The Immunological Basis for Immunization Series

Module 7: Measles
Update 2009

Immunization, Vaccines and Biologicals

World Health Organization

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Contents

Abbreviations and acronyms

AIDS	acquired immunodeficiency syndrome
DNA	deoxyribonucleic acid
DTH	delayed-type hypersensitivity
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EPI	Expanded Programme on Immunization
F	fusion protein
FDC	follicular dendritic cells
FIMV	formalin-inactivated measles vaccine
GIVS	Global Immunization Vision and Strategy
H	haemagglutinin protein
HAART	highly active antiretroviral therapy
HI	haemagglutination inhibition
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IQR	interquartile range
MIBE	measles inclusion body encephalitis
MMR	mumps, measles, rubella vaccine
MR	measles-rubella vaccine
MV	measles virus
N	nucleoprotein
NK	natural killer (cells)
OR	odds ratio
PFU	plaque-forming unit
RNA	ribonucleic acid

SIA	supplemental immunization activity
SLAM	signalling lymphocyte activation molecule (CD150)
SNP	single nucleotide polymorphism
SSPE	subacute sclerosing panencephalitis
TCID	tissue culture infective dose
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Preface

This module is part of the series *The Immunological Basis for Immunization*, which was initially developed in 1993 as a set of eight modules focusing on the vaccines included in the Expanded Programme on Immunization (EPI)[1]. In addition to a general immunology module, each of the seven other modules covered one of the vaccines recommended as part of the EPI programme — diphtheria, measles, pertussis, polio, tetanus, tuberculosis and yellow fever. The modules have become some of the most widely used documents in the field of immunization.

With the development of the Global Immunization Vision and Strategy (GIVS) (2005–2015) (http://www.who.int/vaccines-documents/DocsPDF05/GIVS_Final_EN.pdf) and the expansion of immunization programmes in general, as well as the large accumulation of new knowledge since 1993, the decision was taken to update and extend this series.

The main purpose of the modules — which are published as separate disease/vaccine-specific modules — is to give immunization managers and vaccination professionals a brief and easily-understood overview of the scientific basis of vaccination, and also of the immunological basis for the World Health Organization (WHO) recommendations on vaccine use that, since 1998, have been published in the *Vaccine Position Papers* (http://www.who.int/immunization/documents/positionpapers_intro/en/index.html).

The authors thank Dr. Felicity Cutts, the author of the prior edition of this module, and Dr. Simon Cousens for their contributions to our understanding of measles and assistance in interpreting studies of the antibody responses to measles vaccine.

WHO would like to thank all the people who were involved in the development of the initial *Immunological Basis for Immunization* series, as well as those involved in its updating and the development of new modules.

[1] This programme was established in 1974 with the main aim of providing immunization for children in developing countries.

1. The organism and disease

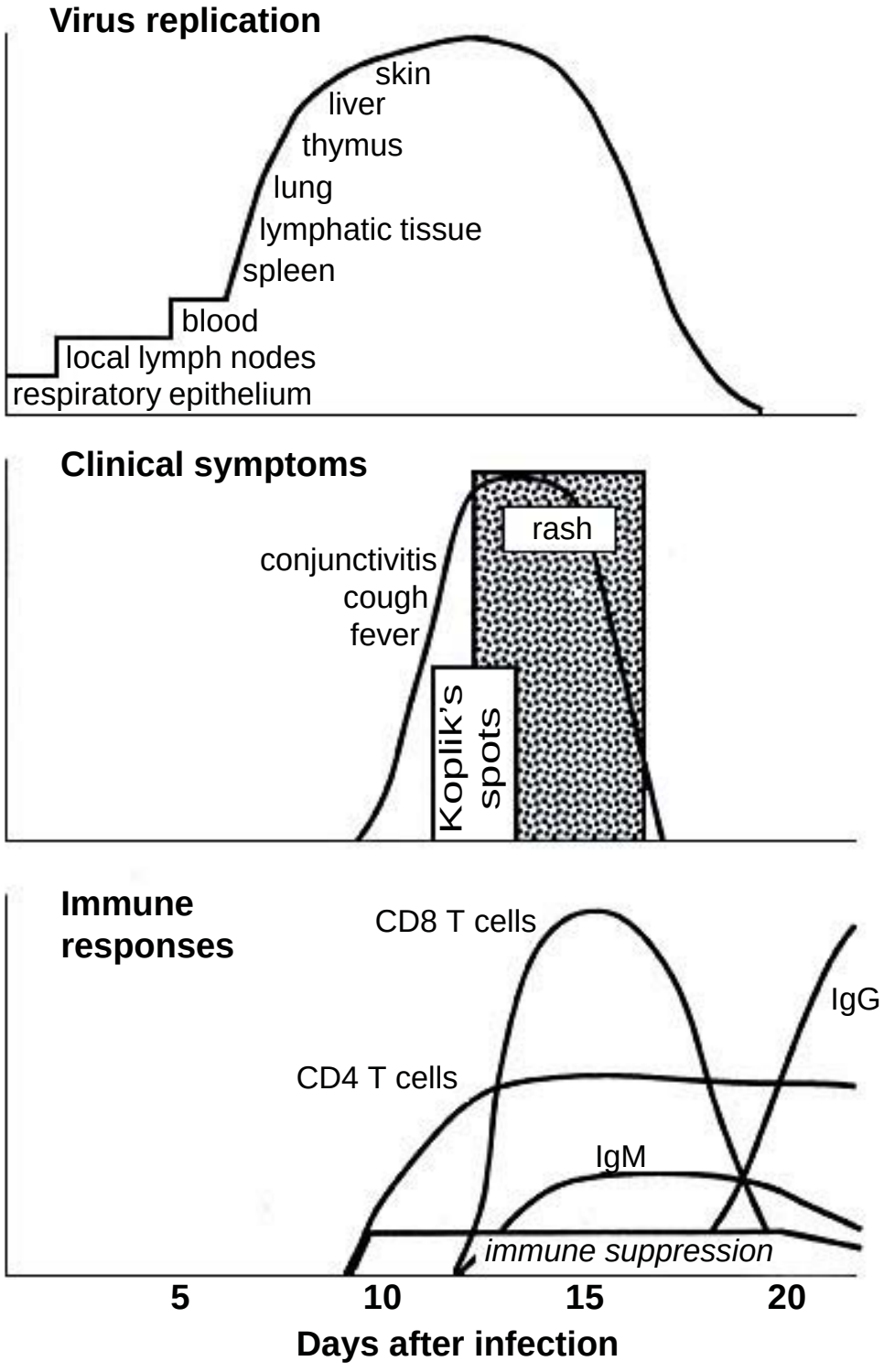
Measles virus infection is one of the most important infectious diseases of humans and has caused millions of deaths since its emergence as a zoonotic infection thousands of years ago. Prior to the development and widespread use of measles vaccines, measles was estimated to cause between five and eight million deaths annually. Remarkable progress in reducing measles incidence and mortality has been made, particularly in sub-Saharan Africa *(1;2)*, as a consequence of increasing routine measles vaccine coverage and provision of a second opportunity for measles vaccination through supplementary immunization activities (SIAs) (*3*). In the Region of the Americas, intensive immunization and surveillance efforts have, since November 2002, stopped endemic transmission of measles virus, in part based upon the successful Pan American Health Organization strategy of nationwide measles vaccine campaigns and high routine measles vaccine coverage (*4*). These achievements attest to the enormous public-health significance of measles vaccination.

In 2003, the World Health Assembly endorsed a resolution urging member countries to reduce the number of deaths attributed to measles by 50% compared with 1999 estimates by the end of 2005. This target was met. Overall, global measles mortality in 2005 was estimated to be 345 000 deaths (uncertainty bounds 247 000 and 458 000 deaths), a 60% decrease from 1999 (*2*). The revised global goal, as stated in the Global Immunization Vision and Strategy 2006–2015 of the World Health Organization and United Nations Children's Fund, is to reduce measles deaths 90% by 2010 compared to the estimated number in 2000 (*5*). To achieve this goal, continued progress needs to be made in delivering measles vaccines to the world's children.

1.1 Measles

Clinically apparent measles begins with a prodrome characterized by fever, cough, coryza (runny nose), and conjunctivitis (Figure 1). Koplik's spots, small bluish-white 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. The characteristic erythematous and maculopapular rash typically appears first on the face and behind the ears, and then spreads in a centrifugal fashion to the trunk and extremities. The rash lasts for three to four days and fades in the same manner as it appeared. Some children, particularly those who are malnourished, may develop a deeply pigmented rash that desquamates or peels during recovery. Because the rash of measles is a consequence of the cellular immune response, persons with impaired cellular immunity, such as those with the acquired immunodeficiency syndrome (AIDS), may not develop the characteristic measles rash.

Figure 1: Pathogenesis of measles virus infection



Source:
Griffin DE. In: Knipe DM et al, eds. Fields Virology, 4th ed. Lippincott Williams & Wilkins, 2001:1401–1441.

In uncomplicated measles, clinical recovery begins soon after appearance of the rash. Complications occur in 10%–40% of measles cases and the risk is increased by extremes of age, malnutrition, and other causes of impaired immunity *(6;7)*. Complications of measles have been described in almost every organ system. The respiratory tract is a frequent site of complication, with pneumonia accounting for most measles-associated deaths (*8*). Pneumonia is caused by secondary viral or bacterial infections, or by measles virus itself. Other respiratory complications include laryngotracheobronchitis (croup), and more commonly, otitis media (ear infection). Mouth ulcers, or stomatitis, may hinder children with measles from eating or drinking. Many children with measles develop diarrhoea, which further contributes to malnutrition. 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. Post-measles encephalomyelitis complicates approximately one in 1000 measles cases, mainly in older children and adults. Other rare central nervous system complications occurring months to years after acute infection are measles inclusion body encephalitis (MIBE) and subacute sclerosing panencephalitis (SSPE). Children with malnutrition, particularly vitamin-A deficiency, and those with severe immunological deficits such as advanced human immunodeficiency virus (HIV-1) infection, are at increased risk of severe or fatal measles. In resource-poor countries where malnutrition and exposure to other infectious diseases is common, the case-fatality ratio for measles is usually 3% to 6%, but can be as high as 30% in refugee camps or in isolated, immunologically naive populations *(2;9)*. However deaths due to measles are rare in developed countries, where the case fatality ratio is 0.01% to 0.1%.

