WHO Immunological Basis for Immunization Series

Module 7: Measles
Update 2020

Immunization, Vaccines and Biologicals

World Health Organization

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Contents

Abbreviations and acronyms

ADEM	Acute demyelinating encephalomyelitis
BCG	Bacillus Calmette–Guérin vaccine
CD	Cluster of differentiation
DTH	Delayed-type hypersensitivity
EIA	Enzyme immunoassay
ELISA	Enzyme linked immunosorbent assay
EPI	Expanded Programme on Immunization
FAO	Food and Agriculture Organization of the United Nations
FI-RSV	Formalin-inactivated respiratory syncytial virus vaccine
F protein	Fusion protein
H protein	Haemagglutinin protein
HAART	Highly active antiretroviral therapy
HI	Hemagglutination inhibition
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IQR	Interquartile range
MCV	Measles-containing vaccine
MIBE	Measles inclusion body encephalitis
MMR	Measles, mumps and rubella
MR	Measles and rubella
MV	Measles virus

N	Nucleoprotein
NIBSC	National Institute for Biological Standards and Control
NK cells	Natural killer cells
PFU	Plaque-forming units
R^0	Basic reproductive number
RNA	Ribonucleic acid
SNPs	Single-nucleotide polymorphisms
SSPE	Subacute sclerosing panencephalitis
TCID	Tissue culture infective dose
WHO	World Health Organization

Preface

This module is part of the World Health Organization (WHO) series *The immunological basis for immunization*, which was initially developed in 1993 as a set of eight modules, comprising one module on general immunology and seven modules each devoted to one of the vaccines recommended for the Expanded Programme on Immunization – i.e. vaccines against diphtheria, measles, pertussis, polio, tetanus, tuberculosis and yellow fever. Since then, this series has been updated and extended to include other vaccines of international importance. The main purpose of the modules is to provide national immunization managers and vaccination professionals with an overview of the scientific basis of vaccination against a range of important infectious diseases. The modules developed since 1993 continue to be vaccine-specific, reflecting the biological differences in immune responses to the individual pathogens and the differing strategies employed to create the best possible level of protection that can be provided by vaccination. The modules also serve as a record of the immunological basis for the WHO recommendations on vaccine use, as published in the WHO vaccine position papers.[1]

[1] See: *http://www.who.int/immunization/documents/positionpapers_intro/en/index.html*, accessed 31 October 2019.

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Conflict of interest

All authors declared their interests ahead of updating the module. One author reported relevant interests, which were assessed not to constitute a conflict of interest in relation to the authorship of the module. All the reported relevant interests are summarized below:

Rik de Swart received research support from Viroclinics Biosciences in 2016 for diagnostic and preclinical studies along with drug development for prevention and treatment of respiratory syncytial virus (RSV) infections. This interest was assessed as non-personal, nonspecific and financially significant.*

Rik de Swart received in 2016 travel support from Viroclinics Biosciences to attend meetings on RSV. This interest was assessed as personal, nonspecific and financially significant.*

Rik de Swart received research support from Themis Bioscience GmbH (Vienna, Austria) in 2018 for a project aimed at detection of chikungunya virus-specific CD8+ T-cell responses in human PBMC collected during clinical trials of measles-based chikungunya virus vaccines. This interest was assessed as non-personal, nonspecific and financially significant.*

* According to WHO's Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or nonfinancial gain to the expert, such as consulting income or a patent. "Specificity" indicates whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fees or other received funding, including those received by expert's organization, from any single vaccine manufacturer or other vaccine-related company exceeds US$ 5000 in a calendar year. Likewise, a shareholding in any one vaccine manufacturer or other vaccine-related company in excess of US$ 1000 would also constitute a "significant shareholding".

1. The organism, disease and vaccines

Measles is one of the most important infectious diseases of humans. The causative agent, measles virus (MV), is a highly infectious virus that is spread via the respiratory route and causes a systemic disease.[1] Prior to the development and widespread use of measles vaccines, measles was estimated to cause millions of deaths annually. Remarkable progress in reducing measles incidence and mortality has been made as a consequence of increasing routine measles vaccine coverage with two doses of measles-containing vaccine (MCV) and through mass vaccination campaigns called supplementary immunization activities.

In 2002 the WHO Region of the Americas was declared free of measles after intensive immunization and surveillance efforts by the Pan American Health Organization.[2] However, as the virus continued to circulate in other parts of the world it was reintroduced into the Americas, leading to both small and large outbreaks, and resulting in sustained endemic transmission in several countries.[3-5] In September 2016, an international expert committee reviewed evidence on measles elimination presented by all countries of the Region of the Americas and decided that the region met the established criteria for elimination. Thus, the Region of the Americas was declared to have eliminated measles for the second time. However, elimination was again transient in the Americas as measles re-emerged.[6,7] These achievements not only attest to the enormous public-health significance of measles vaccination, but also illustrate that MV cannot be fully controlled anywhere until it is controlled everywhere.

In 2010, the World Health Assembly endorsed a resolution that identified a number of goals to be achieved by 2015 – including national-level measles vaccine coverage of 90%, reported measles incidence below five per million population, and 95% mortality reduction compared to 2000. However, despite significant achievements, these goals were not met.[8] In addition, all WHO regions set goals to achieve measles elimination by 2020. But measles outbreaks continue to occur and progress towards regional elimination goals has slowed.

1.1 Measles

Clinically apparent measles begins with a prodrome characterized by fever, cough, coryza (runny nose) and conjunctivitis (Figure 1). Koplik's spots, which are lesions on the buccal mucosa inside the mouth, may be visible during the prodrome. The prodromal symptoms intensify several days before the onset of rash, during which period patients are highly contagious. The characteristic erythematous and maculopapular rash typically appears first on the face and behind the ears, and then spreads to the trunk and extremities. The rash lasts for 3 to 6 days and fades in the same manner as it appeared. Because this rash is a consequence of the virus-specific immune response, persons with impaired cellular immunity may not develop the characteristic measles rash. Nevertheless, these immunocompromised patients are at high risk of developing fatal disease if they contract measles. Illness with fever and rash resembling measles may be caused by several conditions other than MV infection, thus highlighting the crucial importance of laboratory confirmation of diagnosis, especially in settings where measles incidence is low.

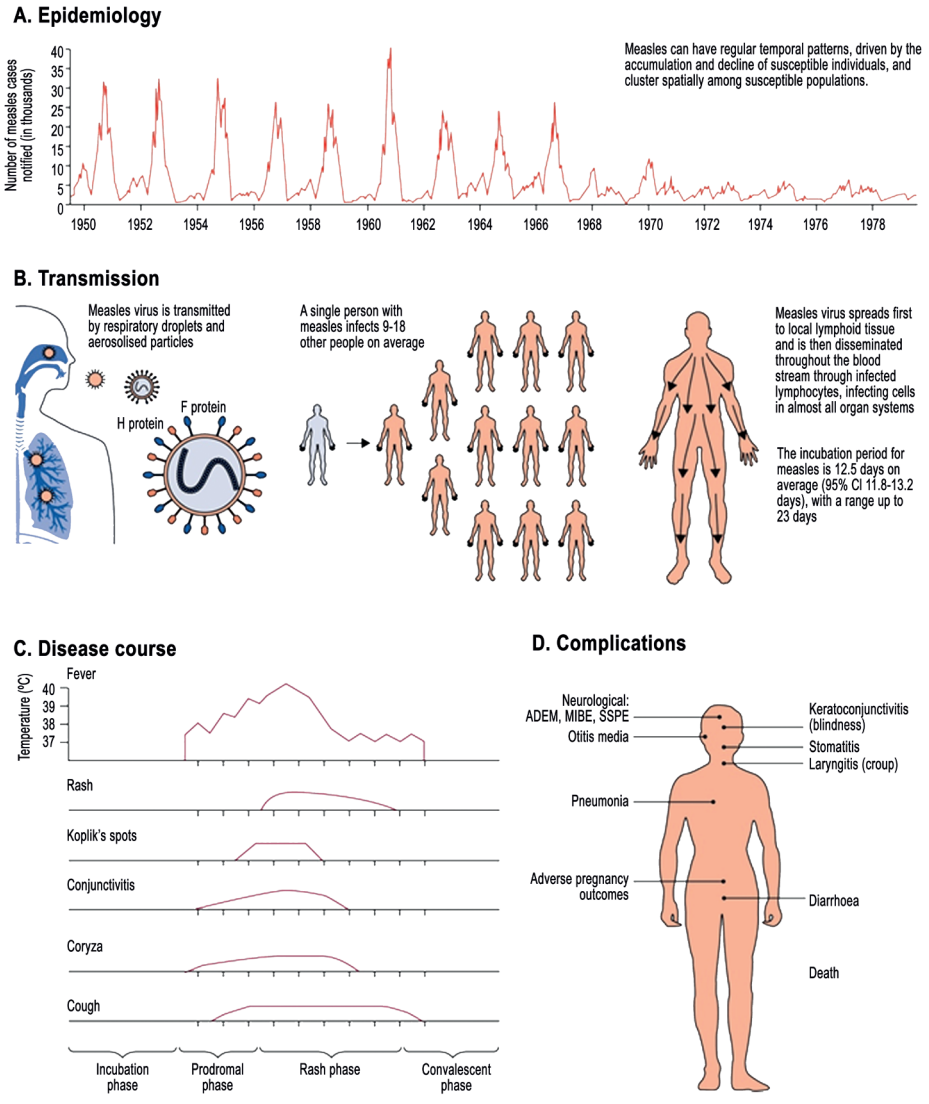
Figure 1. Measles virus transmission, disease course and complications.

A. Epidemiology: Regular temporal pattern of measles driven by accumulation and decline of susceptible individuals.

B. Transmission: Transmission of measles virus by respiratory droplets and aerosolized particles. A single infectious individual can infect 9−18 other people on average. Measles is a systemic infection that spreads throughout the infected host.

C. Disease course: Clinical disease starts with a prodromal illness of fever, cough, coryza and conjunctivitis, followed by Koplik's spots and the characteristic rash.

D. Complications: Complications of measles occurs in multiple organ systems, including the lungs and nervous system.



ADEM = acute demyelinating encephalomyelitis.
MIBE = measles inclusion body encephalitis.
SSPE = subacute sclerosing panencephalitis.

Source: Moss WJ. Measles. Lancet. 2017;390:2490—502.
Part A adapted from Fine PE, Clarkson JA. Measles in England and Wales – I: An analysis of factors underlying seasonal patterns. Int J Epidemiol. 1982; 11: 5–14.

In uncomplicated measles, clinical recovery begins soon after appearance of the rash. However, measles is associated with immune suppression, resulting in increased susceptibility to opportunistic infections. This may lead to complications, which occur in 10–40% of measles cases. The risk of experiencing complications after measles is increased by extremes of age and high transmission intensity due to crowded living conditions associated with poor hygiene and medical care.[9,10] The respiratory tract is a frequent site of complications, with pneumonia accounting for the majority of measles-associated deaths.[11] Pneumonia may be caused either by secondary bacterial infections, viral infections, or by MV itself. The potential impact of bacterial co-infections is well illustrated by a description of a measles outbreak in the United States army in 1917–1918.[12] Additional respiratory complications include laryngotracheobronchitis (croup) and, more commonly, otitis media (ear infection). Mouth ulcers, or stomatitis, may hinder measles patients during eating or drinking. Many children with measles develop diarrhoea, which further contributes to malnutrition and dehydration. Eye disease (keratoconjunctivitis) may occur after measles, particularly in children with vitamin A deficiency, and can result in blindness. Rare but serious complications of measles involve the central nervous system.[13,14] Post-measles encephalomyelitis complicates about one in 1000 measles cases, mainly in older children and adults. Other rare complications of the central nervous system occurring months to years after acute infection are measles inclusion body encephalitis (MIBE, which is mainly seen in immunocompromised patients) and subacute sclerosing panencephalitis (SSPE).

