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The Immunological Basis for Immunization Series

Module 7:

Measles

GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION
EXPANDED PROGRAMME ON IMMUNIZATION

World Health Organization
Geneva

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Module 7:

Measles

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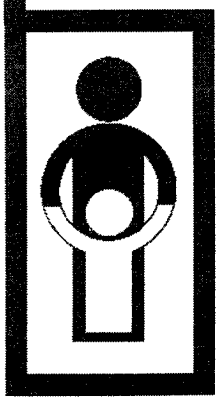

GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION
EXPANDED PROGRAMME ON IMMUNIZATION

World Health Organization
Geneva

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The Immunological Basis for Immunization **series is available in English and French (from the address below). It has also been translated by national health authorities into a number of other languages for local use: Chinese, Italian, Persian, Russian, Turkish, Ukranian and Vietnamese. The series comprises eight independent modules:**

Module 1: General Immunology
Module 2: Diphtheria
Module 3: Tetanus
Module 4: Pertussis
Module 5: Tuberculosis
Module 6: Poliomyelitis
Module 7: Measles
Module 8: Yellow fever

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Contents

Preface

This series of modules on the immunological basis for immunization has grown out of the experience of persons working with the WHO Expanded Programme on Immunization (EPI). The EPI was established in 1974 with the objective of expanding immunization services beyond smallpox, with emphasis on providing these services for children in developing countries.

Six vaccine-preventable diseases have been included within the EPI since its beginning: diphtheria, measles, pertussis, polio, tetanus, and tuberculosis. To protect newborns against neonatal tetanus, tetanus toxoid is administered to the mother either during her pregnancy or prior to pregnancy during the childbearing years.

Two more vaccine preventable-diseases will be addressed by the EPI during the 1990s. The World Health Assembly has set the target of including yellow fever vaccine in the EPI by 1993 in countries where this disease poses a risk. Hepatitis B vaccine is being added gradually, with the target date of 1997 for incorporation of this vaccine in the immunization programme in all countries.

Titles of the nine modules in this series are listed inside the front cover of this module. They are intended to provide information on the immunological basis for WHO-recommended immunization schedules. They have been prepared for the following main audiences:

- immunization programme managers, whose questions and concerns caused this series to be written,
- consultants and advisers on immunization activities,
- teachers of courses on immunization at the university level and facilitators of workshops,
- medical and nursing students as part of the basic curriculum,
- laboratory scientists providing diagnostic or research services for vaccine-preventable diseases, and
- scientists involved in basic research aimed at improving the delivery of vaccines or providing improved vaccines.

Other modules in this series and additional materials on the EPI are available from the Expanded Programme on Immunization, World Health Organization, 1211 Geneva 27, Switzerland.

Measles

1. The Organism and the Disease

1.1 Measles disease

Measles is a ubiquitous, highly infectious disease affecting nearly every person in a given population by adolescence in the absence of immunization programmes *(Black 1982).* Measles is transmitted primarily from person-to-person by large respiratory droplets *(Black 1982),* but can also be spread by the airborne route as aerosolized droplet nuclei *(Bloch et al. 1985).* Measles is most infectious during the prodrome. First there is localized infection of the respiratory epithelium of the nasopharynx and possibly the conjunctivae, with spread to regional lymphatics. Primary viremia occurs 2 to 3 days following exposure, and an intense secondary viremia occurs 3 to 4 days later. The secondary viremia leads to infection of and further replication in the skin, conjunctivae, respiratory tract and other distant organs. The amount of virus in blood and infected tissues peaks 11 to 14 days after exposure and then falls off rapidly over the next 2 to 3 days.

These events correspond with an incubation period between exposure and the onset of symptoms of 10 to 12 days. The prodomal period then begins, with fever, malaise, conjunctivitis, coryza, and tracheobronchitis. Koplik spots appear on the buccal mucosa 1 to 2 days before rash onset and may be noted for an additional 1 to 2 days after rash onset. The rash is an erythematous maculopapular eruption that usually appears 14 days after exposure and spreads from the head to the extremities over a 3 to 4 day period. Over the next 3 to 4 days, the rash fades; in severe cases desquamation may occur. Other constitutional signs and symptoms, such as anorexia, diarrhea and generalized lymphadenopathy may also be present *(Preblud & Katz 1988).*

In industrialized countries, the most commonly cited complications associated with measles infection are otitis media (7% to 9%), pneumonia (1% to 6%), postinfection encephalitis (l/1000 to l/2000 cases), subacute sclerosing panencephalitis (SSPE) (l/100 000 cases) and death (l/10 000 cases) *(Preblud & Katz 1988).* The risk of serious complications and death is increased in young children and adults *(Black 1982).* SSPE is a rare degenerative central nervous system disease caused by a persistent infection with a defective measles-like virus *(Sever 1983),* which develops approximately 7 years after measles infection. Patients develop progressive personality changes, myoclonic seizures, and motor disability, leading to coma and death. SSPE is more common in males than females.