The characteristic clinical features are of sufficient sensitivity and specificity to have high predictive value for the diagnosis of measles in regions where measles virus is endemic. However, laboratory diagnosis is necessary where measles virus transmission rates are low, in immunocompromised persons who may not have the characteristic clinical manifestations, and as part of measles surveillance. Other infections, such as with rubella virus, parvovirus B19 (erythema infectiosum or Fifth disease), human herpes viruses 6 and 7 (roseola infantum), dengue virus and *Streptococcus pyogenes* (scarlet fever), may mimic measles. Detection of IgM antibodies to measles virus by a capture enzyme immunoassay (EIA) is the standard method of diagnosing acute measles, as described below *(10;11)*.

1.2 Measles virus

Measles virus is the causative agent of measles and was first isolated from the blood of infected persons in the 1950s by John Enders and Thomas Peebles (*12*). The development of vaccines against measles soon followed. Measles virus is one of the most infectious directly-transmitted pathogens known, and occurs naturally only in humans. Measles virus is a spherical, nonsegmented, single-stranded, negative-sense, enveloped ribonucleic acid (RNA) virus and a member of the *Morbillivirus* genus in the family of *Paramyxoviridae*. Other members of the *Morbillivirus* genus, although not pathogenic to humans, are rinderpest virus and canine distemper virus. Rinderpest virus causes an important disease of cattle and swine, and is the *Morbillivirus* most closely related to measles virus. Although RNA viruses have high mutation rates, measles virus is considered to be an antigenically monotypic virus, meaning that the surface proteins responsible for inducing protective immunity have retained their antigenic structure over decades and throughout the world. The public-health significance is that measles vaccines developed decades ago from a single measles virus strain remain protective worldwide. However, genetic sequencing has identified 23 different measles virus genotypes, allowing for molecular epidemiological studies of measles virus transmission (*13*). Measles virus is killed by ultraviolet light and heat, and attenuated measles vaccine viruses retain this sensitivity necessitating a cold chain for transporting and storing measles vaccines, particularly after reconstitution.

The measles virus genome encodes eight proteins. In terms of understanding the immunological basis of measles immunization, the two surface proteins of measles virus, 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 uptake into the host cell. The H protein elicits strong host immune responses, and the life-long immunity that follows infection is attributed to neutralizing antibodies against H (*14*).

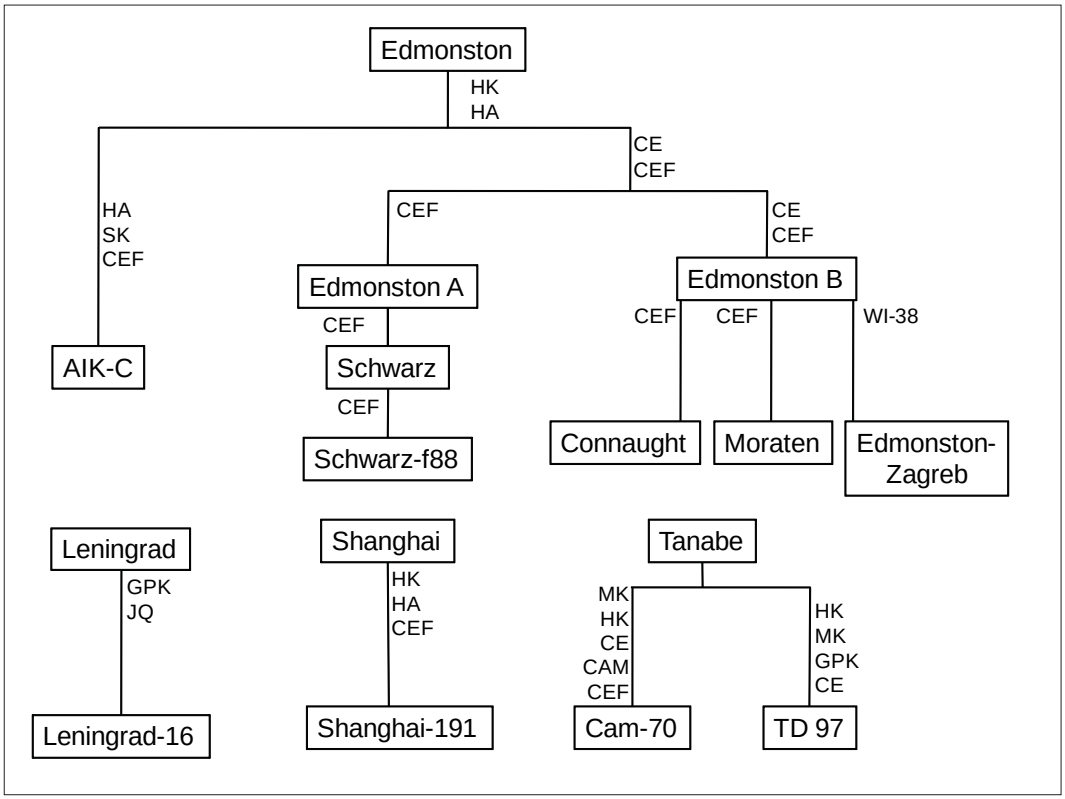
Respiratory droplets from infected persons serve as vehicles of transmission by carrying infectious virus to epithelial cells of the respiratory tract of susceptible hosts. During the 10 to 14 day incubation period between infection and the onset of clinical signs and symptoms, measles virus replicates and spreads within the infected host (Figure 1). Initial viral replication typically occurs in epithelial cells at the portal of entry in the upper respiratory tract, and the virus then spreads to local lymphatic tissue. Replication in local lymph nodes is followed by viremia (the presence of virus in the blood) and the dissemination of measles virus to many organs, including lymph nodes, skin, kidney, gastrointestinal tract and liver, where the virus replicates in epithelial and endothelial cells as well as monocytes, macrophages and lymphocytes. Infected persons are usually contagious from 2–3 days before and up to four days after onset of the rash.

1.3 Measles vaccines

1.3.1 Vaccine strains

Attenuation of wild-type measles virus for the production of measles vaccines is achieved by serial passage in cultured cells. The first licensed attenuated measles vaccine was called Edmonston B (Figure 2). This vaccine was immunogenic and was widely used between 1963 and 1975, but was frequently associated with fever and rash. The Schwarz and Moraten ("more attenuated") strains were derived from the original Edmonston strain but further attenuated through additional passages in chick embryo fibroblasts. Despite differences in their passage history, these two vaccine strains have identical genomic sequences (*15*). The Moraten vaccine is widely used in the United States of America, whereas 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 cells after attenuation in chick embryo fibroblasts. Other attenuated measles vaccines have been produced from locally derived wild-type strains, particularly in the Russian Federation (Leningrad-16), the People's Republic of China (Shanghai-191) and Japan (CAM-70, AIK-C).

Figure 2: Measles virus vaccines



Several attenuated measles vaccines are available in combination with other antigens, such as rubella and mumps vaccines (MR and MMR), and varicella vaccine. Licensed combination vaccines do not reduce the immunogenicity of the measles vaccine component. Measles vaccines are usually injected subcutaneously but can be administered intramuscularly. Measles vaccines may contain sorbitol or gelatin as stabilizers and the antibiotic neomycin, but do not contain thimerosal. The vaccine must be reconstituted in sterile diluent prior to use.

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 is available to standardize reporting of potency measurements. The World Health Organization recommends a minimum potency for measles vaccine of 1000 viral infective units (3.0 $\log_{10}$ $TCID_{50}$) (*16*). Vaccines with potencies between 3.0 and 4.6 $\log_{10}$ are considered to be standard-titre vaccines, and vaccines with potencies above 4.7 $\log_{10}$ are defined as high-titre vaccines (*17*).

Measles vaccines are relatively heat-stable in the lyophilized form, but rapidly lose potency when exposed to heat after reconstitution. The development of effective stabilizers and the formulation of the World Health Organization requirement for heat stability for freeze-dried measles vaccine considerably improved the quality of measles vaccines. In the freeze-dried state, measles vaccines that meet World Health Organization 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 (*16*). However, reconstituted measles vaccines may lose their potency at room temperatures. Although the stability depends in part upon the particular vaccine strain, reconstituted measles vaccines may lose approximately 50% of potency in one hour at 22°C to 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.

2. Immunological responses to natural infection

Host immune responses to measles virus are essential for viral clearance, clinical recovery, and the establishment of long-term protective immunity.

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, and increased production of the antiviral proteins interferon (IFN)-α and IFN-γ. IFN induction by wild-type measles virus strains is generally less efficient than by vaccine strains. These innate immune responses contribute to the control of measles virus replication before the onset of more specific (adaptive) immune responses.