Measles severity and case fatality rates are highly dependent on general health status and health-care infrastructure. Children with vitamin A deficiency, and those with severe immunological deficits such as advanced human immunodeficiency virus (HIV) infection, are at increased risk of severe or fatal measles.[15] In resource-poor countries where malnutrition and exposure to other infectious diseases are common, the case–fatality ratio for measles commonly rises to 5%, but can be as high as 30% in refugee camps or in isolated, immunologically naive populations.[16] In industrialized countries, measles incidence is linked to non-measles infectious disease childhood mortality, and the increased mortality risk extends over a period of more than two years after the acute stage of the disease.[17] However, deaths due to measles are rare in resource-rich countries, where the case fatality ratio is 0.01–0.1%.

1.2 Measles virus

MV is the causative agent of measles and was first isolated from the blood of infected children in the 1950s by John Enders and Thomas Peebles.[18] The development of vaccines against measles soon followed. MV is one of the most infectious directly-transmitted pathogens known and occurs naturally only in humans. MV is a spherical, enveloped virus with a non-segmented, single-stranded, negative-sense ribonucleic acid (RNA) genome and is a member of the *Morbillivirus* genus in the family *Paramyxoviridae*. Closely related animal morbilliviruses include rinderpest virus and canine distemper virus. Rinderpest virus caused an important disease of cattle and swine. As the result of global vaccination efforts of the Food and Agriculture Organization (FAO) of the United Nations, rinderpest virus has been globally eradicated.[19] Canine distemper virus not only infects dogs but also several carnivorous wild animals, including raccoons, wolves, foxes, mustelids, seals and lions.[20]

Although RNA viruses have high mutation rates, MV is remarkably stable and antigenically monotypic, which means that the surface proteins responsible for inducing protective immunity have retained their antigenic structure globally for decades. Consequently, live attenuated MV vaccines developed in the 1960s still provide protection against currently circulating wild-type MV strains – unlike influenza virus, for instance, for which vaccines need to be updated annually.

The MV genome encodes six structural and at least two nonstructural proteins. In terms of the immunological basis for measles immunization, the transmembrane glycoproteins proteins of MV – the haemagglutinin (H) and fusion (F) proteins – are most important. The primary function of the H protein is to bind to host cellular receptors, whereas the F protein mediates membrane fusion and subsequent uptake of the viral genome into the host cell. The H protein elicits strong virus-neutralizing antibody responses, and the lifelong immunity that follows infection (or vaccination) is predominantly attributed to neutralizing antibodies against H.[21]

The pathogenesis of measles is complex and involves several different cell types and at least two different cellular receptors: CD150 and nectin-4 expressed by immune and epithelial cells, respectively.[22] Aerosols and respiratory droplets from infected persons generated during coughing serve as vehicles of transmission by carrying infectious virus to the respiratory tract of susceptible hosts (Figure 1). However, the virus initially does not infect respiratory epithelial cells but is taken up by myeloid cells (most likely dendritic cells or macrophages), which serve as Trojan horses to deliver the virus to the regional lymphoid tissues. Infection of T- and B-lymphocytes leads to a cell-associated viraemia, resulting in high levels of virus replication in all lymphoid tissues – including lymph nodes, thymus and spleen. Infected lymphocytes that migrate to the skin or the submucosa of the respiratory tract mediate infection of epithelial cells. The MV-specific host immune response clears these infected cells, resulting in the onset of clinical signs and symptoms (Figure 1). Infection of respiratory epithelial cells leads to excretion of cell-free virus particles into the respiratory mucus. At the same time, infection of respiratory epithelial cells leads to cough, which generates aerosols and promotes efficient airborne transmission of the virus to the next host (Figure 2). Infection and depletion of B- and T-lymphocytes causes large-scale damage to the immune system. Moreover, infection of memory lymphocytes is thought to cause "immune amnesia" which may contribute to measles-associated immune suppression.[23-26] Interestingly, live attenuated MV strains are apparently able to infect myeloid cells at similar levels as wild-type MV strains, but are highly restricted in subsequent infection and cell-to-cell transmission in lymphoid cells.[27] Consequently, measles vaccine viruses do not lead to widespread infection of lymphoid tissues and do not cause immune suppression.

Figure 2. Measles virus entry, dissemination, transmission and immune suppression

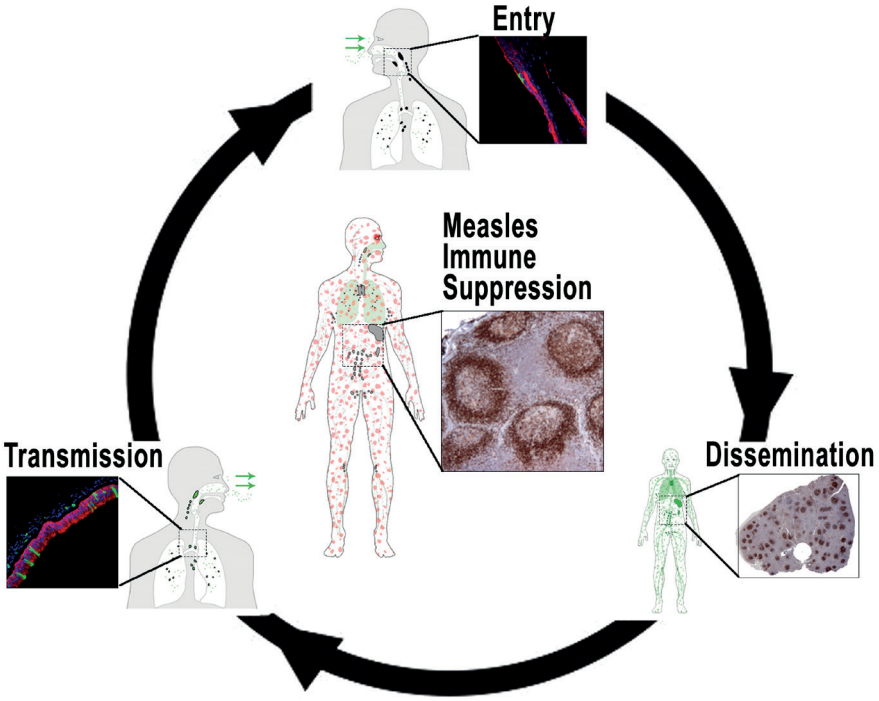
Graphical summary of the four key stages in the life cycle of measles virus, as follows:

1. Entry: The virus initially targets myeloid cells in the respiratory tract which serve as Trojan horses to transmit the virus to CD150$^+$ B- and T-lymphocytes in draining lymphoid tissues.

2. Dissemination: A cell-associated viraemia mediates dissemination of the infection to all lymphoid tissues and tissue-resident immune cells.

3. Transmission: Infected lymphocytes infiltrate into the respiratory submucosa where they transmit the virus to nectin-4$^+$ epithelial cells. Infected epithelial cells produce new virus particles from their apical surface, and induction of a cough reflex supports virus transmission to another host.

4. Immune suppression: Infection and depletion of CD150$^+$ memory lymphocytes (in lymphoid tissues but also including tissue-resident cells) causes immune amnesia, resulting in increased susceptibility to opportunistic infections.



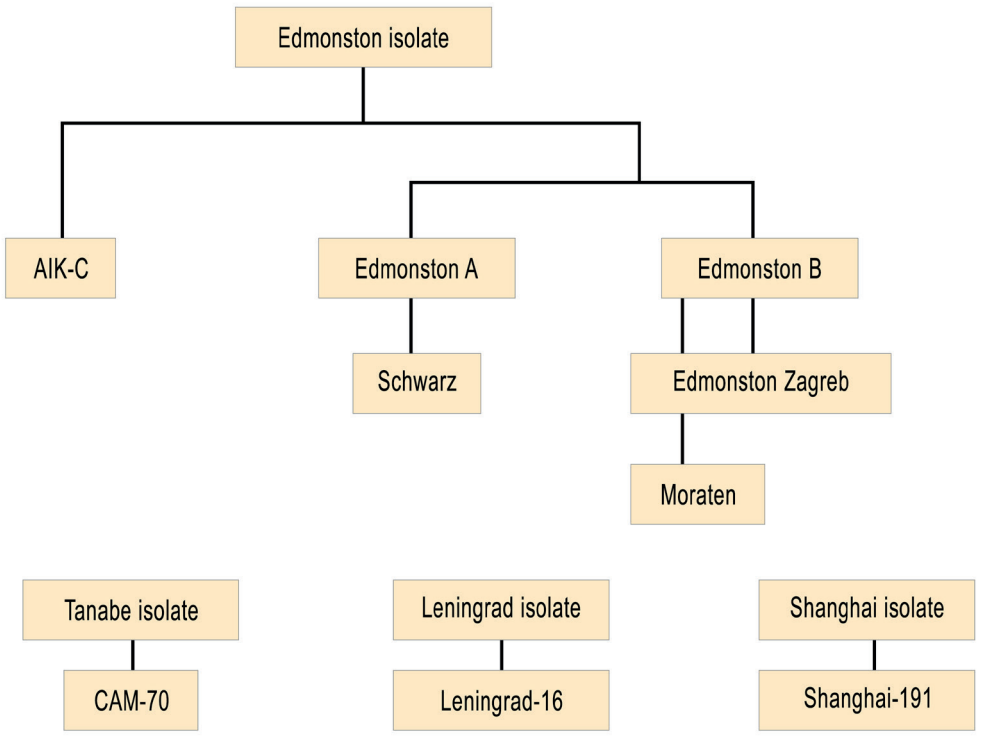
Source: Laksono BM, De Vries RD, McQuaid S, Duprex WP, De Swart RL. Measles virus host invasion and pathogenesis. Viruses. 2016;8:210.

1.3 Measles virus vaccines

1.3.1 Vaccine strains

Currently licensed MCVs contain attenuated MV strains which were obtained by serial passage of wild-type viruses in cultured cells. The first licensed attenuated MV vaccine strain was called Edmonston B (Figure 3). This immunogenic vaccine strain was widely used between 1963 and 1975 but was frequently associated with fever and rash. The Schwarz and Moraten ("more attenuated Enders") strains were derived from the original Edmonston strain but were further attenuated through additional passages in chick embryo fibroblasts. Despite differences in their passage history, these two vaccine strains have identical genomic sequences.[28] The Moraten vaccine is widely used in the United States of America and the Schwarz vaccine is used in many countries throughout the world. The Edmonston-Zagreb vaccine, similarly derived from the Edmonston B strain, is the most widely used strain in developing countries and was passaged in human diploid (MRC-5) cells after attenuation in chick embryo fibroblasts.

Figure 3: Measles virus vaccines



Source: Cutts FT. Measles Module 7: The immunological basis for Immunization Series. World Health Organization [online] http://www.who.int/vaccinesdocuments/DocsPDF-IBI-e/mod7_e.pdf (1993).

Several MCVs are employed in combination with other live attenuated virus vaccines, such as rubella and mumps vaccines (MR and MMR) and varicella vaccine (MMRV). Licensed combination vaccines do not reduce the immunogenicity of the measles vaccine component. Measles vaccines are usually injected subcutaneously but can also be administered intramuscularly. Measles vaccines may contain sorbitol or gelatin as stabilizers, as well as the antibiotic neomycin, but they do not contain thimerosal or an adjuvant. The vaccine must be reconstituted in sterile diluent prior to use. Reconstitution with liquids other than the sterile diluent has led to serious adverse events and must be avoided.

