease surveillance to guide efforts to increase coverage and equity in populations. The identification of susceptible subpopulations and an emphasis on mapping and reaching all communities with immunizations are necessary for the elimination of vaccine-preventable diseases by interrupting chains of transmission from all reservoirs. This elimination or eradication approach has led to the identification and mapping of areas that need EPI strengthening and other public health interventions.

Owing to the highly infectious nature of measles and the high efficacy of the vaccine, measles epidemiology in particular reflects susceptibility in the population. When weaknesses in immunization service delivery occur, measles is frequently the first vaccine-preventable disease detected, identifying areas of low vaccination coverage. Thus, measles is often referred to as the ‘canary in the coalmine’ for EPI and has been used as a signal and driver for strengthening immunization programme strategies and policies (BOX 5). For example, school entry vaccination laws introduced in the United States and other countries have improved vaccine coverage. In China, following the launch of measles elimination strategies, a school entry vaccination check law was established in 2005, but without universal enforcement yet. In Korea, efforts that resulted in measles elimination also led to vaccination requirements for school entry and enhanced vaccine-preventable disease surveillance¹⁴⁵.

The success of elimination and eradication programmes depends on improved surveillance. Analysis of measles surveillance data not only guides strengthening of routine immunization efforts by identifying populations and areas in which immunization coverage is suboptimal but can also indicate areas with likely underperforming disease surveillance. Laboratory systems that were built to support eradication or elimination, such as the Global Polio Laboratory Network

and the GMRLN, provide platforms for monitoring surveillance performance and detecting other vaccine-preventable diseases, such as yellow fever, Japanese encephalitis and emerging pathogens that cause health emergencies. For instance, the recent global response for the West African Ebola outbreak relied on the existing polio eradication infrastructure for rapid case detection, investigation, confirmation and contact tracing. Measles-driven policies and measles elimination strategies can provide opportunities for improving overall immunization service delivery performance and strengthening health systems, a concept of increasing importance as the polio end game unfolds.

Research and emerging technologies

Research is crucial for developing evidence-based policies and strategies and innovations for disease eradication¹⁴⁶. The research priorities for measles eradication have been identified by a group of experts convened by the WHO and the CDC and are periodically updated to reflect changing epidemiology, shifts in measles-susceptible groups, new vaccine development and laboratory techniques that improve on existing tools.

Innovations are needed to overcome the logistic challenges associated with the current vaccine, and alternative delivery methods are being developed. For example, advancements in nanotechnology have led to the development of a prototype measles micro-needle patch that has been shown to be immunogenic for skin vaccination in non-human primates¹⁴⁷. The patch, which can be easily administered by minimally trained volunteers, would be a potential game-changer for strategies to achieve high vaccination coverage, particularly in resource-limited settings¹⁴⁷. In some settings, vaccine hesitancy and low demand for vaccination has contributed to suboptimal vaccination coverage causing sustained virus transmission; research is needed to identify novel strategies that can overcome these and other barriers to vaccination and to reach specific subpopulations or age groups¹⁴⁸. Innovative outreach strategies are needed to improve parents’ knowledge of and confidence in vaccination benefits for their children in order to increase the uptake of measles vaccine. Immunization programmes should be tailored to improve access, demand and use of immunization services, using tools to identify susceptible populations, strategies designed to improve immunization among hard-to-reach populations, and communication plans that increase understanding of the importance of vaccination and reduce uninformed vaccine refusals.

New laboratory techniques have led to the development of high-throughput, multiplex serological assays¹⁴⁹ and prototype point-of-care assays for the detection of IgM and IgG¹⁵⁰, as well as advanced molecular techniques for whole-genome sequencing. New information systems, programmatic dashboards and measles risk assessment tools have been developed to use the existing data more effectively, and these tools are currently being used to improve programme monitoring and performance¹⁵¹.

Box 5 | History of the measles elimination programme in the United States

In 1967, measles elimination strategies were implemented, including routine vaccination of infants, vaccination of all susceptible children at school entry, surveillance and epidemic control. Although measles cases decreased by 95% in 1968, vaccination coverage of preschool children (1–4 years of age) remained approximately 60% in 1970 and outbreaks were occurring in middle schools and high schools¹⁶³. School entry checks on vaccination resulted in further decreases in cases during the late 1970s and 1980s, but measles vaccination in preschool children remained <70% and measles occurred mainly among unvaccinated preschool and school students¹⁶⁴. In the United States, starting in the 1950s, the capacity for high-quality epidemiological investigations was developed and maintained at the federal, state and local level to rapidly detect and aggressively respond to outbreaks. Measles outbreaks in highly vaccinated school populations suggested that a routine second dose of a measles vaccine was needed, which was introduced in 1989. During 1989–1991, a measles resurgence occurred, with 53,685 reported cases resulting in an estimated 11,000 hospitalizations and 123 reported measles-related deaths¹⁶⁵. The resurgence started with school-based outbreaks mostly among vaccinated students, but the primary group affected was unvaccinated preschool-aged children living in poor urban areas in large cities. The changing measles epidemiology exposed an economic disparity in the burden of disease and inequity of vaccination coverage among communities. These findings led to legislation and sustained funding commitments to establish the national Vaccines for Children Program. By the mid-1990s, coverage with a first dose of a measles-containing vaccine (MCV1) among children 19–35 months of age reached 90%, and states enforced school requirements for vaccination. During 1990–1996, measles cases decreased from 27,786 to 508. Since 2000, measles is no longer endemic in the United States^{166,167} and was eliminated from the entire western hemisphere in 2002.

Following the elimination of endemic measles, measles virus (MeV) introduced into the United States by importation, primarily by unvaccinated US citizens returning from international travel, led to subsequent MeV transmission among clusters of under-vaccinated people living in the United States¹⁶⁸. Estimated national coverage with the first dose of measles, mumps and rubella vaccine is 92%, but considerable variability in coverage exists among the 50 US states, in part owing to the increasing rates of vaccine exemption at school entry in some states¹⁶⁹.

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Author contributions

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Competing interests

The authors declare no competing interests.

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