In developing countries, case-fatality rates (CFR) are similar to those found in developed countries in the 1800s *(Morley et al. 1963).* Community studies have shown CFRs varying from 3% to 15% *(Cutts et al. 1991).* CFRs vary depending on the age at infection, intensity of exposure, nutritional status, and availability of treatment.

1.2 Measles antigen

Measles virus is a member of the genus *Morbillivirus* in the family Paramyxoviridae *(Kingsbury et al. 1988),* and is closely related to canine distemper and rinderpest viruses *(Imagawa 1968).* Measles viruses are spherical, enveloped single stranded RNA viruses *(Norrby 1966).* There are six identified structural proteins; three proteins complexed with viral RNA, and three proteins in the virus envelope.

The envelope components comprise the M protein in the inner surface and the H and F proteins on the outer surface. The H protein attaches the virus to cell surfaces. The F protein fuses virus and cell membranes, allowing viral penetration of the cell and cell destruction.

In cell cultures, measles virus causes a distinct cytopathic effect (CPE): the formation of multinucleated syncytia (i.e. giant cells), containing numerous nuclei of fused cells. This CPE corresponds to the pathological process observed in infected tissues, including skin rash and Koplik spots *(Suringa et al. 1970).*

1.3 Measles vaccines

The development of live attenuated measles virus vaccines began soon after the isolation of the virus by Enders and Peebles *(1954).* By the end of the

1950s, Enders and colleagues had developed the Edmonston B strain of live attenuated measles vaccine by subjecting the virus to 24 passages in primary human renal cell cultures, 28 passages in primary human amnion cell cultures, and six serial chick embryo passages before adapting the virus to chick embryo fibroblasts *(Enders 1962).*

Because the Edmonston B vaccine was often associated with a rash and fever greater than 39.5°C *(Krugman et al. 1962),* gamma globulin was often administered simultaneously as this was found to reduce the occurrence of high fever and rash by approximately 50% *(Krugvnan et al. 1963).*

By the mid to late 1960s, new strains of measles vaccine had been developed in the USA, Japan, Yugoslavia, the USSR, and China, by further attenuation of Edmonston (AIK-C), Edmonston A (Schwarz), Edmonston B (Moraten, Edmonston Zagreb) or separate isolates (Leningrad 16, CAM-70, Shanghai-191) (Figure 1). Further attenuation was first achieved by Schwarz by 85 additional passages of Edmonston A virus in chick embryo fibroblast cultures at 32°C, instead of 36°C to 37°C *(Schwarz 1964).* Although antibody levels attained after further attenuation (e.g. Schwarz vaccine) were lower than those after Edmonston B vaccine or natural infection, further attenuated vaccines were associated with lower rates of clinical reactions and were suitable for widespread use without the need for concurrent administration of gamma globulin.