1.3.2 Vaccine potency and stability

The potency of measles vaccines can be determined by measurement of plaque-forming units (PFU) or tissue culture infective doses ($TCID_{50}$). An International Reference Reagent, available from the National Institute for Biological Standards and Control (NIBSC) in the United Kingdom, can be used to standardize the reporting of potency measurements. WHO recommends a minimum potency for measles vaccine of 1000 viral infective units (3.0 $\log_{10}$ $TCID_{50}$).[29] All currently-licensed MV vaccines have potencies between 3.0 and 4.2 $\log_{10}$ infectious units. It is important to note that attenuated virus vaccines contain a low antigenic dose and need to replicate in the host to induce a protective immune response. Studies in non-human primates have shown that the vaccine virus replicates in myeloid cells at the injection site but, in contrast to wild-type MV, does not spread efficiently to lymphocytes and consequently does not usually cause systemic infection.[27,30] However, in individuals with rare immune deficiencies, vaccination can result in disseminated vaccine virus infection.[31,32]

MCVs are relatively heat-stable in the lyophilized form, but rapidly lose potency when exposed to heat after reconstitution. In the freeze-dried state, measles vaccines that meet WHO requirements retain a minimum potency of at least 3.0 $\log_{10}$ live virus particles per human dose after exposure to a temperature of 37 °C for at least one week. However, reconstituted measles vaccines may lose their potency at room temperature. Although the stability depends in part upon the vaccine strain and the excipients used in the formulation, reconstituted measles vaccines may lose approximately 50% of potency in one hour at 22–25 °C and are inactivated within one hour at temperatures over 37 °C. Reconstituted measles vaccines must therefore be kept cool and protected from sunlight.[29]

2. Immunological responses to natural infection

Host immune responses to MV are essential for viral clearance, clinical recovery and the establishment of long-term protective immunity. However, most of the clinical signs associated with measles – including fever, Koplik's spots, skin rash and conjunctivitis – may be considered "collateral damage" of the antiviral immune response.

2.1 Innate immune responses

The early nonspecific (innate) immune responses that occur during the prodromal phase of the illness include activation of natural killer (NK) cells. However, the nonstructural viral V and C proteins effectively suppress the interferon (IFN) response.[33] This allows clinically silent widespread dissemination of MV during the incubation period before the onset of the adaptive immune response.[34]

2.2 Antibody responses

The adaptive immune response consists of MV-specific humoral and cellular immune responses.[33] The protective efficacy of antibodies to MV is illustrated by the protection conferred on infants from passively-acquired maternal antibodies (measles is rarely seen in infants below the age of six months, whereas newborns of non-immune mothers are susceptible[35]) and the protection of exposed, susceptible individuals following administration of anti-MV immune globulin. The most important biological property of MV-specific antibodies is the capacity to neutralize the virus directly, thereby preventing infection. Virus-neutralizing antibodies are exclusively directed to the transmembrane surface glycoproteins H and F,[21] and serum levels of virus-neutralizing antibodies above 120 mIU/mL measured by a plaque-reduction neutralization assay[36] correlate with protection from measles.[37]

The first MV-specific antibodies produced after infection are of the IgM subtype, generally followed by predominantly IgG1 and IgG3 isotypes. The IgM antibody response is usually absent following re-exposure or revaccination and serves as a marker of primary infection. IgA antibodies to MV are found in serum and mucosal secretions. The most abundant and most rapidly produced antibodies are against the nucleoprotein (N) and therefore this antigen is often used as a target in diagnostic assays.[38,39] Avidity, which refers to how tightly the antibody binds MV antigens, is an important characteristic of a mature antibody response. The development of a high avidity antibody response is critical to the development of protective immunity to MV. The avidity of the IgG antibody response can be used to discriminate between primary and secondary vaccine failure in measles patients with a history of measles vaccination.[40-42]

2.3 Cellular immune responses

Evidence of the importance of cellular immune responses to MV is demonstrated by the ability of children with agammaglobulinaemia (congenital inability to produce antibodies) to recover from measles, whereas children with severe defects in T-lymphocyte function often develop severe or fatal disease.[43] Because dissemination of MV within the host is largely mediated by direct cell-to-cell transmission of the virus,[22,44,45] antibody-mediated immune responses are limited in their ability to clear infection.[46] Therefore, although antibodies play a major role in preventing infection,[47] cellular immune responses are crucial in clearance of an established MV infection (i.e. by killing MV-infected cells) and viral RNA. In cell culture, MV-specific $CD8^+$ (but not $CD4^+$) T-cells suppressed dissemination of MV infection in human B-cell cultures.[48] Monkeys provide an animal model to study the immune responses to MV and measles vaccines, and monkeys depleted of $CD8^+$ T lymphocytes and challenged with wild-type MV had a more extensive rash, higher MV loads, and longer duration of viraemia than control animals. This further confirms the importance of cellular immunity to MV clearance.[49]

$CD4^+$ T lymphocytes are also activated in response to MV infection and secrete cytokines that are capable of modulating the humoral and cellular immune responses (Figure 1). Plasma cytokine profiles show increased levels of IFN-γ during the acute phase, followed by a shift to high levels of interleukin (IL)-4 and IL-10 during convalescence.[50] The initial predominant type 1 response (characterized by IFN-γ) is essential for viral clearance; the later type 2 response (characterized by IL-4) promotes the development of MV-specific antibodies.[33] More pronounced activation of macrophages and T cells producing type 1, but not type 2, cytokines was observed in children with fatal MV infection.[51] Thus, the cellular immune response to MV is a dynamic process, with functionally distinct subsets of MV-specific $CD4^+$ and $CD8^+$ T cells at different times following infection.[52]

2.4 Immunological memory

The duration of protective immunity following wild-type MV infection is generally thought to be lifelong. Observations by Peter Panum during the measles epidemic on the isolated Faroe Islands in 1846 demonstrated the long-term protective immunity conferred by wild-type MV infection.[53] Two measles epidemics occurred in this community decades apart. Adults with a history of measles during childhood did not acquire measles after re-exposure 65 years later. Subsequent studies demonstrated that, on rare occasions, adults with a history of natural measles during childhood may undergo subclinical reinfection with MV, leading to a secondary immune response.[54] However, full-blown clinical measles following MV reinfection has never been described in people with natural immunity. The mechanisms involved in sustaining protective immunity to MV are not completely understood. There is no evidence that repeat exposure to MV is required for long-term immunity. It has been speculated that fragments of the MV genome may persist over prolonged periods of time, and may perhaps contribute to the induction of long-term memory responses.[47] Immunological memory to MV includes both continued production of MV-specific antibodies and the circulation of MV-specific $CD4^+$ and $CD8^+$ T lymphocytes. Levels of naturally acquired anti-MV antibodies diminish only a little over time and rapid secondary humoral and cellular immune responses from long-lived memory cells provide protection from infection.[55]

2.5 Immune suppression

The intense immune responses induced by MV infection are paradoxically associated with depressed responses to unrelated (non-MV) antigens, lasting for several weeks to several months or even years beyond resolution of the acute illness.[56] This state of immune suppression enhances susceptibility to secondary bacterial and viral infections that cause pneumonia and diarrhoea and is responsible for the majority of measles-related morbidity and mortality. Delayed-type hypersensitivity (DTH) responses to recall antigens, such as tuberculin, are suppressed, and cellular and humoral responses to new antigens are impaired, following MV infection. Reactivation of tuberculosis and remission of autoimmune diseases have been described after measles and are attributed to this state of immune suppression. Measles immune suppression may result either from functional changes in antigen-presenting cells and/or effector lymphocytes[56] or from depletion of pre-existing $CD150^+$ memory lymphocytes.[23,24,57] MV infects $CD150^+$ immune cells, including memory T- and B-lymphocytes.[24,58] Analysis of paired blood samples collected from unvaccinated children before and after measles demonstrated incomplete reconstitution of B-lymphocyte pools after measles.[25] Moreover, measles was shown to result in depletion of a substantial fraction of circulating antibodies against an array of viruses and bacteria.[26] Collectively, these data demonstrate that measles causes damage to the immunological memory to previously encountered pathogens, resulting in 'immune amnesia'. This mechanism may explain why the incidence of childhood morbidity and mortality is increased for more than two years after measles.[17,59]

Abnormalities of both the innate and adaptive immune responses follow MV infection. Transient lymphopenia (a reduction in the number of lymphocytes in the blood) with a reduction in both T and B lymphocytes, occurs in children following MV infection.[60] This process is paralleled in both experimentally infected monkeys and naturally infected children by depletion of lymphocytes from lymphoid tissues.[23,57] Functional abnormalities of immune cells are also detected. Dendritic cells, which are major antigen-presenting cells, mature poorly, lose the ability to stimulate proliferative responses in lymphocytes and undergo cell death when infected with MV in vitro.

3. Immunological responses to immunization

3.1 Immunological basis for measles immunization

MCVs induce humoral and cellular immune responses similar to natural MV infection, with attenuated vaccine virus replicating within the host to stimulate the immune system.[61] IgG antibodies first appear 12—15 days after vaccination and typically peak at 21—28 days. IgM antibodies appear transiently in blood and IgA antibodies are predominant in mucosal secretions. Production of IgM antibodies signifies a primary response to measles vaccine. IgG antibodies to the H and F proteins on the surface of MV confer protection by blocking the ability of the virus to attach to and invade host cells. This protection can persist for decades following immunization. Measles vaccination also induces long-lived MV-specific CD4+ and CD8+ T-lymphocyte responses.[62] As with immune responses following natural infection, the CD4+ T-lymphocyte responses facilitate antibody maturation and the CD8+ T-lymphocyte responses are critical to clearing MV infected cells.[63] Although both humoral and cellular responses are induced by MCV, these responses are generally of lower magnitude and may be of shorter duration compared to those following natural MV infection.

The proportion of children who develop protective antibody levels following measles vaccination depends on the presence of inhibitory maternal antibodies and the immunological maturity of the vaccine recipient, as well as on the dose and strain of the vaccine virus as described in detail below. In general, some 85–90% of children develop protective antibody levels when given one dose of MCV at 9 months of age, and 90–95% respond when first vaccinated at 12 months of age.[29] Median MCV effectiveness (i.e. protection from disease) following a single dose of MCV administered at 9–11 months of age was 84% (interquartile range [IQR] 72–95%) across several studies, and increased to 92.5% (IQR 84.8–97%) among children first vaccinated at 12 months or older.[64] Thus most, but not all, children are protected following a single dose of MCV.

3.2 Immunological basis for two doses of measles-containing vaccine

The immunological basis for providing a second dose of MCV is to immunize those children who failed to develop a protective immune response to the first dose. As an added benefit, another opportunity for measles vaccination in the second year of life or later also allows vaccination of children who have not received a first dose.

Immune responses to revaccination depend on the adequacy of the response to the first dose of MCV. Those with poor immune responses to initial vaccination, i.e. those with primary vaccine failure, usually have a characteristic primary immune response after receiving a second dose, with production of IgM antibodies followed by high levels of IgG antibodies. When a second dose is administered to children older than one year of age who failed to develop protective antibody levels following the first dose, as many as 95% will develop protective antibody levels.[29] For example, among 679 children 4–6 years of age who previously received a single dose of MCV between 12 and 17 months of age, 97% of the 37 seronegative children seroconverted after revaccination.[65]

An increase in MV-specific IgG antibody levels, or boosting, can be seen in persons with moderate antibody levels after the first dose of MCV.[66,67] In these individuals, an anamnestic immune response develops, IgM antibodies typically are not produced, and IgG antibodies are detected within 5–6 days and peak around 12 days. This anamnestic response therefore occurs earlier and faster than a primary response. However, antibody levels after revaccination may return to pre-vaccination levels within several months or years.[68]

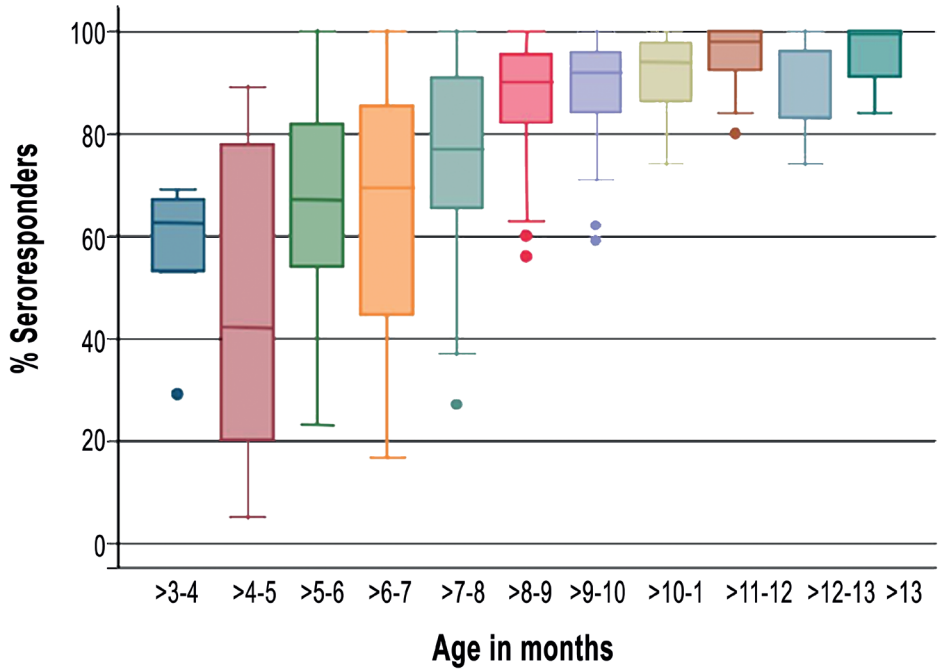
In persons with high levels of pre-existing antibodies to MV, vaccine virus does not replicate sufficiently to boost antibody levels following revaccination. Measles revaccination of children with pre-existing antibodies to MV is not harmful; indeed, it is less likely to result in side-effects because the vaccine virus is inhibited from replicating.