2.2 Antibody responses

The adaptive immune responses consist of measles virus-specific antibody and cellular immune responses (Figure 1). The protective efficacy of antibodies to measles virus is illustrated by the protection conferred to infants from passively-acquired maternal antibodies and the protection of exposed, susceptible individuals following administration of anti-measles virus immune globulin (*18*). The first measles virus-specific antibodies produced after infection are of the IgM subtype, generally followed by a switch to predominantly IgG1 and IgG4 isotypes (*19*). The IgM antibody response usually is absent following re-exposure or revaccination, and serves as a marker of primary infection. IgA antibodies to measles virus are found in mucosal secretions. The most abundant and most rapidly produced antibodies are against the nucleoprotein (N), and the absence of antibodies to N is the most accurate indicator of the lack of antibodies to measles virus. Although not as abundant, antibodies to H and F proteins contribute to virus neutralization and are the best correlates of protection against measles virus infection. Avidity is an important characteristic of a mature antibody response and refers to how tightly the antibody binds measles virus antigens. The development of a high avidity antibody response is critical to the development of protective immunity to measles virus. Antibody avidity to measles virus is generally lower in children vaccinated at six or nine months of age compared with children vaccinated at 12 months of age (*20*).

2.3 Cellular immune responses

Evidence of the importance of cellular immune responses to measles virus is demonstrated by the ability of children with agammaglobulinemia (congenital inability to produce antibodies) to fully recover from measles, whereas children with severe defects in T-lymphocyte function often develop severe or fatal disease (*21*). Monkeys provide an animal model to study the immune responses to measles virus and measles vaccines, and monkeys depleted of $CD8^+$ T lymphocytes and challenged with wild-type measles virus had a more extensive rash, higher measles virus loads, and longer duration of viremia than control animals, further confirming the importance of cellular immunity to measles virus clearance (*22*).

$CD4^+$ T lymphocytes are also activated in response to measles virus infection and secrete cytokines 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 (*23*). The initial predominant type 1 response (characterized by IFN-γ) is essential for viral clearance, and the later type 2 response (characterized by IL-4) promotes the development of measles virus-specific antibodies (*24*).

2.4 Immunological memory

The duration of protective immunity following wild-type measles virus infection is generally thought to be life-long. 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 measles virus infection (*25*). Two measles epidemics occurred in this community decades apart. Adults with a history of measles as children did not acquire measles after re-exposure 65 years later. The mechanisms involved in sustaining protective immunity to measles virus are not completely understood, but general principles of the development and maintenance of immunological memory probably govern this process. There is no evidence that repeat exposure to measles virus is required for long-term immunity, although studies in the Republic of Senegal suggested that subclinical boosting of antibody levels may result from frequent exposure in regions where measles virus is circulating (*26*). Immunological memory to measles virus includes both continued production of measles virus-specific antibodies and the circulation of measles virus-specific $CD4^+$ and $CD8^+$ T lymphocytes (*27*). Although levels of anti-measles virus antibodies may diminish over time, the ability to rapidly mount secondary humoral and cellular immune responses is important in providing protection from infection.

2.5 Immune suppression

The intense immune responses induced by measles virus infection are paradoxically associated with depressed responses to unrelated (non-measles virus) antigens, lasting for several weeks to months beyond resolution of the acute illness. This state of immune suppression enhances susceptibility to secondary bacterial and viral infections causing pneumonia and diarrhoea, and is responsible for much measles-related morbidity and mortality (28;29). Delayed-type hypersensitivity (DTH) responses to recall antigens, such as tuberculin, are suppressed and cellular and humoral responses to new antigens are impaired, following measles virus infection (*30*). Reactivation of tuberculosis and remission of autoimmune diseases have been described after measles and are attributed to this state of immune suppression.

Abnormalities of both the innate and adaptive immune responses follow measles virus infection. Transient lymphopenia (a reduction in the number of lymphocytes in the blood) with a reduction in both CD4+ and CD8+ T lymphocytes, occurs in children following measles virus infection, although this may reflect redistribution of lymphocytes to lymphoid tissue in addition to cell death (*31*). Functional abnormalities of immune cells are also detected, including decreased lymphocyte proliferative responses (*32*). Dendritic cells, major antigen-presenting cells, mature poorly, lose the ability to stimulate proliferative responses in lymphocytes, and undergo cell death when infected with measles virus in vitro (*33*). The dominant type 2 response in children recovering from measles can inhibit type 1 responses and increase susceptibility to intracellular pathogens (34;35). The production of IL-12, important for the generation of type1 immune responses, decreases following binding of the CD46 receptor for measles virus (*36*) and is low for several weeks in children with measles (*37*). This diminished ability to produce IL-12 could result in limited type 1 immune responses to other pathogens. A role for immunomodulatory cytokines in the immune suppression following measles is supported by evidence of elevated plasma levels of IL-10 in children with measles, a cytokine capable of inhibiting immune responses (*23*).

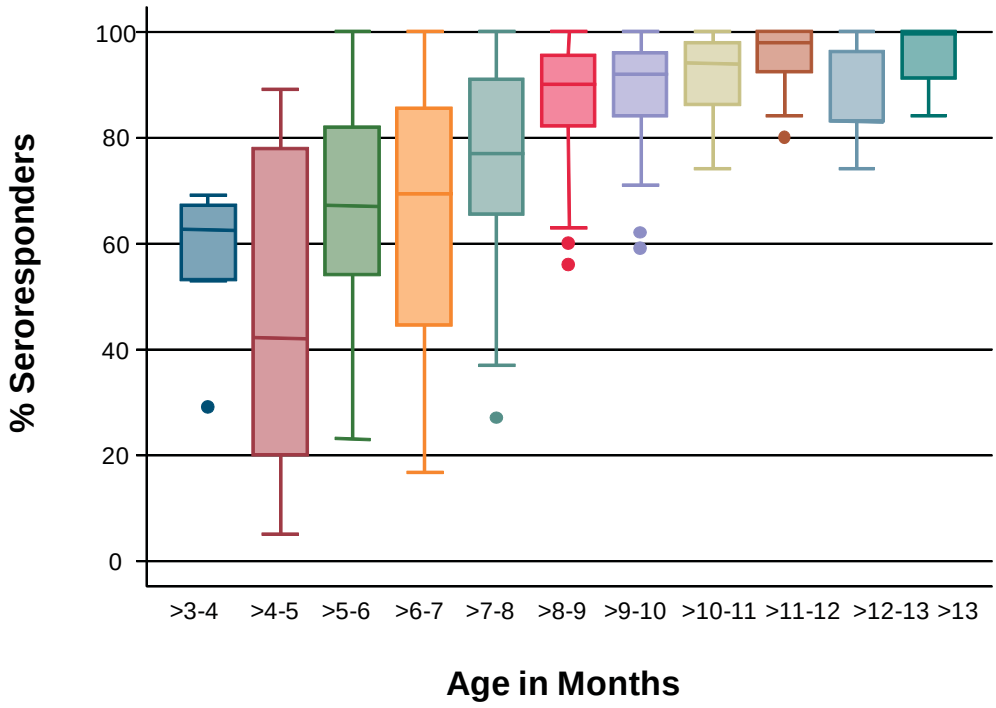
3. Immunological responses to immunization

3.1 Antibody and cellular immune responses

Measles vaccines induce humoral and cellular immune responses similar to natural measles virus infection. Antibodies first appear between 12 and 15 days after vaccination and typically peak at 21 to 28 days. IgM antibodies appear transiently in blood, IgA antibodies are predominant in mucosal secretions, and IgG antibodies persist in blood for years. Vaccination also induces measles virus-specific CD4+ and CD8+ T-lymphocytes (*27*;38). Although both humoral and cellular responses can be induced by measles vaccines, these responses are of lower magnitude and shorter duration compared to those following wild-type measles virus infection (*39*).

The proportion of children who develop protective antibody levels following measles vaccination depends on the presence of inhibitory maternal antibodies and the immunologic maturity of the vaccine recipient, as well as the dose and strain of vaccine virus (Figure 3, Table 1). Frequently cited figures are that approximately 85% of children develop protective antibody levels when given one dose of measles vaccine at nine months of age, and 90% to 95% respond when vaccinated at 12 months of age (*17*). Among the 44 studies listed in Table 1 in which children were vaccinated between 8 and 9 months of age, the median proportion of children responding was 89.6% (mean 86.7; minimum 56; maximum 100; interquartile range (IQR) 82, 95). Among the 24 studies listed in Table 1 in which children were vaccinated between 9 and 10 months of age, the median proportion of children responding was 92.2% (mean 88.2; minimum 59; maximum 100; IQR 84, 96). Among the 21 studies listed in Table 1 in which children were vaccinated between 11 and 12 months of age, the median proportion of children responding was 99% (mean 95.7; minimum 80; maximum 100; IQR 93, 100).

Figure 3: Box plots showing the proportion of children who respond to standard-titre measles vaccine by age at vaccination



Adapted, by permission of the publisher, from Scott S, [thesis] 2006, (237).

3.2 Immune responses to revaccination

The immunological basis for providing a second opportunity for measles vaccination is to immunize those children who fail to respond to the first dose, as well as to vaccinate those who never received a dose. Immune responses to revaccination depend in part on the adequacy of the response to the first dose of measles vaccine. Those with poor immune responses to initial vaccination usually have a characteristic primary immune response, with production of IgM antibodies followed by high levels of IgG antibodies. When a second dose is administered to children over one year of age who failed to develop protective antibody levels following the first dose, the majority will develop protective antibody levels (Table 2). For example, among 679 children four to six years of age who received a single dose of measles vaccine between 12 and 17 months of age, 97% of the 37 seronegative children seroconverted after revaccination (*40*). In another study of children in the United States, 82% of 130 seronegative children seroconverted after revaccination after a single dose of measles vaccine (*41*).