1.3.1 Inactivated vaccine

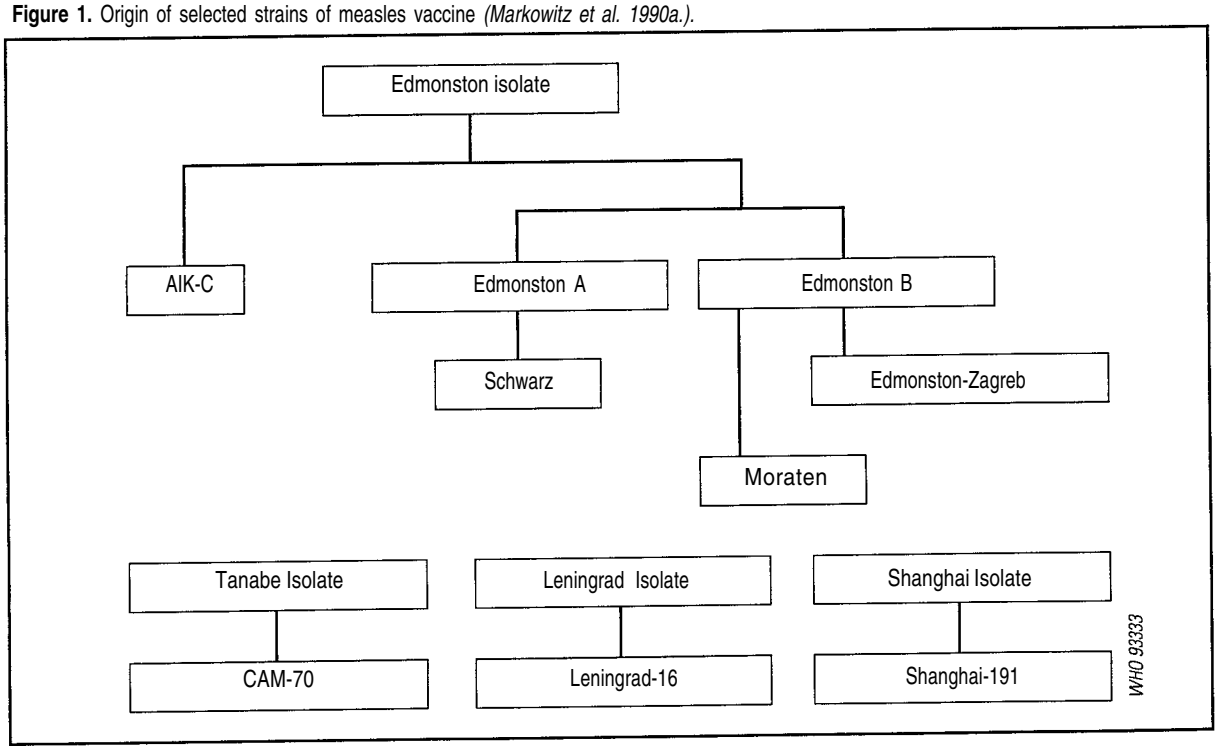
One of the first measles vaccines was a formalin-inactivated vaccine derived from the Edmonston strain. Usually, three doses of inactivated vaccine or two doses of inactivated and one dose of live vaccine were administered at monthly intervals, with few side effects *(Krugman et al. 1965).* Use of inactivated vaccine was stopped in 1967, when it was realised that immunity was short-lived, and that recipients were at risk of atypical measles on exposure to live measles virus *(ACIP 1967).*

1.3.2 Vaccine potency measurements

The World Health Organization (WHO) requirements describe two alternative ways of determining the potency of live measles vaccine: by measurement of plaque forming units (PFU) or by determinations of tissue culture infective doses (TCD_{50}), both methods being conducted in Vero *cells (Expert Committee* on *Biological Standardization 1966, 1982, 1988).* The potency measurements vary depending on the method of determination, the laboratory, and the conditions at the time of the test. An International Reference Reagent is available to help standardize reporting of potency measurements.

In 1988, WHO recommended that "the virus content in each of at least 3 vials selected at random from each lot shall be determined individually. The national control authority shall determine the minimum content of the vaccine virus that should be contained in one human dose. The minimum quantity of the vaccine virus that should be contained in one human dose is generally considered to be 1000 (3.0 log,,) viral infective units" *(Expert Committee on Biological Standardization 1988).*

Figure 1. Origin of selected strains of measles vaccine *(Markowitz et al. 1990a.).*



To demonstrate that vaccines meet the WHO potency and stability requirements (see "vaccine stability" below), two vials of the test vaccine and two vials of the reference vaccine must be tested in parallel. For the assay to be considered valid, the mean level of the reference vaccine as measured in the laboratory must not deviate more than 0.5 log,, from the established titer, and the variation between the two vials of test vaccine or the two vials of the reference vaccine must not exceed 0.5 $\log_{10}$ *(Biologicals Unit 1989).*

A collaborative study performed under contract for WHO showed that when potency values for measles vaccine were expressed relative to that of the International Reference Reagent, interlaboratory variation was substantially reduced *(Milstien 1990). WHO* therefore recommends that when vaccine potency tests are conducted, the reference vaccine be tested in parallel and the results obtained for the reference vaccine be reported together with the potency of the vaccine under test *(Clements et al. 1988).*