3.3 Immunological basis for the optimal age of measles immunization

3.3.1 Age at vaccination

The age at vaccination is one of the most important determinants of the immune response to MCV, with older infants usually showing better responses than younger infants (Figure 4). The optimal age for measles vaccination is determined by consideration of the age-dependent increase in seroconversion rates following measles vaccination and the average age of infection. In regions of intense MV transmission, the average age of infection is low and the optimal strategy is to vaccinate against measles at as young an age as possible (usually 9 months of age, Figure 4). By contrast, in settings where MV transmission has been reduced, the age of administration of the first dose of MCV can be increased to 12 months or older. Antibody responses to MCV increase with age up to around 15 months because of the declining levels of inhibitory maternal antibodies and decreasing immaturity of the immune system. This immaturity of the immune system in neonates and very young infants includes a limited B-cell repertoire and inefficient mechanisms of antigen presentation and T-lymphocyte help.[69,70] The recommended age at vaccination must balance the risk of primary vaccine failure, which decreases with age, against the risk of MV infection prior to vaccination, which increases with age.

Figure 4. Box plots showing the proportion of children who respond to standard-titre measles vaccine by age at vaccination



Source: Scott S. The Impact of HIV on Measles and Measles Immunisation. 2006. London School of Hygiene and Tropical Medicine. (Thesis).

In communities with intense MV transmission, a significant proportion of children may acquire measles before 9 months of age. For instance, in Lusaka, in the Republic of Zambia, one quarter of HIV-uninfected and one third of HIV-infected children hospitalized with measles were younger than 9 months of age.[72] In some circumstances, provision of a supplementary, early dose of MCV at 6 months may be indicated. WHO recommends administration of a supplementary dose of MCV as early as 6 months of age in certain cases, namely: (1) during measles outbreaks; (2) during vaccination campaigns when the risk of measles in young infants is high; (3) for internally displaced populations and refugees and populations in conflict zones; (4) for infants known to be HIV-infected or exposed (i.e. born to an HIV-infected mother); (5) for individual infants at high risk of contracting measles; and (6) for infants travelling to countries experiencing measles outbreaks.[29] Because a smaller proportion of children vaccinated below 9 months of age will develop protective antibody levels,[73] MCV also should be administered to these children according to the routine immunization schedule (i.e. at 9 or 12 months of age). That is why early doses are called "supplementary". However, in such cases the short-term beneficial effect should outbalance the potential long-term impact on the host, because children who develop low antibody responses to their first MCV may maintain low antibody levels throughout life.[74]

3.3.2 Passively-acquired maternal antibodies

A major reason why age at measles vaccination is a strong predictor of an adequate immune response is the presence of passively-acquired maternal antibodies. Young infants in the first months of life are protected against measles by passively-acquired maternal IgG antibodies. An active transport mechanism in the placenta transfers IgG antibodies from the maternal circulation to the fetus, starting at approximately 28 weeks of gestation and continuing until birth.[75]

Three factors determine the degree and duration of protection against measles in the young infant, namely: (1) the level of maternal antibodies to MV; (2) the efficiency of placental transfer; and (3) the rate of catabolism in the child.[76] Maternally-acquired antibodies provide protection against wild-type MV infection but also interfere with the immune responses to MCV by inhibiting replication of the attenuated vaccine virus, thereby suppressing induction of a robust immune response to the vaccine.[77] In general, maternally-acquired antibodies are no longer present in most children by 6–9 months of age. The half-life of antibodies to MV is the time required for one half of the amount of antibody to decay. Estimates of this half-life are remarkably consistent across studies, varying between 40 and 61 days, with no apparent regional differences in decay rates.[76]

However, women with vaccine-induced immunity tend to have lower anti-MV antibody levels than women with naturally-acquired immunity, and the children of the former may become susceptible to measles at an earlier age.[78,79] Lower levels of measles antibodies in vaccinated individuals, including pregnant women, result not only from the direct effects of vaccination on the individual but also from indirect effects because successful vaccination programmes reduce MV transmission and thus lower the probability of boosting immunity through exposure to wild-type MV. Infants in such settings may become susceptible to measles well before the age of vaccination,[79,80] but they may also be more likely to develop protective immune responses when vaccinated.

Placental transfer of maternal antibodies, including antibodies to MV, is impaired in HIV-infected women.[81] Thus, children born to HIV-infected women may become susceptible to MV infection earlier than children born to uninfected women.[82] However, the lower levels of maternal antibody may also result in better immune responses of their HIV-infected and uninfected infants to MCV administered at 6 months of age.[83] The efficiency of placental transfer also depends on the total IgG concentration, with decreased efficiency of transfer of specific antibodies in mothers who have high total IgG concentrations.[84]

Malaria – particularly infection with *Plasmodium falciparum* – can cause pathological changes in the placenta, including thickening of the basement membrane and inflammation, which can impair the transplacental transfer of maternal antibodies. Reduced placental transfer of antibodies to MV has been reported in the presence of placental malaria infection.[85,86]

3.3.3 Immunological immaturity

A second factor that has an impact on the age dependence of immune responses to MCV is immunological immaturity. Very young infants (i.e. those aged 6 months or younger) do not develop high levels of anti-MV antibodies after immunization with attenuated MV vaccines even in the absence of detectable passively-acquired maternal antibodies. Neonates have impaired antibody responses to many antigens. This results from characteristics of the innate and adaptive neonatal immune system, including: (1) a propensity for anti-inflammatory rather than pro-inflammatory responses; (2) preferential Th2 differentiation of cellular immune responses that inhibits Th1 and cytotoxic T cell responses; (3) a tendency toward immunoregulatory responses; and (4) poor plasma cell and germinal centre B cell responses.[87]

3.3.4 Potential blunting of the immune response following early vaccination

Several studies published in the late 1980s and early 1990s suggested that measles vaccination before 9 months of age results in a lower or blunted immune response to a subsequent dose of MCV.[88] Presumably such blunting would be due to the presence of antibodies that neutralize the vaccine virus on second administration. However, a recent systematic review found that administration of the first dose of MCV before 9 months of age followed by a second dose resulted in high seroprevalence and vaccine efficacy.[89] Several studies found that antibody levels were lower after the second dose of MCV in children who had received an early first dose, but these findings were not consistent across studies.[89,90]

3.4 Co-infections, nutritional status and host factors

3.4.1 HIV infection

Antibody responses to MCV can be impaired in HIV-infected children. At 6 months of age, measles vaccination of untreated HIV-infected and uninfected children resulted in similar levels of protection, probably because of the early loss of maternal antibodies in children born to HIV-infected women and less damage to the immune system in surviving infants.[91-93] However, HIV-infected children were less likely to respond to MCV than uninfected children when vaccinated at 9 months of age or older (combined RR, 0.79; 95% CI, 0.61–1.02).[91] Several studies have suggested that the antibody response in HIV-infected children wanes faster than the response in uninfected children.[94]

Immune restoration follows effective highly active antiretroviral therapy (HAART) in many HIV-infected children and can improve responses to vaccination.[95] HAART does not restore measles immunity from previous vaccine doses but improves antibody responses following revaccination.[96] WHO recommends that an additional dose of MCV should be administered to HIV-infected children receiving HAART following immune reconstitution.[97] If $CD4^+$ T-lymphocyte counts are available, the additional dose of MCV should be administered when immune reconstitution has been achieved and the $CD4^+$ T-lymphocyte count reaches 20–25%. In settings where $CD4^+$ T-lymphocyte monitoring is not available, children should receive an additional dose of MCV at 6–12 months after starting HAART. Most children will have achieved immune reconstitution after 6 months of successful treatment. A supplementary dose

of MCV should be considered soon after the diagnosis of HIV infection in children older than 6 months who are not receiving HAART, and for whom the risk of measles is high, in order to provide partial protection until they are revaccinated after immune reconstitution.[97] Current evidence is insufficient to recommend an additional dose for children who start HAART before the first dose of MCV, but HIV-infected adults do not require revaccination.[98] This is because the vast majority of adults will have acquired HIV infection after exposure to MV or MCV, and their immunity persists.[99]

3.4.2 Concurrent acute infections

Concurrent acute infections rarely interfere with the immune response to MCV, and mild illnesses are not a contraindication to measles vaccination. Several small studies published in the 1990s suggested that illness at the time of measles vaccination – particularly upper respiratory tract infections – interfered with the protective antibody response to measles vaccination. However, other studies, also published in the 1990s, found that minor illnesses do not interfere with seroconversion following measles vaccination.[100] Neither malaria nor malaria chemoprophylaxis impair the immune response to MCV, although investigators in the Republic of Gambia speculated that repeated malaria infections may be responsible for waning immunity to MV 5–7 years after vaccination.[101]

3.4.3 Nutritional status

Most published studies found that under-nourished children have equivalent seroconversion rates after measles vaccination compared to children who are well-nourished. In one exception, stunting was found to be significantly associated with low antibody responses to MCV among Ugandan children.[102] Although investigators in the Republic of Indonesia found a lower rate of seroconversion among children vaccinated at 6 months of age who received vitamin A supplements compared to children who did not receive such supplements,[103] subsequent trials found similar or higher rates of seroconversion among children receiving vitamin A supplements.[104,105] These studies support WHO's policy of administering vitamin A supplements at the time of measles vaccination.

3.4.4 Host genetics

Studies have shown that host genetics affect the likelihood of seroconversion, antibody levels and cellular immune responses following measles vaccination,[106] although MCVs are highly effective in preventing measles worldwide. Polymorphisms in human immune response genes that influence immune responses to MCV include class I and class II human leukocyte antigen (HLA) types and non-HLA alleles. Single-nucleotide polymorphisms (SNPs) in cytokine and cytokine receptor genes, as well as SNPs in the MV receptors, have also been associated with differences in antibody and cellular immune responses to MCV. However, in general, most people develop protective antibody levels after two doses of MCV regardless of genetic background.