Table 1 A: Seroconversion by age at vaccination with standard-titre measles vaccine for the African Region

Country (reference)	Year	Vaccine strain	Assay	Percentage of children who seroconvert by age at time of vaccination in months (number of children studied)										
				>3–4	>4–5	>5–6	>6–7	>7–8	>8–9	>9–10	>10–11	>11–12	>12–13	>13
Nigeria (141)	1973	Schwarz	HI	—	—	—	64 (22)	—	—	—	89 (66)	—	—	—
Côte d'Ivoire (142)	1975	Not stated	HI	—	—	—	84 (127)	—	—	—	—	—	—	—
South Africa (143)	1975	Moraten	CF	—	—	2 (13)	45 (11)	57 (14)	86 (7)	71 (7)	86 (7)	80 (5)	—	—
Zimbabwe (144)	1976	Beckenham	HI	—	—	—	40 (15)	—	—	—	—	—	—	—
Kenya (145)	1979	Schwarz	HI	—	24 (29)	54 (37)	43 (35)	93 (28)	90 (29)	—	100 (38)	—	—	—
United Republic of Tanzania (146)	1981	Schwarz	HI	—	17 (6)	—	44 (41)	—	63 (43)	—	74 (34)	—	83 (18)	8 (24)
Nigeria (147)	1981	Moraten	HI	—	5 (18)	25 (24)	28 (14)	54 (11)	60 (10)	—	—	—	—	—
Tanzania (148)	1985	Schwarz	HI	—	—	—	46 (37)	—	64 (39)	—	78 (32)	—	83 (18)	91 (23)
Nigeria (149)	1985	Moraten	HI	—	—	—	74 (39)	75 (24)	88 (9)	—	85 (21)	—	—	84 (13)
The Gambia (150)	1988	Edmonston-Zagreb	PRN	—	73 (40)	—	—	—	—	—	—	—	—	—
Côte d'Ivoire (101)	1989	Schwarz	HI	—	—	—	93 (33)	—	—	96 (27)	—	—	—	—
Togo (151)	1989	AIK-C	HI	—	85.8 (190)	—	—	—	—	90.6 (32)	—	—	—	—
Togo (151)	1989	Schwarz	HI	—	—	—	—	—	—	73.4 (64)	—	—	—	—
The Gambia (152)	1990	Schwarz	HI	—	—	—	—	—	95 (105)	—	—	—	—	—

Table 1 A: Seroconversion by age at vaccination with standard-titre measles vaccine for the African Region *(cont'd...)*

Country (reference)	Year	Vaccine strain	Assay	Percentage of children who seroconvert by age at time of vaccination in months (number of children studied)										
				>3–4	>4–5	>5–6	>6–7	>7–8	>8–9	>9–10	>10–11	>11–12	>12–13	>13
South Africa (153)	1990	Schwarz	ELISA	—	—	—	—	—	89.2 (176)	—	—	—	—	—
Côte d'Ivoire (101)	1992	Schwarz	HI	—	—	—	—	—	98 (343)	—	—	—	—	—
Guinea (154)	1992	Edmonston-Zagreb	HI				91							
South Africa (155)	1991	Edmonston-Zagreb	ELISA	—	31 (26)	—	71 (14)	63 (8)	—	—	—	—	—	—
South Africa (155)	1991	Schwarz	ELISA	—	25 (20)	—	41 (17)	27 (11)	—	59 (27)	—	—	—	—
Guinea-Bissau (156)	1994	Schwarz	HI	—	—	—	—	—	—	96 (74)	—	—	—	—
Guinea-Bissau (156)	1994	Schwarz	ELISA	—	—	—	—	—	—	100 (96)	—	—	—	—
Ghana (157)	1994	Schwarz	HI	50	50	37.5	86.7	100	92.3	92.3	87.5	100		
Cameroon (158)	1995	Connaught	ELISA	52.9 (17)	77.8 (18)	82.4 (17)	87.5 (8)	100 (3)	—	—	—	—	—	—
Cameroon (158)	1995	Schwarz	ELISA	62.5 (16)	57.1 (7)	87.5 (8)	50 (6)	66.7 (3)	—	—	—	—	—	—
Guinea-Bissau (159)	2001	Edmonston-Zagreb	HI	—	—	95.1 (81)	—	—	98.6 (211)	—	—	—	—	—
Guinea-Bissau (159)	2001	Schwarz	HI	—	—	78.3 (106)	—	—	97.1 (310)	—	—	—	—	—

HI = haemagglutination inhibition assay
CF = complement fixation assay
PRN = plaque reduction neutralization test
ELISA = enzyme linked immunosorbent assay

Table 1 B: Seroconversion by age at vaccination with standard-titre measles vaccine for the Latin American region

Country (reference)	Year	Vaccine strain	Assay	Seroconversion rates (%) by age at time of vaccination in month (number of children studied)											
				>3–4	>4–5	>5–6	>6–7	>7–8	>8–9	>9–10	>10–11	>11–12	>12–13	>13
Brazil (160)	1978	Schwarz	HI	—	—	—	17 (6)	67 (6)	75 (4)	71 (7)	88 (8)	100 (7)	—	—
Chile (161;162)	1982	Moraten	HI	—	—	64 (1)	74 (43)	84 (61)	82 (22)	83 (6)	100 (1)	100 (2)	—	—
Equador (161;162)	1982	Moraten	HI	—	—	65 (31)	77 (30)	91 (33)	91 (32)	92 (24)	86 (21)	100 (23)	—	—
Brazil (161;162)	1982	Moraten	HI	—	—	55 (53)	70 (50)	85 (52)	90 (40)	95 (41)	94 (32)	97 (34)	—	—
Brazil (161;162)	1982	Moraten	HI	—	—	72 (58)	83 (58)	87 (63)	91 (74)	96 (48)	98 (43)	100 (31)	—	—
Brazil (161;162)	1982	Moraten	HI	—	—	52 (79)	52 (71)	73 (59)	84 (49)	92 (37)	94 (49)	93 (41)	—	—
Brazil (161;162)	1982	Moraten	HI	—	—	48 (42)	68 (57)	86 (44)	75 (16)	91 (11)	100 (8)	100 (8)	—	—
Mexico (163)	1984	EZ-Mx	PRN	29(13)	20(9)	77 (10)	—	—	—	—	—	—	—	—
Mexico (163)	1984	EZ-Mx	PRN	69 (13)	89(9)	100(10)	—	—	—	—	—	—	—	—
Haiti (76)	1985	Moraten	HI	—	—	45 (51)	71 (52)	77 (39)	85 (58)	94 (53)	95 (40)	100 (40)	—	—
Guatemala (164)	1989	Schwarz	HI	—	—	—	—	81 (11)	89 (66)	96 (46)	98 (45)	92 (39)	100 (32)	100 (19)
Guatemala (164)	1989	Moraten	HI	—	—	—	—	100 (10)	89.1 (55)	100 (38)	96.7 (60)	100 (44)	96.2 (26)	100 (19)
Peru (165)	1990	Connaught	ELISA	—	—	—	—	—	94 (34)	—	—	—	—	—

Table 1 B: Seroconversion by age at vaccination with standard-titre measles vaccine for the Latin American region *(cont'd...)*

Country (reference)	Year	Vaccine strain	Assay	Seroconversion rates (%) by age at time of vaccination in month (number of children studied)										
				>3–4	>4–5	>5–6	>6–7	>7–8	>8–9	>9–10	>10–11	>11–12	>12–13	>13
Mexico (166)	1990	EZ-M	PRN	—	—	82 (151)	—	—	97 (171)	—	—	—	—	—
Mexico (166)	1990	Schwarz	PRN	—	—	57 (146)	—	—	85 (128)	—	—	—	—	—
Mexico (166)	1990	EZ-M	PRN	—	—	92 (151)	—	—	96 (171)	—	—	—	—	—
Mexico (166)	1990	Schwarz	PRN	—	—	66 (146)	—	—	87 (128)	—	—	—	—	—
Mexico (166)	1990	EZ-M	PRN	—	—	66 (151)	—	—	79 (171)	—	—	—	—	—
Mexico (166)	1990	Schwarz	PRN	—	—	49 (146)	—	—	82 (128)	—	—	—	—	—
Brazil (167)	2002	BIKEN-CAM	ELISA	—	—	—	31 (126)	37 (102)	56 (65)	62 (67)	84 (73)	84 (57)	74 (62)	—

HI = haemagglutination inhibition assay
PRN = plaque reduction neutralization test
ELISA = enzyme linked immunosorbent assay

Table 1 C: Seroconversion by age at vaccination with standard-titre measles vaccine for countries in Asia

Country (reference)	Year	Vaccine strain	Assay	Seroconversion rates (%) by age at time of vaccination in month (number tested)										
				>3–4	>4–5	>5–6	>6–7	>7–8	>8–9	>9–10	>10–11	>11–12	>12–13	>13
China (Province of Taiwan) (168)	1983	Moraten	HI	—	—	82 (17)	92 (13)	94 (16)	100 (22)	100 (19)	100 (14)	100 (12)	—	—
Papua New Guinea (169)	1984	Schwarz	HI	—	—	—	—	—	100 (12)	100 (12)	92 (13)	100 (15)	—	100 (23)
India (170)	1984	Moraten	HI	—	—	74 (31)	87 (38)	100 (28)	97 (37)	88 (24)	96 (27)	95 (19)	—	100 (26)
Malaysia (171)	1985	Schwarz	HI	—	—	—	—	—	95 (107)	94 (158)	98 (92)	99 (89)	—	99 (240)
Bangladesh (172)	1987	EZ-Z	HI	—	53 (19)	62 (21)	100 (2)	—	—	—	—	—	—	—
Bangladesh (172)	1987	Schwarz	HI	—	17 (30)	50 (32)	—	—	—	—	—	—	—	—
China (Province of Taiwan) (173)	1990	Schwarz	ELISA	—	—	—	—	—	—	84 (118)	—	88 (104)	—	—
Indonesia (101)	1992	Schwarz	HI	—	—	—	—	—	97 (33)	—	—	—	—	—
Papua New Guinea (174)	1992	EZ-Z	ELISA	67 (15)	83 (12)	100 (5)	100 (7)	—	—	—	—	—	—	—
Saudi Arabia (175)	1992	EZ	Indirect immuno flourescent	—	—	96 (27)	—	—	—	—	—	—	—	—
Saudi Arabia (175)	1992	Schwarz	Indirect immuno flourescent	—	—	56 (25)	—	—	70 (53)	—	—	—	—	—