1.3.3 Vaccine stability

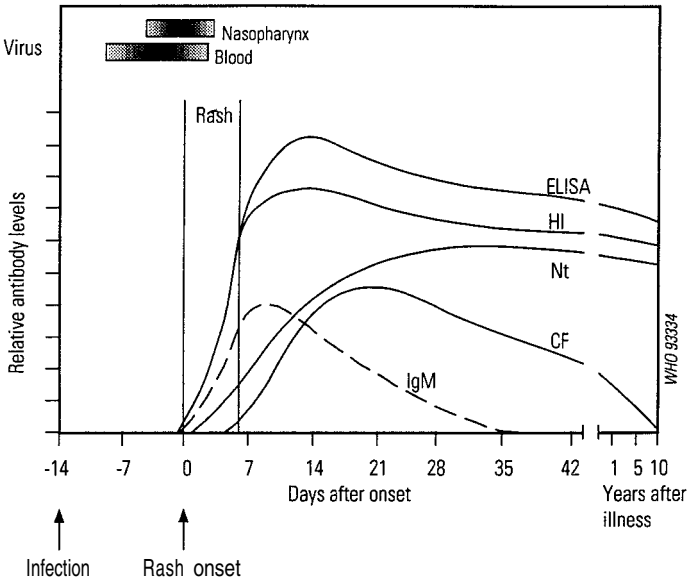
Prior to 1980, measles vaccines were heat-labile, causing difficulty in their use in the tropics *(Hendrickse 1975).* The development of effective stabilizers and the formulation of the WHO requirements for heat stability for freeze-dried measles vaccine *(Expanded Programme on Immunization 1981)* have considerably improved the quality of measles vaccines available since 1980, although there are still variations in the stability of vaccines produced by different manufacturers.

In the freeze-dried state, present measles vaccines which 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, and the virus titer does not decrease by more than 1.0 $\log_{10}$ during incubation *(Expanded Programme on Immunization 1990).* However, reconstituted measles vaccines quickly lose their potency at exposure to room temperatures. At 22°C to 25°, they suffer approximately 50% loss in potency in one hour. At temperatures over 37°C they are inactivated within one hour. It is therefore extremely important to keep reconstituted measles vaccine cool and protected from sunlight.

2. The Immunological Response to Natural Infection

In primary acute infection, T-cell *(Graziano et al. 1975)* and B-cell *(Norrby & Gollman 1972)* responses can be detected to most of the six measles virus proteins. Both IgG and IgM antibodies are initially produced, however IgM antibodies peak at 7 to 10 days after rash onset and fall rapidly, rarely being detectable more than 4 weeks after rash onset. Serum and secretory IgA are also produced but are usually transient *(Pederson et al. 1986).*

Figure 2. The antibody response in acute measles infection *(Preblud and Katz, 1987).*



IgG antibody: ELISA; H I= hemagglutination inhibition; Nt = neutralization assay; CF= complement fixation

The presence of IgM is generally accepted as evidence of primary measles infection (by disease or vaccine). However, absence of IgM does not exclude infection, as the sensitivity of some IgM assays is low *(Schluederberg et al. 1973),* and the timing of specimen collection is important, because of the short-lived IgM response (Figure 2) *(Heffner & Schluederberg 1967).* Furthermore, IgM has been detected in secondary responses to some other viral infections such as rubella *(Grangoe-Keros et al. 1985),* and it is theoretically possible that this may occur in measles.

IgG becomes detectable in the serum soon after rash onset, peaks within about 4 weeks and subsequently declines, but persists for life (Figure 2) *(Stokes et al.* 1961). The IgG antibodies to the H protein appear to be most important in determining immunity *(Black 1989).* Immunity after natural infection is usually lifelong *(Panum 1940).* Of interest is the immune response in patients with SSPE. Although these patients have high titers of measles-specific antibodies in the sera and cerebrospinal fluid, there appears to be a relative lack of synthesis of antibody against the M protein.

Measles infection is diagnosed serologically by either detecting IgM or demonstrating a significant rise in IgG between paired acute and convalescent sera. Measles-specific IgM is often measured by ELISA

Figure 3. Antibody response 4 weeks post-vaccination with Edmonston B measles vaccine among 75 children, Upper Volta, *(Meyer et al. 1964)*