3.4.5 Sex

Several studies reported intriguing sex differences in the immunogenicity and reactogenicity of MCV, with higher post-vaccination antibody levels and rates of fever and rash in girls.[107] Interest in sex differences in response to MCV was stimulated by reports of increased mortality in girls following receipt of the high-titre MCV (see 3.7.1, below). However, sex differences in seroconversion rates were not reported in most studies on the immunogenicity of standard-titre MCV. The immunological basis for any sex differences in the responses to MCVs is not known, although it would likely involve a combination of genes, epigenetic modification and hormones.[108,109]

3.4.6 The immunological basis underlying different MCV strains

In addition to host factors, characteristics of the vaccine strain and mode of administration can affect the immune response to MCV. In general, all currently used live, attenuated MCVs are effective in inducing protective immunity. At 9 months of age, the proportion of children who respond to measles vaccination does not differ substantially between vaccine strains. However, at 6 months of age, a higher proportion of children respond to the Edmonston-Zagreb vaccine than to the Schwarz vaccine strain.[110,111] In contrast, above the age of one year the Schwarz vaccine strain reportedly induced higher geometric mean antibody titres than the Edmonston-Zagreb vaccine.[111] Despite the fact that the Edmonston strain was isolated in the 1950s, MCVs derived from the original Edmonston isolate – including the Moraten, Schwarz and Edmonston-Zagreb strains – continue to be efficacious against currently-circulating wild-type MV strains.

3.5 Measurement of protection after immunization

3.5.1 Correlates of protection

Protection against measles following vaccination can be measured in several ways. Vaccine efficacy is a measure of the proportion of children who are protected against clinically apparent disease. MCV efficacy under study conditions (e.g. in clinical trials) or effectiveness under field conditions is measured as 1 minus a measure of the incidence of measles in the vaccinated group compared to the unvaccinated group. Because of the large number of children and the long duration of follow-up required to measure MCV efficacy in clinical trials, immunological markers of protective immunity are more commonly used to assess MCV efficacy.

Several immunological assays are used to measure antibodies to MV, although not all of them measure functional or protective antibodies. Measurement of antibodies to MV by the plaque-reduction neutralization assay correlates with protection from infection and remains the "gold standard" for measuring protective antibody levels. This assay provides a quantitative measurement of the level of neutralizing antibodies. However, the assay is expensive and labour-intensive. The level of measles neutralizing antibody needed to protect from disease is estimated to be 120 mIU/mL,[29] although the supporting data is scant.[112] Evidence for this protective threshold comes from a blood drive at Boston University, USA, in 1985, just prior to a measles outbreak on the campus.[37] Of nine blood donors with detectable pre-exposure antibody titre less than or equal to 120 by plaque-reduction neutralization assay, eight met the clinical criteria for measles (seven of whom were confirmed by serology) compared with none of 71 individuals with pre-exposure antibody titres greater than 120. Further evidence was

obtained from a study assessing measles attack rates among vaccinated and unvaccinated children in rural Senegal [154]

Enzyme-linked immunosorbent assays (EIA or ELISA) are the most widely used tests to measure measles IgM and IgG antibodies because results can be obtained quickly using commercially-manufactured kits. They also require a small volume of serum or plasma and are less labour-intensive than the plaque-reduction neutralization assay. However, antibody levels measured by EIA may be unreliable for assessment of protection or susceptibility, especially in the low-titre range.[36,113-117] Much of the IgG antibody detected when using commercially-manufactured EIA kits are non-protective antibodies to the nucleoprotein (N), and the EIAs are less sensitive than plaque-reduction neutralization tests at low antibody levels.[113,114] A comparative study of two commercial measles IgG EIA assays with plaque-reduction neutralization tests found the EIA assays to have a sensitivity of 90% and specificity of 100%, with false negative EIA results most common in sera with low levels of neutralizing antibodies.[36] Comparison of results between EIA assays are problematic because there are different sources and concentrations of antigens, and thresholds for determining protective antibody levels have not been standardized. Although no longer commonly used, hemagglutination inhibition (HI) assays measure the ability of antibodies to the MV H protein to block agglutination of monkey red-blood cells and correlate with neutralization assays.

Dried blood spots are easier to collect, transport and store than capillary or venous blood samples, and can also be used to measure antibodies to MV; however, standard protocols for processing and interpretation of EIAs using dried blood spots have not been developed.[118] Point-of-care measles IgM and IgG tests have been developed and are similar to malaria rapid diagnostic tests but are not yet commercially available.[119,120] Multiplex bead arrays to measure antibody responses to a wide range of vaccine-preventable and other infectious diseases, including measles, will make serological testing more efficient and informative.[121,122] These assays are basically bead-based EIAs. The method is easy to multiplex in one reaction and requires less serum than is needed for testing in a standard EIA. Beads can be engineered in the laboratory and the antigen is linked to colour-coded beads that are distinguishable by fluorescent signatures.

3.5.2 Antibody avidity

Antibody avidity, also referred to as functional affinity, measures the strength of antibody binding to multiple epitopes on a specific antigen. High antibody avidity takes months to develop and is a sign of a mature antibody response. Avidity assays are typically based on the use of increasing concentrations of chaotropic agents such as urea or isothiocyanate to break the bond between antibody and antigen, thus providing a measure of how tightly antibodies are bound. In vaccinated persons with measles, IgG avidity assays can be used to distinguish primary and secondary vaccine failure.[42,123] Primary vaccine failure refers to those persons who fail to develop a protective immune response. After exposure to MV, these individuals will mount a primary immune response associated with IgM antibodies and low-avidity IgG antibodies. In contrast, persons with secondary vaccine failure – i.e. those who developed a good primary vaccine response but in whom protective antibody levels have waned – will mount a secondary immune response to revaccination, as characterized by the absence of IgM antibodies and an early, high-avidity IG antibody response.

3.6 Duration of protection and waning immunity

The duration of immunity following measles vaccination is more variable and shorter than that following wild-type MV infection but typically lasts for decades. Even in settings where measles is no longer endemic, antibodies to MV can persist without boosting,[124] although data on waning immunity are limited.[125] In countries where measles remains endemic, immune responses may be boosted by re-exposure to wild-type MV.[126] Antibody levels induced by vaccination can decline over time and may become undetectable. Nevertheless, immunological memory is likely to persist in many of these individuals. Following exposure to MV, most vaccinated persons produce an MV-specific immune response without clinical symptoms. However, secondary vaccine failure may occur. Measles in vaccinated persons tends to be mild but such individuals can transmit MV.[127]

3.7 Unintended immunological consequences of measles vaccination

3.7.1 Adverse events associated with live attenuated measles vaccines

Adverse events following measles vaccination are generally mild and transient, resulting from host immune responses to replicating vaccine virus. Mild pain and tenderness may occur at the site of injection within 24 hours of vaccination and resolve after several days.[29] Fever of at least 39°C occurs in approximately 5–15% of recipients 7–12 days after measles vaccination, and a transient rash occurs in approximately 2% of recipients.[29] These signs and symptoms do not result in serious morbidity or mortality. Rarely, thrombocytopenia (low platelet count) may occur,[128] as with the transient idiopathic thrombocytopenic purpura that follows acute infection with wild-type MV. These adverse events are less likely to occur following a second dose of MCV.

Allergic reactions to vaccine components, including neomycin and the stabilizers gelatin or sorbitol, may follow measles vaccination. Anaphylactic reactions are rare, occurring at a rate of 3.5–10 cases per million doses.[29] There is no association between a history of egg allergy and allergic reactions to MCVs.

3.7.2 Adverse immunological responses to the formalin-inactivated measles vaccine

In the 1960s, a formalin-inactivated, alum-precipitated non-replicating MCV (FI-MV) was licensed and administered to children in the USA. Three doses of inactivated vaccine elicited a protective antibody response that waned within months. Up to 60% of immunized children exposed to wild-type MV developed an unusual immunological response called atypical measles,[129,130] which was characterized by high fever, inflammation of the lungs (pneumonitis), and a petechial rash on the extremities. This led to the withdrawal of FI-MV in 1967. In a rhesus macaque model, atypical measles was shown to be associated with strong T-helper type 2 cellular responses, immune complex deposition in affected tissues, and a systemic and pulmonary eosinophilia.[131] The antibody response consisted of high levels of complement-fixing antibodies with low avidity for MV – characteristics that may have promoted exaggerated immune complex formation and disease. These immunopathological responses showed a resemblance to adverse events observed in the same era in children immunized with formalin-inactivated respiratory syncytial virus vaccines (FI-RSV). Upon natural RSV

infection, a high percentage of the vaccinated children required hospitalization and there were two fatalities.[132] Similar adverse events were shown for formalin-inactivated human metapneumovirus in non-human primates,[133] suggesting a common adverse response to non-replicating vaccines for these closely related viruses.

3.7.3 Potential adverse immunological responses to high-titre MCVs

To overcome the inhibitory effect of maternal antibodies and protect young infants against measles, high-titre preparations containing 10–100 times the standard dose of vaccine virus were evaluated in several countries in the 1980s. Seroconversion rates in 4–6-month-old infants immunized with high-titre MCV were comparable to those of 9–15-month-old children vaccinated with standard-titre MCV.[111] However, high-titre MCV resulted in a poorly understood smaller reduction in mortality in immunized girls 1–2 years after vaccination in some developing countries, compared with girls immunized with standard-titre vaccine at 9 months of age.[134,135] The high-titre MCV was withdrawn and is no longer used.

3.7.4 Adverse events in HIV-infected persons

Because MCVs consist of attenuated viruses that need to replicate within the host to induce protective immune responses, such vaccine viruses have the potential to cause diseases in persons who are severely immunocompromised. Although assumed to be rare, the risk of disease caused by attenuated MCV virus in HIV-infected persons is unknown. The only documented case of fatal disease associated with MCV virus in an HIV-infected person was in a 20-year-old man in the USA who died 15 months after receiving his second dose of MCV.[136] He had a very low $CD4^+$ T-lymphocyte cell count but no HIV-related symptoms at the time of vaccination. However, 10 months later he developed a giant cell pneumonitis, and MCV virus was identified in his lung. Fatal, disseminated infection with measles vaccine virus has been reported rarely in persons with other impairments of immune function, and measles inclusion-body encephalitis caused by vaccine virus was reported in a child with an uncharacterized immune deficiency.[137]

3.7.5 Adverse events incorrectly associated with measles vaccine

Much public attention has focused on a purported association between MMR vaccine and autism following publication of a report in 1998 hypothesizing that MMR vaccine may cause a syndrome of autism and intestinal inflammation.[138] The publication that incited the concern was a case series describing 12 children with a regressive developmental disorder and chronic enterocolitis. Nine of the children had autism. Several parents reported that the onset of the developmental delay was associated with MMR vaccination. This temporal association was misleadingly presented as a possible causal relationship, first by the lead author of the study and then by the media and public. No immunological process adequately explains this purported association. Many comprehensive reviews and follow-up studies rejected a causal relationship between MMR vaccination and autism.[139] One of the most conclusive studies was a large retrospective cohort study of over half a million Danish children that found no association between MMR vaccine and risk of autistic disorder (relative risk 0.92, 95% CI, 0.68–1.24).[140]

3.7.6 Potential nonspecific effects of measles vaccination

A group of investigators have suggested for more than two decades that vaccination with standard-titre MCV may have nonspecific beneficial effects resulting in reduced child mortality in excess of deaths attributable to measles.[141] Although controversial, this claim has generated much interest and commentary. MV has long been known to result in prolonged immunosuppression, increasing the risk of morbidity and mortality from other infectious diseases – particularly pneumonia and diarrhoea. Although this effect was assumed to last for several weeks to several months after measles, a population-level study of mortality in Denmark, England and the USA showed the impact of measles on mortality extending over 2–3 years, providing a potential explanation for the long-term benefits of measles vaccination in preventing all-cause infectious disease mortality.[17]

Several systematic reviews have been conducted on the nonspecific effects of vaccines.[142,143] One review of 34 birth cohorts reported in published studies found that receipt of BCG and MCV reduced overall mortality by more than would be expected through their effects on the diseases they prevent, and receipt of DTP may be associated with an increase in all-cause mortality.[142] WHO has not recommended changes to the vaccination schedule based on optimization of nonspecific effects and many experts believe that further high-quality data – particularly from randomized controlled trials – are needed for a better understanding of the public health importance of these observations.[144]

Although the immunological basis for nonspecific effects of measles vaccination has not been demonstrated, some experts believe that heterologous lymphocyte activation and innate immune memory could promote protection beyond the intended target pathogen and could confer nonspecific benefits.[145]

4. Immunological basis for measles elimination

Interrupting MV transmission in order to achieve regional elimination and global eradication requires sustained, high levels of population immunity. The high contagiousness of MV is expressed by the basic reproductive number (R_0) – i.e. the average number of secondary cases resulting from the introduction of an infectious individual into a completely susceptible population. A function of pathogen transmission characteristics, population density and social contact patterns, the basic reproductive number of MV is typically stated to be in the range 12–18, although this number is highly variable across settings and ranges from approximately 5 to 50.[146] Nevertheless, measles has one of the highest basic reproductive numbers for a directly transmitted pathogen. This epidemiological characteristic of measles is the major obstacle to elimination because the virus spreads rapidly in susceptible populations and the interruption of transmission requires high levels of population immunity. Moreover, MV-infected humans start spreading the virus before developing the characteristic symptoms, thus reducing the effectiveness of classic quarantine measures. A simple analytical estimate, assuming random mixing of individuals, is that levels of population immunity as high as 90–95% are required to achieve measles elimination. The remaining 5–10% are protected by "community protection" or "herd immunity" whereby the probability of a susceptible person coming into contact with an infectious one is extremely low.[147] These estimates do not account, however, for spatial heterogeneities in susceptibility and non-random contact patterns, which can further increase the level of population immunity needed to interrupt transmission.[148] The high level of population immunity required to eliminate measles is the basis of the need for two doses of MCV.