Table 1 C: Seroconversion by age at vaccination with standard-titre measles vaccine for countries in Asia *(cont'd...)*

Country (reference)	Year	Vaccine strain	Assay	Seroconversion rates (%) by age at time of vaccination in month (number tested)										
				>3–4	>4–5	>5–6	>6–7	>7–8	>8–9	>9–10	>10–11	>11–12	>12–13	>13
India (176)	1994	Schwarz-MMR	HI	—	—	—	—	—	80 (49)	—	—	98 (47)	—	95 (27)
India (176)	1994	Schwarz-MMR	ELISA	—	—	—	—	—	93 (48)	—	—	89 (46)	—	100 (27)
Uzbekistan (177)	1994	EZ-SK	HI	—	—	67 (142)	—	—	91 (154)	—	—	—	—	—
Uzbekistan (177)	1994	L-16	HI	—	—	75 (151)	—	—	95 (137)	—	—	—	—	—
Uzbekistan (177)	1994	AIK-C	HI	—	—	83 (125)	—	—	94 (156)	—	—	—	—	—
Thailand (178)	2000	Schwarz	ELISA	—	—	—	—	—	100 (14)	—	—	—	—	—
Bangladesh (179)	2001	EZ-Z or Schwarz	PRN	—	—	56 (23)	—	—	83 (21)	—	—	—	—	—
Bangladesh (179)	2001	EZ-Z or Schwarz	PRN	—	—	70 (23)	—	—	93 (21)	—	—	—	—	—
India (180)	2001	Not stated	HI	—	—	41 (17)	50 (32)	65 (26)	74 (49)	86 (22)	100 (4)	—	—	—
China (181)	2001	Hu191	ELISA	—	—	81 (65)	91 (62)	—	—	—	—	94 (355)	—	—

HI = haemagglutination inhibition assay
PRN = plaque reduction neutralization test
ELISA = enzyme linked immunosorbent assay

An increase in IgG antibody levels, or boosting, can be seen in persons with moderate levels of protective immunity after the first dose of measles vaccine (42;43). In these individuals, an anamnestic immune response develops, IgM antibodies typically are not produced, and IgG antibodies are detected within five to six days and peak around 12 days. Antibody levels after revaccination tend to return to pre-vaccination levels within several months to years (Table 2), although cell-mediated immune responses after revaccination may persist (*39*). In persons with high levels of pre-existing antibodies to measles virus, vaccine virus does not replicate sufficiently to boost antibody levels. Children who were revaccinated were at lower risk of acquiring measles in Finland (*44*) and Zimbabwe (*45*).

3.3 Determinants of the immune responses to immunization

3.3.1 Host factors

3.3.1.1 Age at vaccination

The age at vaccination is an important determinant of the immune response to measles vaccine, with older infants having better responses than younger infants. 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 measles virus transmission, the average age of infection is low and the optimal strategy is to vaccinate against measles as young as possible (usually nine months of age — see below). By contrast, in settings where measles virus transmission has been reduced, the age of routine measles vaccination can be increased to 12 months or older. Antibody responses to measles vaccine increase with age up to approximately 15 months, due to the presence of inhibitory maternal antibodies and immaturity of the immune system (Figure 3). This immaturity of the immune system in neonates and young infants includes a limited B-cell repertoire and inefficient mechanisms of antigen presentation and T-cell help (46;47). The recommended age at vaccination must balance the risk of primary vaccine failure, which decreases with age, against the risk of measles virus infection prior to vaccination, which increases with increasing age.

In communities with intense measles virus transmission, a significant proportion of children may acquire measles before nine months of age. For example, 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 nine months old (*48*). Under some circumstances, provision of an extra, early dose of measles vaccine at six months (e.g. in outbreaks or for HIV-infected children) is appropriate. Additional doses of measles vaccine should be administered to these children, according to the routine immunization schedule.

Table 2: Antibody responses to measles revaccination

Author, Date of publication (Reference)	Year	Country of study	Age at first vaccination	Age at revaccination	Number	% with measles antibodies before revaccination	% with measles antibodies after revaccination	Comments
Krugman (182)	1965	USA	NA	NA	36	0	100	Antibody levels declined within 1 to 3 years after revaccination
Bass (183)	1976	USA	childhood	3–18 years	15	0	100	95% of 318 children were seropositive prior to revaccination; 75% of 12 revaccinated children lost antibody by 6 months
Deseda (184)	1978	USA	childhood	< 18 years	26	0	100	Children with secondary response (IgG only) had lower antibody levels that declined by 10 months
Linnemann (185)	1982	USA	< 10 months	mean 7.8 years	72	NA	60	Antibody levels measured at a mean of 12.6 years
Yeager (186)	1983	USA	11–12 months	NA	42	0	86	Age at revaccination between 6 and 20 years
Murphy (187)	1984	USA	5–11 months	14–23 months	291	NA	98	98% seropositive after single dose at 15 months
Lampe (188)	1985	USA	7–13 months	14–18 months	5	0	100	72% of 18 children seropositive before revaccination
Stetler (42)	1986	USA	< 10 months	15 months	121	0	96	
McGraw (189)	1986	USA	7–12 months	15–18 months	52	89	94	
Wittler (43)	1991	USA	childhood	4–20 years	183	90	100	“Susceptible” defined as having 4-fold or greater rise in antibody level after revaccination
Markowitz (190)	1992	USA	11 - >24 months	12–19 years	7	0	100	90% of 33 children with low pre-vaccination antibody levels responded to revaccination but were more likely to lose antibody at 6 years
Cote (191)	1993	USA	childhood	16–27 years	37	0	97	
Ward (39)	1995	Canada	11–36 months	mean 9 years	60	0	100	PRN titres at one month after revaccination were not sustained at 6 months in two-thirds
Mendelson (192)	1996	Israel	NA	18–25 years	46	0	78	

Table 2: Antibody responses to measles revaccination *(cont'd...)*

Author, Date of publication (Reference)	Year	Country of study	Age at first vaccination	Age at revaccination	Number	% with measles antibodies before revaccination	% with measles antibodies after revaccination	Comments
Watson (40)	1996	USA	15–17 months	4–6 years	37	0	97	
Bartoloni (193)	1997	Bolivia	NA	school age	26	0	100	52% had a significant loss of antibodies at one year
Poland (41)	1997	USA Canada	median 1.2 years	median 10 years	130	0	82	
Broliden (194)	1998	Sweden	18 months	12 years	310	98	99	
Khalil (195)	1999	Saudi Arabia	6 months	12 months	93	81	100	
Dilraj (136)	2000	South Africa	NA	mean 9 years mean 8.8 years	128 128	0 0	81 73	EZ subcutaneously Schwarz subcutaneously
Ceyhan (196)	2001	Turkey	9 months	15 months	442	NA	70	
Gans (197)	2001	USA	6–9 months	12 months	31	NA	100	PRN titres increased from 267–776 mIU to 1487–1994 mIU after revaccination
Hutchins (198)	2001	USA	6–11 months	≥ 12months	209	NA	94	98% of children who received a single dose at ≥ 12 months had protective antibodies
Wong-Chew (199)	2003	Mexico	NA	adults	7			Boosting of cellular immune responses in those with high pre-existing antibody levels
Isik (200)	2003	Turkey	9	15	15	0	87	78% and 82% of 116 children were seropositive after the 1st and 2nd doses
Rager (201)	2003	Israel	6–23 months	5–7 years	12	0	92	Some children received three doses of vaccine
Saffar (202)	2006	Islamic Republic of Iran	childhood	adolescents and adults	105	0	82	
Kremer (203)	2006	Luxembourg	childhood	adolescents	112	89	90	
Moss (59)	2007	Zambia	9 months	11–21 months	115 13	95 92	97 92	HIV-1 uninfected HIV infected

3.3.1.2 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 is responsible for the transfer of IgG antibodies from the maternal circulation to the fetus, starting at approximately 28 weeks gestation and continuing until birth (*47*). Three factors determine the degree and duration of protection in the newborn: (1) the level of maternal antibodies to measles virus; (2) the efficiency of placental transfer; (3) the rate of catabolism in the child (*49*). Although protective, maternally-acquired antibodies also interfere with the immune responses to the attenuated measles vaccine by inhibiting replication of vaccine virus necessary for a robust immune response to the vaccine. In general, maternally-acquired antibodies are no longer present in the majority of children by six to nine months of age (*49*). The half-life of antibodies to measles virus is the time required for one half of the amount of antibody to decay, and estimates of this half-life are remarkably consistent across studies (Table 3). Estimates vary between 40 and 61 days, and there do not seem to be regional differences in decay rates.