The live attenuated measles vaccines currently in use have a history of proven safety and effectiveness over more than 50 years and have resulted in dramatic reductions in measles incidence, morbidity and mortality. However, the current vaccines also have some limitations. The ideal measles vaccine would be inexpensive, safe, heat-stable, immunogenic in neonates or very young infants, and administered as a single dose without a needle or syringe. The age at vaccination would ideally coincide with that of other vaccines in the Expanded Programme on Immunization (EPI) schedule in order to maximize compliance and share resources. Additionally, a new vaccine should not prime individuals for atypical measles upon exposure of immunized persons to wild-type MV (a complication of FI-MV) and should not be associated with prolonged immunosuppression which adversely affects immune responses to subsequent infections (a complication of high-titre MCVs). Alternative measles vaccines or delivery systems may avoid some of these limitations.

Aerosol administration of measles vaccine was first evaluated in the early 1960s in several countries, including Mexico, the former Soviet Union and the USA. Administration of measles vaccine by aerosol has the potential to facilitate measles vaccination during mass campaigns and eliminate the problems of medical waste associated with needles and syringes. Indeed, this route of immunization was shown to be biologically feasible in studies in non-human primates.[149,150] However, a large, open-label non-inferiority trial in India which enrolled some 1000 children in each arm found that aerosolized measles vaccine was immunogenic but inferior to subcutaneous delivery of measles vaccine.[151] The proportion of children who seroconverted after receiving the aerosolized vaccine was 85.4% (95% CI, 82.5–88.0) compared to 94.6% (95% CI, 92.7–96.1) in the subcutaneous group. Immunogenicity of aerosol measles vaccine is enhanced if delivered to the lower respiratory tract.[27]

Another vaccine delivery system that has the potential to facilitate measles elimination is the use of microarray patches. These patches (which are like miniature band aids or sticking plasters) are applied to the skin for just a few minutes and allow painless vaccination without needles and syringes. They can be administered by nonmedical staff, door-to-door if necessary, without the need for a cold chain because the vaccine in them is more heat stable. Although not yet tested in humans, a measles microarray patch induced protective antibody levels in a higher proportion of monkeys than was achieved with subcutaneous injection.[152] However, neither delivery method could generate protective immune responses in infant macaques pretreated with measles immunoglobulin to simulate maternal antibodies. Nevertheless, this alternative route of administration of the existing MCV has the potential to overcome many of the limitations of the current injected MCV – including reduction of problems associated with injection safety, contaminated waste disposal and vaccine stability.

In conclusion, measles continues to have a high clinical impact around the world and this disease remains a leading cause of vaccine-preventable deaths. The available live attenuated MCVs are safe and effective, and the current understanding of the immunological basis for immunization supports the biological feasibility of global measles eradication.[153]

References

1. **Rota PA, Moss WJ, Takeda M, de Swart RL, Thompson KM, Goodson JL.** Measles. *Nat Rev Dis Primers* 2016;2:16049.

2. **De Quadros CA, Izurieta H, Carrasco P, Brana M, Tambini G.** Progress toward measles eradication in the region of the Americas. *J Infect Dis* 2003;187 (Suppl 1):S102-10.

3. **Andrus JK, de Quadros CA, Solorzano CC, Periago MR, Henderson DA.** Measles and rubella eradication in the Americas. *Vaccine* 2011; 29 Suppl 4: D91-6.

4. **De Serres G, Markowski F, Toth E, et al.** Largest measles epidemic in North America in a decade--Quebec, Canada, 2011: contribution of susceptibility, serendipity, and superspreading events. *J Infect Dis* 2013;207(6):990-8.

5. **Le NK, Mhaskar R, Hoare I, et al.** Reemergence of measles in the Americas: the genotype B3 2011-2012 outbreak in Ecuador. *Vaccines* 2017; 5(2).

6. **Paniz-Mondolfi AE, Tami A, Grillet ME, et al.** Resurgence of vaccine-preventable diseases in Venezuela as a regional public health threat in the Americas. *Emerg Infect Dis* 2019;25(4):625-32.

7. **Patel M, Lee AD, Redd SB, et al.** Increase in measles cases - United States, January 1-April 26, 2019. *MMWR* 2019;68(17):402-4.

8. **Patel MK, Gacic-Dobo M, Strebel PM, et al.** Progress toward regional measles elimination - worldwide, 2000-2015. *MMWR* 2016;65(44):1228-33.

9. **Morley D.** Severe measles in the tropics. I. *Br Med J* 1969;1(5639):297-300

10. **Perry RT, Halsey NA.** The clinical significance of measles: a review. *J Infect Dis* 2004;189(Suppl 1):S4-16.

11. **Duke T, Mgone CS.** Measles: not just another viral exanthem. *Lancet* 2003;361(9359):763-73.

12. **Morens DM, Taubenberger JK.** A forgotten epidemic that changed medicine: measles in the US Army, 1917-18. *Lancet Infect Dis* 2015;15(7):852-61.

13. **Watanabe S, Shirogane Y, Sato Y, Hashiguchi T, Yanagi Y.** New insights into measles virus brain infections. *Trends Microbiol* 2019; 27(2): 164-75.

14. **Ferren M, Horvat B, Mathieu C.** Measles encephalitis: towards new therapeutics. *Viruses* 2019; 11(11):e1017.

15. **Moss WJ, Fisher C, Scott S, et al.** HIV type 1 infection is a risk factor for mortality in hospitalized Zambian children with measles. *Clin Infect Dis* 2008;46(4):523-7.

16. **Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM.** Estimates of measles case fatality ratios: a comprehensive review of community-based studies. *Int J Epidemiol* 2009;38(1):192-205.

17. **Mina MJ, Metcalf CJ, de Swart RL, Osterhaus AD, Grenfell BT.** Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. *Science* 2015;348(6235):694-9.

18. **Enders JF, Peebles TC.** Propagation in tissue cultures of cytopathogenic agents from patients with measles. *Proc Soc Exp Biol Med* 1954;86(2):277-86.

19. **Morens DM, Holmes EC, Davis AS, Taubenberger JK.** Global rinderpest eradication: lessons learned and why humans should celebrate too. *J Infect Dis* 2011; 204(4): 502-5.

20. **Ludlow M, Rennick LJ, Nambulli S, de Swart RL, Duprex WP.** Using the ferret model to study morbillivirus entry, spread, transmission and cross-species infection. *Curr Opin Virol* 2014;4:15-23.

21. **de Swart RL, Yuksel S, Osterhaus AD.** Relative contributions of measles virus hemagglutinin- and fusion protein-specific serum antibodies to virus neutralization. *J Virol* 2005;79(17):11547-51.

22. **Laksono BM, de Vries RD, McQuaid S, Duprex WP, de Swart RL.** Measles virus host invasion and pathogenesis. *Viruses* 2016; 8(8).

23. **de Vries RD, de Swart RL.** Measles immune suppression: functional impairment or numbers game? *PLoS Pathog* 2014; 10(12): e1004482.

24. **Laksono BM, de Vries RD, Verburgh RJ, et al.** Studies into the mechanism of measles-associated immune suppression during a measles outbreak in the Netherlands. *Nat Commun* 2018; 9(1):4944.

25. **Petrova VN, Sawatsky B, Han AX, et al.** Incomplete genetic reconstitution of B cell pools contributes to prolonged immunosuppression after measles. *Science Immunol* 2019;4(41):eaay6125.

26. **Mina MJ, Kula T, Leng Y, et al.** Measles virus infection diminishes preexisting antibodies that offer protection from other pathogens. *Science* 2019; **366**(6465):599-606.

27. **de Swart RL, de Vries RD, Rennick LJ, et al.** Needle-free delivery of measles virus vaccine to the lower respiratory tract of non-human primates elicits optimal immunity and protection. *NPJ Vaccines* 2017; 2: 22.

28. **Parks CL, Lerch RA, Walpita P, Wang HP, Sidhu MS, Udem SA.** Comparison of predicted amino acid sequences of measles virus strains in the Edmonston vaccine lineage. *J Virol* 2001;75(2):910-20.

29. **Measles vaccines.** WHO position paper, April 2017. *Wkly Epidemiol Rec* 2017;92(17):205-27.

30. **Rennick LJ, de Vries RD, Carsillo TJ, et al.** Live-attenuated measles virus vaccine targets dendritic cells and macrophages in muscle of nonhuman primates. *J Virol* 2015;89(4):2192-200.

31. **Duncan CJ, Mohamad SM, Young DF, et al.** Human IFNAR2 deficiency: Lessons for antiviral immunity. *Sci Transl Med* 2015;7(307):307ra154.

32. **Hambleton S, Goodbourn S, Young DF, et al.** STAT2 deficiency and susceptibility to viral illness in humans. *Proc Natl Acad Sci* 2013;110(8):3053-8.

33. **Griffin DE.** The immune response in measles: virus control, clearance and protective immunity. *Viruses* 2016;8(10).

34. **Shivakoti R, Hauer D, Adams RJ, et al.** Limited in vivo production of type I or type III interferon after infection of macaques with vaccine or wild-type strains of measles virus. *J Interferon Cytokine Res* 2015;35(4):292-301.

35. **Holzmann H, Hengel H, Tenbusch M, Doerr HW.** Eradication of measles: remaining challenges. *Med Microbiol Immunol* 2016;205(3):201-8.

36. **Cohen BJ, Doblas D, Andrews N.** Comparison of plaque reduction neutralisation test (PRNT) and measles virus-specific IgG ELISA for assessing immunogenicity of measles vaccination. *Vaccine* 2008; 26(50):6392-7.

37. **Chen RT, Markowitz LE, Albrecht P, et al.** Measles antibody: reevaluation of protective titers. *J Infect Dis* 1990;162(5):1036-42.

38. **Hummel KB, Erdman DD, Heath J, Bellini WJ.** Baculovirus expression of the nucleoprotein gene of measles virus and utility of the recombinant protein in diagnostic enzyme immunoassays. *J Clin Microbiol* 1992;30(11):2874-80.

39. **Warnes A, Fooks AR, Stephenson JR.** Production of measles nucleoprotein in different expression systems and its use as a diagnostic reagent. *J Virol Methods* 1994;49(3):257-68.

40. **Paunio M, Hedman K, Davidkin I, et al.** Secondary measles vaccine failures identified by measurement of IgG avidity: high occurrence among teenagers vaccinated at a young age. *Epidemiol Infect* 2000;124(2):263-71.