Table 3: Half-life of maternally-acquired antibodies to measles virus

Country (reference)	Number of children	Estimated half-life for maternal antibodies (days)	Test
USA (49;204-206) [a]	42	48.4	HI
Kenya (205;207) [a]	35–116	46.1	HI
China (Province of Taiwan) (205;206) [a]	14–88	53.3	HI
Jamaica (208)	155 155	60.8[a] 43.5[b]	HI PRNT
Jamaica (206)	173	44.3	PRNT
Ghana (206)	35	39.7	PRNT
Canada (209) [c] Group 1 Group 2 Group 3	 164 60 54	 40 64 52	PRNT
Peru (165) [d] Low birth weight Medium weight High birth weight	34 15 9 10	56.3 (± SE) 61 ± 13 59 ± 15 46 ± 16	EIA
Nigeria (210)	206	48	EIA

a Studies that specify that seronegative children were excluded in half-life estimates.
b Decline of median titres, with seronegative children included in the estimation.
c Group1; mothers born before 1958, Group 2; mothers born >1964 and received killed measles vaccine followed by live attenuated measles vaccine, Group 3; mothers born >1964 and received live attenuated measles vaccine.
d High titres >3000, medium titres 2000–3000 and low titres 1000–2000.

SE = standard error for each group
HI = haemagglutination inhibition assay
PRN = plaque reduction neutralization test
ELISA = enzyme linked immunosorbent assay

Women with vaccine-induced immunity tend to have lower anti-measles virus antibody levels than women with naturally-acquired immunity, and their children may be susceptible to measles at an earlier age. Lower levels of measles antibodies in vaccinated individuals may result not only from the direct effects of vaccination but because successful vaccination programmes reduce measles virus transmission and thus boosting of immunity through exposure to wild-type measles virus.

Placental transfer of maternal antibodies, including antibody to measles virus, is impaired in HIV-1-infected women (50;51). Children born to HIV-1-infected women may be susceptible to measles virus infection earlier than children born to uninfected women. In the Republic of Kenya, 9% of 109 children born to HIV-1-infected women acquired measles before nine months of age, compared with 3% of 194 children born to uninfected women (*52*). However, the lower levels of maternal antibody may also result in a better response of their HIV-1-infected and uninfected infants to measles vaccine administered at six months of age.

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. Studies in the Republics of the Gambia and Malawi reported reduced placental transfer of antibodies to measles virus in the presence of placental malaria infection (53;54).

3.3.1.3 Immunological immaturity

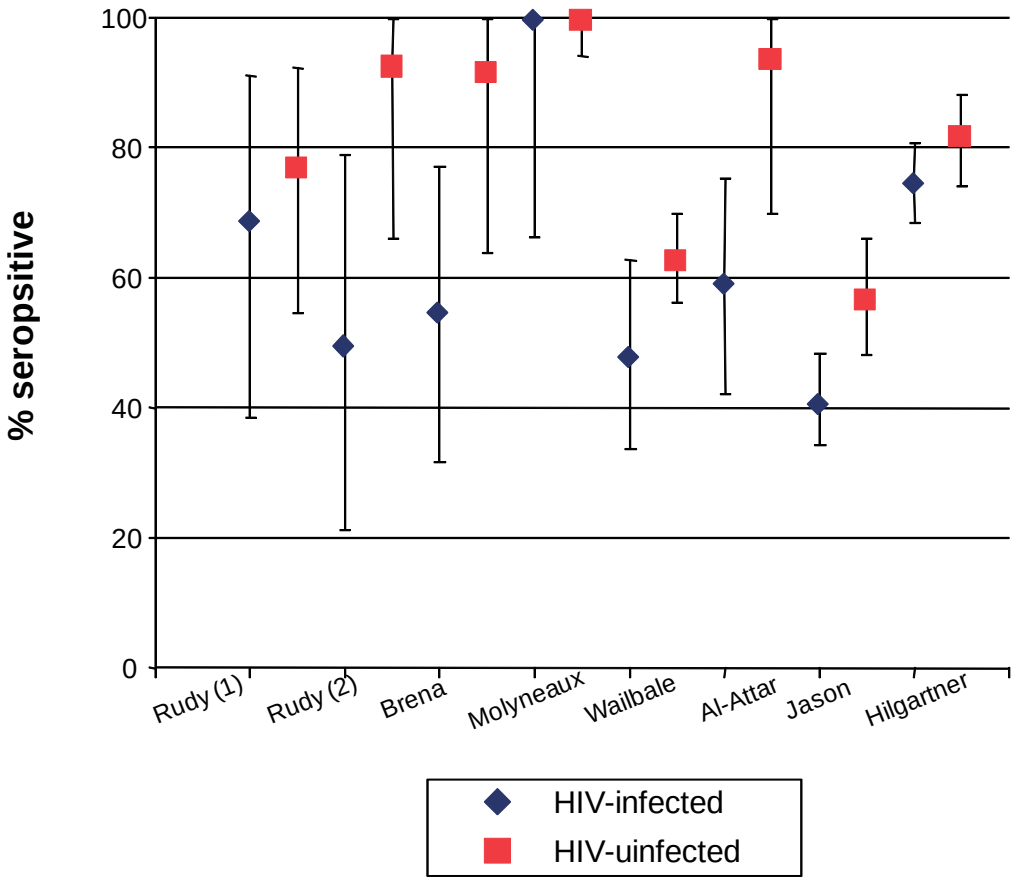
Very young infants (six months or younger) do not develop high levels of neutralizing antibodies after immunization with attenuated measles virus vaccines, even in the absence of passively-acquired maternal antibodies. Neonates have impaired antibody responses to many antigens. The magnitude of the IgG antibody response is lower than in adults and antibody avidity is decreased (*55*). Inefficient immune responses in neonates may be due to impaired interactions between T-lymphocytes and antigen-presenting cells. Specifically, neonatal immunologic immaturity may result from failure of neonatal follicular dendritic cells (FDC) to respond to lymphoid-mediated signals, with subsequent failure in maturation of FDC and formation of germinal centres (*56*).

3.3.1.4 HIV-1 infection and other immunosuppressive conditions

The antibody response to measles vaccine can be impaired in HIV-1-infected children (Figure 4, Tables 4 and 5) (*57*). In three prospective studies conducted early in the HIV-1 epidemic in the United States, only approximately one-quarter to one-third of HIV-1-infected children responded to a single dose of standard-titre measles vaccine (*57*). In a study of HIV-seropositive children in the Democratic Republic of the Congo, 65% had protective levels of measles antibody three months after measles vaccination at nine months of age, although only 36% of 11 symptomatic children seroconverted compared with 77% of 26 asymptomatic children (*58*). In Malawi, the proportion of measles seropositive children (by EIA) following two doses of measles vaccine at 6 and 9 months of age was only 64% for 45 HIV-infected children, compared with 94% of 202 HIV-exposed but uninfected children and 92% of 417 HIV-unexposed children (Felicity Cutts, personal communication). By contrast, 88% of 50 HIV-1-infected Zambian children developed protective antibody levels (by plaque reduction neutralization assay) within six months of vaccination compared to

94% of 98 HIV-seronegative children and 94% of 211 HIV-seropositive but uninfected children (P = 0.3) (*59*). By 27 months after vaccination, however, only half of the 18 HIV-1-infected children who survived and returned for follow-up maintained protective measles antibody levels compared with 89% of 71 uninfected children (P = 0.001) (*59*). Studies in the United States also found that HIV-1-infected children have a more rapid decline in measles antibody levels compared with HIV-1-uninfected children (*60*), with a median time to loss of EIA–detectable antibody of 30 months in one study of 17 HIV-1-infected children (*61*). However, the majority of HIV-1-infected adults who were vaccinated as children remain seropositive (62;63).

Figure 4: Proportion of children who responded to measles vaccine by HIV infection status in cross-sectional studies



First authors are shown on the x-axis (see Table 4 for details).
Vertical bars show 95% confidence intervals.
Adapted, by permission of the publisher, from Scott S, [thesis] 2006, (237).

The response of HIV-1-infected children to a second dose of vaccine in five studies was variable, but generally poor (Table 5) (*57*). However, in the study of Zambian children cited above, 92% of 12 HIV-1-infected children revaccinated during a supplemental measles immunization activity had protective measles antibody levels (*59*), although the time between revaccination and testing was shorter than in many previous studies.

Table 4: Cross-sectional studies on responses to measles vaccine in HIV-infected children

Author, date of publication (ref)	Year	Country of study	Age at vaccination in months (range)	Assay	HIV-infected % with measles antibody (N)	HIV-uninfected % with measles antibody (N)
Rudy (1) 1994 (211)	1994	USA	(6-12)	EIA	69 (13)	77.3 (22)
Rudy (2) 1994 (211)	1994	USA	(12-15)	EIA	50 (12)	92.8 (14)
Brena 1993 (212)	1993	USA	median: 16 (14-36)	EIA	55 (20)	92 (13)
Molyneaux 1993 (213)	1993	UK	12	EIA	100 (9)	100 (61)
Waibale 1999 (88)	1999	Uganda	median: 25.3 (16.8-39.7)	EIA	48 (50)	63 (193)
Al-Attar 1995 (61)	1995	USA	median: 16 (14-28)	EIA	59.4 (37)	94 (16)
Jason 1994 (214) [a,c]	1994	USA	—	EIA	41 (199)	57 (126)
Hilgartner 2001 (215) [b,c]	2001	USA	—	EIA	75 (207)	82 (126)

Age at testing; age at vaccination not provided:

[a] median 13.2 years (range 7–19)

[b] mean 13.2 year (range 6–19)

[c] Children with haemophilia

EIA = enzyme immunoassay

Table 5: Prospective studies on responses to measles vaccine in HIV-infected children

Author, date of publication (ref)	Country	Number of Children	Age in Months	Response to Primary Immunization	Response to Repeat Immunization
Oxtoby 1989 (58)	Zaire	37	21	36% of 11 symptomatic 77% of 26 asymptomatic	NA
Krasinski 1989 (216)	USA	8	11-41	25%	NA
Palumbo 1992 (217)	USA	35	12-194	37%	0%[a]
Brena 1993 (212)	USA	2	NA	NA	50%
Frenkel 1994 (218)	USA	4	22-121	NA	0%
Brunell 1995 (219)	USA	11	72-120	NA	36%
Arpadi 1996 (60)	USA	7	31-120	NA	14%
Thaithumyanon 2000 (178)	Thailand	16	9	57%	NA
Moss 2007 (59)	Zambia	50	9	88%	92%[b]
Helfand 2008	Malawi	61	6	59%	64%[c]

[a] Four children received repeat imunization

[b] Antibody levels were not measured prior to revaccination of these 12 HIV-infected children

[c] 45 HIV-infected children were revaccinated at 9 months of age

Immune restoration follows effective highly active antiretroviral therapy (HAART) in many HIV-1-infected children, and can improve the response to revaccination against measles (*64*). Repeat vaccination with MMR vaccine was more likely to result in an antibody responses in children receiving HAART than in children receiving non-HAART antiretroviral regimens (*65*). Deferring vaccination in HIV-1-infected children with advanced immunosuppression until HIV-1 replication is controlled by HAART could result in improved responses to vaccination, and should be considered if they are not at immediate risk of contracting measles. However, antibody responses may wane even in HIV-1-infected children receiving effective HAART (66). Only 73% of 11 children receiving HAART who responded to MMR after reimmunization had measurable antibody levels to measles virus one year later (67).

3.3.1.5 Concurrent acute infections

Although probably uncommon, concurrent acute infections may interfere with the immune response to measles vaccine, but mild illnesses are not a contraindication to measles vaccination (68). Several small studies suggested that illness at the time of measles vaccination, particularly upper-respiratory tract infections, interfered with the protective antibody response to measles vaccination (69-71). However, the majority of studies found that minor illnesses do not interfere with seroconversion following measles vaccination (68;72-75), including studies conducted in the Republic of Haiti (76) and the Rwandese Republic (77) as well as in more developed countries. Neither malaria (78;79) nor malaria chemoprophylaxis (80-82) impair the immune response to measles vaccine, although investigators in the Republic of Gambia speculated that repeated malaria infections may be responsible for waning immunity to measles virus 5–7 years after vaccination (83).

3.3.1.6 Nutritional status

Most published studies have found that malnourished children have equivalent seroconversion rates after measles vaccination compared to children who are well-nourished (76;84-87). In one exception, stunting was found to be significantly associated with low antibody levels to measles virus among Ugandan children (OR 1.8, $P = 0.04$) (88). Although investigators in the Republic of Indonesia found a lower rate of seroconversion among children vaccinated at six months of age who received vitamin-A supplements compared to children who did not (89), subsequent trials have found similar or higher rates of seroconversion among children receiving vitamin-A supplements (90-93). These studies support the World Health Organization policy of administering vitamin-A supplements at the time of measles vaccination (94).

3.3.1.7 Host genetics

Host genetic background affects the likelihood of seroconversion, antibody levels and cellular immune responses following measles vaccination. Polymorphisms in human immune response genes influence immune responses to measles vaccine, including class I and class II human leukocyte antigen (HLA) types and non-HLA alleles (95). Single-nucleotide polymorphisms (SNPs) in cytokine and cytokine receptor genes (96), as well as SNPs in the measles virus receptors (SLAM and CD46) (97), have also been associated with differences in antibody and cellular immune responses to measles vaccine. However, in general, most people develop protective antibody levels after a second dose of measles vaccine, regardless of genetic background.

3.3.1.8 Sex

Several studies reported intriguing sex differences in the immunogenicity (90;98;99) and reactogenicity (100) of measles vaccine, with higher post-vaccination antibody levels and rates of fever and rash in girls. Interest in sex differences in response to measles vaccine was stimulated by reports of increased mortality in girls following receipt of the high-titre measles vaccine (see below — *Adverse events associated with high-titre measles vaccines*). However, sex differences in seroconversion rates were not reported in the majority of studies on the immunogenicity of standard-titre measles vaccine. The immunological basis for any sex differences in the responses to measles vaccines is not known.

3.3.2 Vaccine characteristics

In general, the currently used live, attenuated measles vaccines are effective in inducing protective immunity. At nine months of age, the proportion of children who respond to measles vaccination does not differ substantially between vaccine strains. However, at six months of age, a higher proportion of children respond to the Edmonston-Zagreb vaccine than to the Schwarz vaccine strain (17;101).

3.4 Measurement of protection after immunization

3.4.1 Measures of protection

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

There are several immunological assays used to measure antibodies to measles virus, not all of which measure functional or protective antibodies. Measurement of antibodies to measles virus by the plaque reduction neutralization assay is best correlated 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 protective level of measles neutralizing antibody is estimated to be 200 mIU/mL when based on the First International Reference serum, and 120 mIU/mL when based on the Second International Reference serum (102). The WHO Expert Committee on Biological Standardization recently endorsed the use of the 3rd International Standard for measles antibody and assigned a concentration of 3 IU per ampoule, compared with 5 IU per ampoule for the 2nd International Standard (103).

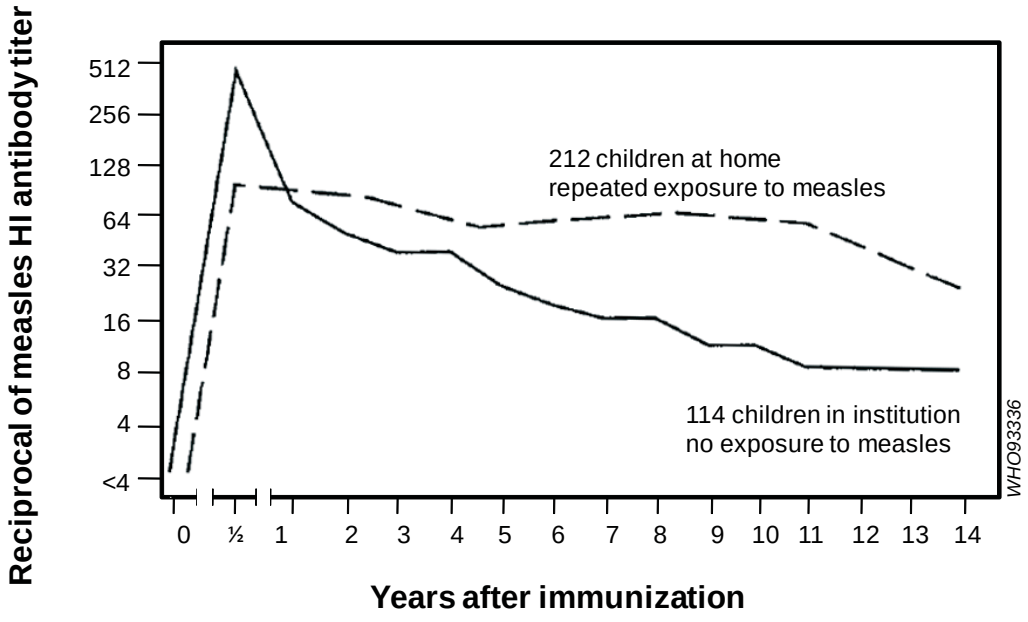
When using the 3rd International Standard Reference serum the level of measles neutralizing antibody that corresponds with clinical protection is ≥120 mIU/mL.

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 assays. Most IgM EIA assays used to diagnose acute measles have a high sensitivity (83%–89%) and specificity (95%–100%) using samples collected 3–28 days after onset of the rash (*10*). However, much of the IgG antibody detected using commercially-manufactured EIA kits are non-protective antibodies to the nucleoprotein (N), and the EIA are less sensitive than plaque-reduction neutralization tests at low antibody levels (104). 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 (105). Due to the variable sensitivity of IgG EIAs it is recommended that all seroepidemiological assessments include a standard calibrating serum. Comparison of results between EIA assays are problematic due to different sources and concentrations of antigens, and thresholds for determining protective antibody levels have not been standardized (101). Although no longer commonly used, haemagglutination inhibition (HI) assays measure the ability of cross-reacting antibodies to measles virus to block agglutination of monkey red-blood cells.

3.4.2 Duration of protective immunity

The duration of immunity following measles vaccination is more variable and shorter than following wild-type measles virus infection, but persists for decades. Even in countries where measles is no longer endemic, antibodies to measles virus persist for years (Table 6, Figure 5) (106-108). In countries where measles remains endemic, or in early studies where measles vaccine coverage rates were low, immune responses may be boosted by re-exposure to wild-type measles virus (*26*). The antibody levels induced by vaccination decline over time and may become undetectable. Nevertheless, immunological memory persists and, following exposure to measles virus, most vaccinated persons produce a measles virus-specific immune response without clinical symptoms.

Figure 5: Measles antibody response and persistence following immunization with Schwarz vaccine



Adapted, by permission of the publisher, from Krugman S, 1977 (224).

3.5 Unintended immunological consequences of measles vaccination

3.5.1 Adverse events associated with live attenuated measles vaccines

Adverse events following measles vaccination are generally mild and transient, and result from host immune responses to replicating vaccine virus. Mild pain and tenderness may occur at the site of injection. Fever of at least 39.4 °C occurs in approximately 5% of recipients 7–12 days following measles vaccination, and a transient rash occurs in approximately 2% of recipients (*16*). These signs and symptoms are a consequence of the host immune response to replicating measles vaccine virus, but do not result in serious morbidity or mortality. Rarely, thrombocytopenia (low number of platelets) may occur (109), similar to the transient idiopathic thrombocytopenic purpura that follows acute infections. These adverse events are less likely to occur following a second dose of measles vaccine.