41. **Kontio M, Jokinen S, Paunio M, Peltola H, Davidkin I.** Waning antibody levels and avidity: implications for MMR vaccine-induced protection. *J Infect Dis* 2012;206(10):1542-8.

42. **Sowers SB, Rota JS, Hickman CJ, et al.** High Concentrations of Measles Neutralizing Antibodies and High-Avidity Measles IgG Accurately Identify Measles Reinfection Cases. *Clin Vaccine Immunol* 2016;23(8):707-16.

43. **Good RA, Zak SJ.** Disturbances in gamma globulin synthesis as experiments of nature. *Pediatrics* 1956;18(1):109-49.

44. **Cifuentes-Munoz N, Dutch RE, Cattaneo R.** Direct cell-to-cell transmission of respiratory viruses: The fast lanes. *PLoS Pathog* 2018; 14(6):e1007015.

45. **Singh BK, Pfaller CK, Cattaneo R, Sinn PL.** Measles virus ribonucleoprotein complexes rapidly spread across well-differentiated primary human airway epithelial cells along F-actin rings. *mBio* 2019;10(6):e02434-19.

46. **Permar SR, Klumpp SA, Mansfield KG, et al.** Limited contribution of humoral immunity to the clearance of measles viremia in rhesus monkeys. *J Infect Dis* 2004;190(5):998-1005.

47. **Lin WH, Kouyos RD, Adams RJ, Grenfell BT, Griffin DE.** Prolonged persistence of measles virus RNA is characteristic of primary infection dynamics. *Proc Natl Acad Sci* 2012;109(37):14989-94.

48. **de Vries RD, Yuksel S, Osterhaus AD, de Swart RL.** Specific CD8(+) T-lymphocytes control dissemination of measles virus. *Eur J Immunol* 2010;40(2):388-95.

49. **Permar SR, Klumpp SA, Mansfield KG, et al.** Role of CD8(+) lymphocytes in control and clearance of measles virus infection of rhesus monkeys. *J Virol* 2003;77(7):4396-400.

50. **Moss WJ, Ryon JJ, Monze M, Griffin DE.** Differential regulation of interleukin (IL)-4, IL-5, and IL-10 during measles in Zambian children. *J Infect Dis* 2002;186(7):879-87.

51. **Lin WW, Nelson AN, Ryon JJ, Moss WJ, Griffin DE.** Plasma cytokines and chemokines in Zambian children with measles: innate responses and association with HIV-1 coinfection and in-hospital mortality. *J Infect Dis* 2017;215(5):830-9.

52. **Nelson AN, Putnam N, Hauer D, Baxter VK, Adams RJ, Griffin DE.** Evolution of T Cell responses during measles virus infection and RNA clearance. *Sci Rep* 2017;7(1):11474.

53. **Panum P.** Observations Made During the Epidemic of Measles on the Faroe Islands in the Year 1846. New York: American Public Health Association. 1940.

54. **Muller CP, Huiss S, Schneider F.** Secondary immune responses in parents of children with recent measles. *Lancet* 1996;348(9038):1379-80.

55. **Amanna IJ, Carlson NE, Slifka MK.** Duration of humoral immunity to common viral and vaccine antigens. *N Engl J Med* 2007;357(19):1903-15.

56. **Griffin DE.** Measles virus-induced suppression of immune responses. *N Engl J Med* 2007;357(19):1903-15.

57. **de Vries RD, McQuaid S, van Amerongen G, et al.** Measles immune suppression: lessons from the macaque model. *PLoS Pathog* 2012;8(8):e1002885.

58. **Laksono BM, Grosserichter-Wagener C, de Vries RD, et al.** In vitro measles virus infection of human lymphocyte subsets demonstrates high susceptibility and permissiveness of both naive and memory B cells. *J Virol* 2018;92(8).

59. **Gadroen K, Dodd CN, Masclee GMC, et al.** Impact and longevity of measles-associated immune suppression: a matched cohort study using data from the THIN general practice database in the UK. *BMJ Open* 2018;8(11):e021465.

60. **Ryon JJ, Moss WJ, Monze M, Griffin DE.** Functional and phenotypic changes in circulating lymphocytes from hospitalized zambian children with measles. *Clin Diagn Lab Immunol* 2002;9(5):994-1003.

61. **Griffin DE.** Measles Vaccine. *Viral Immunol* 2018;31(2):86-95.

62. **Gans HA, Yasukawa LL, Sung P, et al.** Measles humoral and cell-mediated immunity in children aged 5-10 years after primary measles immunization administered at 6 or 9 months of age. *J Infect Dis* 2013;207(4):574-82.

63. **Lin WH, Pan CH, Adams RJ, Laube BL, Griffin DE.** Vaccine-induced measles virus-specific T cells do not prevent infection or disease but facilitate subsequent clearance of viral RNA *mBio* 2014; 5(2):e01047.

64. **Uzicanin A, Zimmerman L.** Field effectiveness of live attenuated measles-containing vaccines: a review of published literature. *J Infect Dis* 2011;204(Suppl 1):S133-48.

65. **Watson JC, Pearson JA, Markowitz LE, et al.** An evaluation of measles revaccination among school-entry-aged children. *Pediatrics* 1996;97(5):613-8.

66. **Stetler HC, Orenstein WA, Bernier RH, et al.** Impact of revaccinating children who initially received measles vaccine before 10 months of age. *Pediatrics* 1986;77(4):471-6.

67. **Wittler RR, Veit BC, McIntyre S, Schydlower M.** Measles revaccination response in a school-age population. *Pediatrics* 1991;88(5):1024-30.

68. **Davidkin I, Valle M.** Vaccine-induced measles virus antibodies after two doses of combined measles, mumps and rubella vaccine: a 12-year follow-up in two cohorts. *Vaccine* 1998;16(20):2052-7.

69. **Gans HA, Arvin AM, Galinus J, Logan L, DeHovitz R, Maldonado Y.** Deficiency of the humoral immune response to measles vaccine in infants immunized at age 6 months. *JAMA* 1998;280(6):527-32.

70. **Crowe JE, Jr.** Influence of maternal antibodies on neonatal immunization against respiratory viruses. *Clin Infect Dis* 2001;33(10):1720-7.

71. **Abt M, Gassert E, Schneider-Schaulies S.** Measles virus modulates chemokine release and chemotactic responses of dendritic cells. *J Gen Virol* 2009;90(Pt 4):909-14.

72. **Moss WJ, Monze M, Ryon JJ, Quinn TC, Griffin DE, Cutts F.** Prospective study of measles in hospitalized, human immunodeficiency virus (HIV)-infected and HIV-uninfected children in Zambia. *Clin Infect Dis* 2002;35(2):189-96.

73. **Nic Lochlainn LM, de Gier B, van der Maas N, et al.** Immunogenicity, effectiveness, and safety of measles vaccination in infants younger than 9 months: a systematic review and meta-analysis. *Lancet Infect Dis* 2019;19(11):1235-45.

74. **Brinkman ID, de Wit J, Smits GP, et al.** Early measles vaccination during an outbreak in The Netherlands: reduced short and long-term antibody responses in children vaccinated before 12 months of age. *J Infect Dis* 2019; 220(4):594-602.

75. **Edwards KM.** Maternal antibodies and infant immune responses to vaccines. *Vaccine* 2015;33(47):6469-72.

76. **Caceres VM, Strebel PM, Sutter RW.** Factors determining prevalence of maternal antibody to measles virus throughout infancy: a review. *Clin Infect Dis* 2000;31(1):110-9.

77. **Kim D, Niewiesk S.** Sidestepping maternal antibody: a lesson from measles virus vaccination. *Expert Rev Clin Immunol* 2011;7(5):557-9.

78. **Waaijenborg S, Hahne SJ, Mollema L, et al.** Waning of maternal antibodies against measles, mumps, rubella, and varicella in communities with contrasting vaccination coverage. *J Infect Dis* 2013;208(1):10-6.

79. **Science M, Savage R, Severini A, et al.** Measles antibody levels in young infants. *Pediatrics* 2019;**144**(6):e20190630.

80. **Guerra FM, Crowcroft NS, Friedman L, et al.** Waning of measles maternal antibody in infants in measles elimination settings - A systematic literature review. *Vaccine* 2018; 36(10):1248-55.

81. **Scott S, Moss WJ, Cousens S, et al.** The influence of HIV-1 exposure and infection on levels of passively acquired antibodies to measles virus in Zambian infants. *Clin Infect Dis* 2007;45(11):1417-24.

82. **Jallow S, Cutland CL, Masbou AK, Adrian P, Madhi SA.** Maternal HIV infection associated with reduced transplacental transfer of measles antibodies and increased susceptibility to disease. *J Clin Virol* 2017;94:50-6.

83. **Helfand RF, Witte D, Fowlkes A, et al.** Evaluation of the immune response to a 2-dose measles vaccination schedule administered at 6 and 9 months of age to HIV-infected and HIV-uninfected children in Malawi. *J Infect Dis* 2008;198(10):1457-65.

84. **Hartter HK, Oyedele OI, Dietz K, Kreis S, Hoffman JP, Muller CP.** Placental transfer and decay of maternally acquired antimeasles antibodies in Nigerian children. *Pediatr Infect Dis J* 2000;19(7):635-41.

85. **Scott S, Cumberland P, Shulman CE, et al.** Neonatal measles immunity in rural Kenya: the influence of HIV and placental malaria infections on placental transfer of antibodies and levels of antibody in maternal and cord serum samples. *J Infect Dis* 2005;191(11):1854-60.

86. **McLean ARD, Stanisic D, McGready R, et al.** P. falciparum infection and maternofetal antibody transfer in malaria-endemic settings of varying transmission. *PloS One* 2017;12(10):e0186577.

87. **Mohr E, Siegrist CA.** Vaccination in early life: standing up to the challenges. *Curr Opin Immunol* 2016;41:1-8.

88. **Black FL.** Measles active and passive immunity in a worldwide perspective. *Prog Med Virol* 1989;36:1-33.

89. **Nic Lochlainn LM, de Gier B, van der Maas N, et al.** Effect of measles vaccination in infants younger than 9 months on the immune response to subsequent measles vaccine doses: a systematic review and meta-analysis. *Lancet Infect Dis* 2019;19(11):1246-54.

90. **Brinkman ID, de Wit J, Smits GP, et al.** Early measles vaccination during an outbreak in The Netherlands: reduced short and long-term antibody responses in children vaccinated before 12 months of age. *J Infect Dis* 2019;220(4):594-602.

91. **Scott P, Moss WJ, Gilani Z, Low N.** Measles vaccination in HIV-infected children: systematic review and meta-analysis of safety and immunogenicity. *J Infect Dis* 2011;204 Suppl 1:S164-78.

92. **Mehtani NJ, Rosman L, Moss WJ.** Immunogenicity and Safety of Measles Vaccine in HIV-infected Children: an Updated Systematic Review. *Am J Epidemiol* 2019;188(12):2240-51..

93. **Mutsaerts E, Nunes MC, van Rijswijk MN, Klipstein-Grobusch K, Grobbee DE, Madhi SA.** Safety and Immunogenicity of Measles Vaccination in HIV-Infected and HIV-Exposed Uninfected Children: A Systematic Review and Meta-Analysis. *E Clinical Medicine* 2018**;1**:28-42.

94. **Moss WJ, Scott S, Mugala N, et al.** Immunogenicity of standard-titer measles vaccine in HIV-1-infected and uninfected Zambian children: an observational study. *J Infect Dis* 2007;196(3):347-55.

95. **Rainwater-Lovett K, Moss WJ.** Immunologic basis for revaccination of HIV-infected children receiving HAART. *Future Virol* 2011;6(1):59-71.

96. **Rainwater-Lovett K, Nkamba HC, Mubiana-Mbewe M, Bolton-Moore C, Moss WJ.** Changes in measles serostatus among HIV-infected Zambian children initiating antiretroviral therapy before and after the 2010 measles outbreak and supplemental immunization activities. *J Infect Dis* 2013;208(11):1747-55.

97. Meeting of the Strategic Advisory Group of Experts on Immunization, October 2015 - conclusions and recommendations. *Wkly Epidemiol Rec* 2015;90(50):681-99.

98. Meeting of the Strategic Advisory Group of Experts on Immunization, October 2017 - conclusions and recommendations. *Wkly Epidemiol Rec* 2017; 92(48):729-47.

99. **Loevinsohn G, Rosman L, Moss WJ.** Measles seroprevalence and vaccine responses in HIV-infected adolescents and adults: a systematic review. *Clin Infect Dis* 2019;69(5):836-44.

100. **Scott S, Cutts FT, Nyandu B.** Mild illness at or after measles vaccination does not reduce seroresponse in young children. *Vaccine* 1999;17(7-8):837-43.

101. **Whittle H, Aaby P, Samb B, et al.** Poor serologic responses five to seven years after immunization with high and standard titer measles vaccines. *Pediatr Infect Dis J* 1999;18(1):53-7.

102. **Waibale P, Bowlin SJ, Mortimer EA, Jr., Whalen C.** The effect of human immunodeficiency virus-1 infection and stunting on measles immunoglobulin-G levels in children vaccinated against measles in Uganda. *Int J Epidemiol* 1999;28(2):341-6.

103. **Semba RD, Munasir Z, Beeler J, et al.** Reduced seroconversion to measles in infants given vitamin A with measles vaccination. *Lancet* 1995;345(8961):1330-2.

104. WHO/CHD Immunisation-Linked Vitamin A Supplementation Study Group. Randomised trial to assess benefits and safety of vitamin A supplementation linked to immunisation in early infancy. *Lancet* 1998;352(9136):125763.

105. **Cherian T, Varkki S, Raghupathy P, Ratnam S, Chandra RK.** Effect of vitamin A supplementation on the immune response to measles vaccination. *Vaccine* 2003; 21(19-20):2418-20.

106. **Mentzer AJ, O'Connor D, Pollard AJ, Hill AV.** Searching for the human genetic factors standing in the way of universally effective vaccines. *Philos Trans R Soc Lond B Biol Sci* 2015;370(1671).

107. **Voysey M, Pollard AJ, Perera R, Fanshawe TR.** Assessing sex-differences and the effect of timing of vaccination on immunogenicity, reactogenicity and efficacy of vaccines in young children: study protocol for an individual participant data meta-analysis of randomised controlled trials. *BMJ Open* 2016;6(7):e011680.

108. **Klein SL, Flanagan KL.** Sex differences in immune responses. *Nat Rev Immunol* 2016;16(10):626-38.

109. **de Bree LCJ, Koeken V, Joosten LAB, et al.** Non-specific effects of vaccines: Current evidence and potential implications. *Seminar Immunol* 2018;39:35-43.

110. **Diaz-Ortega JL, Forsey T, Clements CJ, Milstien J.** The relationship between dose and response of standard measles vaccines. *Biologicals* 1994;22(1):35-44.

111. **Cutts FT, Grabowsky M, Markowitz LE.** The effect of dose and strain of live attenuated measles vaccines on serological responses in young infants. *Biologicals* 1995;23(1):95-106.

112. **Bolotin S, Hughes SL, Gul N, et al.** What is the evidence to support a correlate of protection for measles? A systematic review. *J Infect Dis* 20 (in press).

113. **Ratnam S, Gadag V, West R, et al.** Comparison of commercial enzyme immunoassay kits with plaque reduction neutralization test for detection of measles virus antibody. *J Clin Microbiol* 1995;33(4):811-5.

114. **van den Hof S, van Gageldonk-Lafeber AB, van Binnendijk RS, van Gageldonk PG, Berbers GA**. Comparison of measles virus-specific antibody titres as measured by enzyme-linked immunosorbent assay and virus neutralisation assay. *Vaccine* 2003;21(27-30):4210-4.

115. **Tischer A, Gassner M, Richard JL, Suter-Riniker F, Mankertz A, Heininger U.** Vaccinated students with negative enzyme immunoassay results show positive measles virus-specific antibody levels by immunofluorescence and plaque neutralisation tests. *J Clin Virol* 2007;38(3):204-9.

116. **Mancuso JD, Krauss MR, Audet S, Beeler JA.** ELISA underestimates measles antibody seroprevalence in US military recruits. *Vaccine* 2008;26(38):4877-8.

117. **Dorigo-Zetsma JW, Leverstein-van Hall MA, Vreeswijk J, et al.** Immune status of health care workers to measles virus: evaluation of protective titers in four measles IgG EIAs. *J Clin Virol* 2015;69:214-8.

118. **Dimech W, Mulders MN.** A review of testing used in seroprevalence studies on measles and rubella. *Vaccine* 2016;34(35):4119-22.

119. **Warrener L, Slibinskas R, Chua KB, et al.** A point-of-care test for measles diagnosis: detection of measles-specific IgM antibodies and viral nucleic acid. *Bull World Health Organ* 2011;89(9):6750-82.

120. **Shonhai A, Warrener L, Mangwanya D, et al.** Investigation of a measles outbreak in Zimbabwe, 2010: potential of a point of care test to replace laboratory confirmation of suspected cases. *Epidemiol Infect* 2015;143(16):3442-50.

121. **Arnold BF, Scobie HM, Priest JW, Lammie PJ.** Integrated Serologic Surveillance of Population Immunity and Disease Transmission. *Emerg Infect Dis* 2018;24(7):1188-94.

122. **Smits GP, van Gageldonk PG, Schouls LM, van der Klis FR, Berbers GA.** Development of a bead-based multiplex immunoassay for simultaneous quantitative detection of IgG serum antibodies against measles, mumps, rubella, and varicella-zoster virus. *Clin Vaccine Immunol* 2012;19(3):396-400.

123. **Mercader S, Garcia P, Bellini WJ.** Measles virus IgG avidity assay for use in classification of measles vaccine failure in measles elimination settings. *Clin Vaccine Immunol* 2012;19(11):1810-7.

124. **Dine MS, Hutchins SS, Thomas A, Williams I, Bellini WJ, Redd SC.** Persistence of vaccine-induced antibody to measles 26-33 years after vaccination. *J Infect Dis* 2004;189(Suppl 1):S123-30.

125. **Hughes SL, Bolotin S, Khan S, et al.** The effect of time since measles vaccination and age at first dose on measles vaccine effectiveness - A systematic review. *Vaccine* 2020;38(3):460-9.

126. **Whittle HC, Aaby P, Samb B, Jensen H, Bennett J, Simondon F.** Effect of subclinical infection on maintaining immunity against measles in vaccinated children in West Africa. *Lancet* 1999;353(9147):98-102.

127. **Moss W.** Measles in vaccinated individuals and the future of measles elimination. *Clin Infect Dis* 2018;67(9):1320-1.

128. **Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj C.** Vaccines for measles, mumps and rubella in children. *Cochrane Database Syst Rev* 2012;(2):Cd004407.

129. **Fulginiti VA, Eller JJ, Downie AW, Kempe CH.** Altered reactivity to measles virus. Atypical measles in children previously immunized with inactivated measles virus vaccines. *JAMA* 1967;202(12):1075-80.

130. **Toltzis P.** 50 Years Ago in The Journal of Pediatrics: Atypical Exanthem after Exposure to Natural Measles: Eleven Cases in Children Previously Inoculated with Killed Vaccine. *J Pediatr* 2018;193:84.

131. **Polack FP, Hoffman SJ, Crujeiras G, Griffin DE.** A role for nonprotective complement-fixing antibodies with low avidity for measles virus in atypical measles. *Nature Med* 2003;9(9):1209-13.

132. **Graham BS.** Pathogenesis of respiratory syncytial virus vaccine-augmented pathology. *Am J Respir Crit Care Med* 1995;152(4 Pt 2):S63-6.

133. **de Swart RL, van den Hoogen BG, Kuiken T, et al.** Immunization of macaques with formalin-inactivated human metapneumovirus induces hypersensitivity to hMPV infection. *Vaccine* 2007;25(51):8518-28.

134. **Holt EA, Moulton LH, Siberry GK, Halsey NA.** Differential mortality by measles vaccine titer and sex. *J Infect Dis* 1993;168(5):1087-96.

135. **Aaby P, Samb B, Simondon F, et al.** A comparison of vaccine efficacy and mortality during routine use of high-titre Edmonston-Zagreb and Schwarz standard measles vaccines in rural Senegal. *Trans R Soc Trop Med Hyg* 1996;90(3):326-30.

136. **Angel JB, Walpita P, Lerch RA, et al.** Vaccine-associated measles pneumonitis in an adult with AIDS. *Ann Intern Med* 1998;129(2):104-6.

137. **Bitnun A, Shannon P, Durward A, et al.** Measles inclusion-body encephalitis caused by the vaccine strain of measles virus. *Clin Infect Dis* 1999;29(4):855-61.

138. **Gerber JS, Offit PA.** Vaccines and autism: a tale of shifting hypotheses. *Clin Infect Dis* 2009;48(4):456-61.

139. **DeStefano F, Thompson WW.** MMR vaccine and autism: an update of the scientific evidence. *Expert Rev Vaccines* 2004;3(1):19-22.

140. **Madsen KM, Hviid A, Vestergaard M, et al.** A population-based study of measles, mumps, and rubella vaccination and autism. *N Engl J Med* 2002;347(19):1477-82.

141. **Aaby P, Samb B, Simondon F, Seck AM, Knudsen K, Whittle H.** Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries. *BMJ* 1995;311(7003):481-5.

142. **Higgins JP, Soares-Weiser K, Lopez-Lopez JA, et al.** Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *BMJ* 2016;355:i5170.

143. **Kandasamy R, Voysey M, McQuaid F, et al.** Non-specific immunological effects of selected routine childhood immunisations: systematic review. *BMJ* 2016;355:i5225.

144. **Pollard AJ, Finn A, Curtis N.** Non-specific effects of vaccines: plausible and potentially important, but implications uncertain. *Arch Dis Child* 2017;102(11):1077-81.

145. **Goodridge HS, Ahmed SS, Curtis N, et al.** Harnessing the beneficial heterologous effects of vaccination. *Nat Rev Immunol* 2016;16(6):392-400.

146. **Guerra FM, Bolotin S, Lim G, et al.** The basic reproduction number (R0) of measles: a systematic review. *Lancet Infect Dis* 2017;17(12):e420-e428.

147. **Anderson EJ, Daugherty MA, Pickering LK, Orenstein WA, Yogev R.** Protecting the Community Through Child Vaccination. *Clin Infect Dis* 2018;67(3):464-71.

148. **Keeling MJ, Grenfell BT.** Disease extinction and community size: modeling the persistence of measles. *Science* 1997;275(5296):65-7.

149. **de Swart RL, Kuiken T, Fernandez-de Castro J, et al.** Aerosol measles vaccination in macaques: preclinical studies of immune responses and safety. *Vaccine* 2006;24(40-41):6424-36.

150. **Lin WH, Griffin DE, Rota PA, et al.** Successful respiratory immunization with dry powder live-attenuated measles virus vaccine in rhesus macaques. *Proc Natl Acad Sci* 2011;108(7):2987-92.

151. **Low N, Bavdekar A, Jeyaseelan L, et al.** A randomized, controlled trial of an aerosolized vaccine against measles. *N Engl J Med* 2015;372(16):1519-29.

152. **Joyce JC, Carroll TD, Collins ML, et al.** A Microneedle Patch for Measles and Rubella Vaccination Is Immunogenic and Protective in Infant Rhesus Macaques. *J Infect Dis* 2018;218(1):124-32.

153. **Moss WJ, Strebel P.** Biological feasibility of measles eradication. *J Infect Dis* 2011;204(Suppl 1):S47-53.

154. **Samb B, Aaby P, Whittle HC et al**. Serologic status and measles attack rates among vaccinated and unvaccinated children in rural Senegal. *Pediatr Infect Dis J* 1995; 14(3):203-9.)

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