Allergic reactions to vaccine components, including neomycin and the stabilizers gelatin or sorbitol, can follow measles vaccination. Anaphylactic reactions are rare, occurring in one in 20 000 to one in 1 000 000 vaccinees (*16*). There is no association between a history of egg allergy and allergic reactions to measles vaccines (*16*).

Table 6: Measles antibody response and persistence following vaccination with a single dose of measles vaccine

Author, date of publication (reference)	Country of study	Age at vaccination	Vaccine strain	Assay	Years since vaccine	% with measles antibodies
Brown et al, 1969 (220)	Pacific Atoll: Ulithi	5 years	Edmonston B	HI	5	95
Arbeter et al, 1972 (221)	USA	≥12 months	Edmonston B+ immunoglobulin	HI	6–9	100
Bass et al, 1976 (183)	Hawaii	NA	NA	HI	8	83
Yeager et al, 1977 (222)	USA	≥13 months	NA	HI	12–14	93
Shasby et al, 1977 (223)	USA	>12 months	NA	HI	9	91
Krugman, 1977 (224)	USA	NA	Schwarz	HI	14	99
Krugman, 1977 (224)	USA	NA	Schwarz	HI	12	91
Krugman, 1977 (224)	USA	NA	Edmonston B+ immunoglobulin	HI	12	100
Balfour & Amren, 1978 (225)	USA	≥14 months	Moraten	HI	6.5	95
Weibel et al, 1979 (226)	USA	Na	Schwarz, Moraten	HI	10	100
Weibel et al, 1979 (226)	USA	Na	Edmonston B	HI	10	93
Krugman, 1983 (227)	USA	3–9 years	Schwarz	HI	16	87
Peradze & Smorodintsev, 1983 (228)	Former Soviet Union	10 months–8 years	Leningrad-16	HI	11–15	94
Xiang & Chen, 1983 (229)	China	8–27 months	Shanghai-191	HI	8	87
Orenstein et al, 1986 (230)	USA	>15 months	NA	HI	10–14	94
Pedersen et al, 1986 (231)	Greenland	5–68 years	Schwarz	EIA	16	70
Isomura et al, 1986 (232)	Japan	3–5 years	CAM-70	HI	12	100
Miller, 1987 (106)	England and Wales	10 months–2 years	Schwarz	HI	15	100
Gustafson et al, 1987 (233)	USA	12–24 months	NA	EIA	11–17	95

Table 6: Measles antibody response and persistence following vaccination with a single dose of measles vaccine *(cont'd...)*

Author, date of publication (reference)	Country of study	Age at vaccination	Vaccine strain	Assay	Years since vaccine	% with measles antibodies
Dai Bin et al, 1991 (234)	China	8–12 months 13–16 months	HU191	HI	14	87.2 91.9
Dai Bin et al, 1991 (234)	China	8–12 months 13–16 months	Chang47	HI	14	88.9 89.8
Dai Bin et al, 1991 (234)	China	8–12 months 13–16 months	Schwarz	HI	14	84.6 90.3
Dai Bin et al, 1991 (234)	China	8–12 months 13–16 months	L-16	HI	14	87.3 80.0
Flugsrud et al, 1997 (108)[a]	Norway	2 years	Schwarz	ELISA	18	92.3
Whittle et al, 1999 (83)	Senegal	10 months	Schwarz	HI	5–7	81
van den Hof et al, 1999 (235)	The Netherlands	14 months	MMR	ELISA	6	91.4
Viviani et al, 2004 (236)	The Gambia	9 months	NA	HI	3–4 8–9	91.4 96.0

[a] 79% also received a second dose at 12–13 years of age

Updated, by permission of the publisher, from Markowitz et al. 1990, (104).

NA = information not available.
HI = haemagglutination inhibition assay
EIA = enzyme immunoassay
ELISA = enzyme linked immunosorbent assay

3.5.2 *Adverse events associated with formalin-inactivated measles vaccine*

In the 1960s, a formalin-inactivated, alum-precipitated measles vaccine (FIMV) was licensed and administered to children in the United States. Three doses of inactivated vaccine elicited a protective antibody response that waned within months (110). Up to 60% of immunized children exposed to measles developed an unusual immunological response called atypical measles, characterized by high fever, inflammation of the lungs (pneumonitis), and a petechial rash on the extremities (111;112) and this lead to withdrawal of the FIMV in 1967. In a rhesus macaque model, atypical measles was shown to be associated with immune complex deposition in affected tissues and a systemic and pulmonary eosinophilia (113). The antibody response consisted of high levels of complement-fixing antibodies with low avidity for measles virus, characteristics that may have promoted exaggerated immune complex formation and disease. Atypical measles is not seen after exposure to wild-type measles virus in children who received live, attenuated measles vaccines.

3.5.3 *Adverse events associated with high-titre measles vaccines*

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. Seroconversion rates in four to six month old infants immunized with high-titre measles vaccine were comparable to those of nine to 15 month old children vaccinated with standard-titre measles vaccine (*17*), but high-titre measles vaccine resulted in a poorly understood increase in mortality in immunized girls 1–2 years after vaccination in some developing countries, compared with girls immunized with standard-titre vaccine at nine months of age (114;115). The high-titre measles vaccine was withdrawn and is no longer used. The pathogenesis of the delayed increased mortality after the high-titre vaccine is not understood, but may be related to long-term suppression of immune responses similar to that induced by wild-type measles virus, or to alteration of immune responses associated with a change in the sequence of childhood vaccination (116).

3.5.4 *Adverse events in HIV-infected persons*

Although assumed to be rare, the risk of disease caused by attenuated measles vaccine virus in HIV-1-infected persons is unknown. The only documented case of fatal disease associated with measles vaccine virus in an HIV-1-infected person was in a 20 year old man in the United States who died 15 months after receiving his second dose of measles vaccine (117). He had a very low CD4+ T-lymphocyte cell count but no HIV-1 related symptoms at the time of vaccination. Ten months later he developed a giant cell pneumonitis, and measles vaccine 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 (118), and measles inclusion body encephalitis caused by vaccine virus was reported in a child with an uncharacterized immune deficiency (119). However, there is no evidence that measles vaccines cause or accelerate the course of SSPE in immunocompromised or immunocompetent persons (120).

3.5.5 Adverse events incorrectly associated with measles vaccine

Much public attention has focused on a purported association between measles, mumps and rubella (MMR) vaccine and autism following publication of a report in 1998 hypothesizing that MMR vaccine may cause a syndrome of autism and intestinal inflammation (121). 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 simple temporal association was misinterpreted and misrepresented 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. Subsequently, several comprehensive reviews and additional epidemiological studies rejected evidence of a causal relationship between MMR vaccination and autism (122). 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% confidence interval, 0.68–1.24) (123).

3.5.6 Potential nonspecific benefits of measles vaccination

A group of investigators has suggested that vaccination with standard-titre measles vaccine, or mild infection with wild-type measles virus, may have nonspecific beneficial effects resulting in reduced child mortality in excess of deaths attributable to measles (124-126). However, no plausible immunological explanation has been put forth, and the hypothesis that measles vaccination results in a nonspecific reduction in childhood mortality remains controversial and unproven, and is based on potentially biased or confounded data (127;128).

4. Prospects for improving immune response with new measles vaccines

The live attenuated measles vaccines currently used have a history of proven safety and effectiveness over the past 40 years, and have resulted in dramatic reductions in measles incidence, morbidity and mortality. However, the vaccines currently used 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 needle or syringe. The age at vaccination would ideally coincide with other vaccines in the Expanded Programme on Immunization (EPI) schedule to maximize compliance and share resources. Finally, a new vaccine should not prime individuals for atypical measles upon exposure of immunized individuals to wild-type measles virus (MV) (a complication of formalin-inactivated measles vaccines), and should not be associated with prolonged immunosuppression, adversely affecting immune responses to subsequent infections (a complication of high-titre measles vaccines).

Several candidate vaccines with some of these characteristics are undergoing development and testing. Naked cDNA vaccines are thermostable and inexpensive and could theoretically elicit antibody responses in the presence of passively-acquired maternal antibody. Deoxyribonucleic acid (DNA) vaccines encoding either or both the measles H and F proteins are safe, immunogenic and protective against measles challenge in naive, juvenile rhesus macaques (129). A different construct, containing H, F and N genes and an IL-2 molecular adjuvant, provided protection to infant macaques in the presence of neutralizing antibody (130;131). Alternative techniques for administering MV genes, such as alphavirus (132), parainfluenza virus (133) or enteric bacterial (134) vectors, are also under investigation. New oral immunization strategies have been developed using plant-based expression of the MV H protein in tobacco (135).

Aerosol administration of measles vaccine was first evaluated in the early 1960s in several countries, including in the former Soviet Union and the United States. More recent studies in the Republic of South Africa (136) and the United Mexican States (137) have shown that aerosol administration of measles vaccine is highly effective in boosting antibody levels, although the primary humoral and cellular immune responses to aerosolized measles vaccines are lower than following subcutaneous administration at nine (138) and 12 months of age (*38*). A systematic review and meta-analysis concluded that the seroconversion rate with aerosolized measles vaccine was 94% in children 10 to 36 months of age, compared with 97% for subcutaneously administered vaccine (139). Measles antibody levels and the proportion of children who were seropositive six years after revaccination were significantly higher among children who received aerosol vaccine compared with those who received measles vaccines subcutaneously, suggesting a stronger and longer-lasting antibody response after revaccination with aerosol measles vaccine (140). Administration of measles vaccine by aerosol has the potential to facilitate measles vaccination during mass campaigns and eliminate the medical waste problems associated with needles and syringes, and the World Health Organization is working to test and bring to licensure an aerosol measles vaccine by 2009.

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The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization, Vaccines and Biologicals (IVB).

IVB's mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director's Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.

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