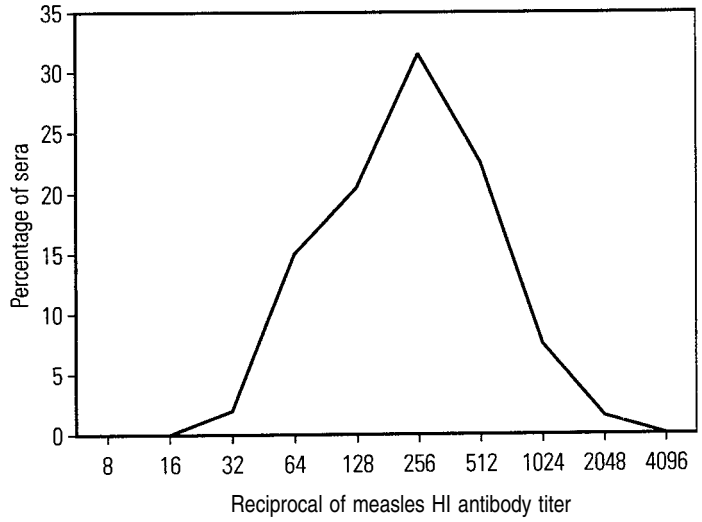
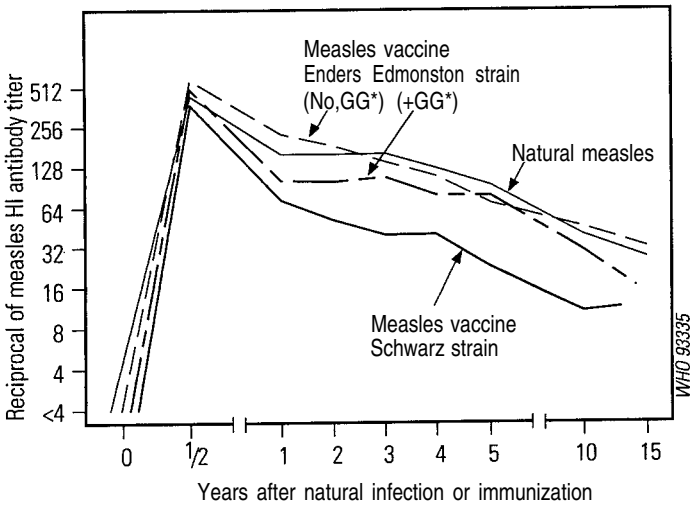
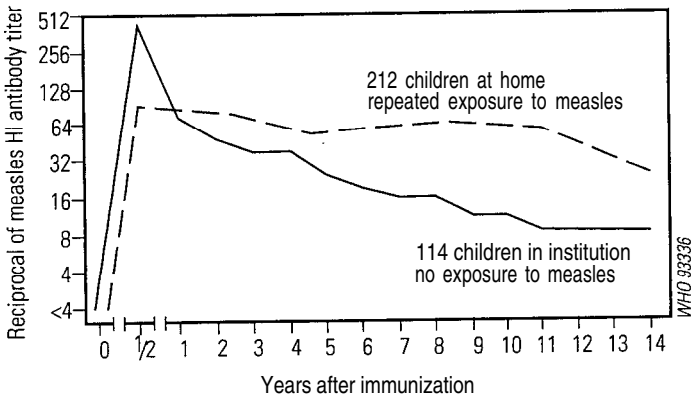


Figure 4. Measles antibody response and persistence after natural infection or immunization *(Krugman 1977).*



* GG = gamma globulin

Figure 5. Measles antibody response and persistence following immunization with Schwarz vaccine in 212 home-dwelling and 114 institutionalized children *(Krugman 1977).*



assays. Early assays used an indirect method, which had the disadvantage of false positive reactions produced by interference by IgM rheumatoid factor. Modern assays may use a more highly purified IgM in antibody capture assays, which is unlikely to show interference from rheumatoid factor *(Tuokko 1984).*

For IgG, the paired specimens should be analyzed in the same laboratory in the same test procedure, so that variations in test conditions do not reduce the comparability of the two results. A significant rise is usually taken to be a rise in antibody titer by a factor of at least two twofold dilutions (fourfold increase) between the first and second specimens *(Centers for Disease Control 1982),* or a change from an undetectable antibody level (seronegativity) to seropositivity. For ELISA results, data are expressed in optical density (OD), and the convalescent serum result is divided by the acute serum result to compute a ratio. Evidence of recent or acute infection is given by a ratio equal to or greater than a value defined by comparison with paired reference sera.

Cell-mediated immunity plays an important role in recovery from, and possibly, prevention of measles, and it has been postulated that sufficient stimulation of cell-mediated immunity may be a prerequisite for the development of lifelong protection *(Gallagher et al. 1981).* However, tests for cell-mediated immunity are less readily available than those for humoral immunity.

Acute measles infection is associated with a wide range of immunological abnormalities, including depressed general cellular reactivity (manifest, for example, in a depressed delayed hypersensitivity reaction to the tuberculin test *(Hirsch et al. 1984),* and cytokine production abnormalities. Studies are in progress to elucidate further the mechanisms of immune disruption after measles and possible variation by age at infection.

3. The Response to Immunization

3.1 Description of the serological response

At present, no serological tests can distinguish between antibody, whether IgG or IgM, produced by measles infection and that produced by immunization. The levels of antibody induced by immunization with attenuated measles virus vary with an approximately log-normal distribution (Figure 3), and reach lower peak levels than those induced by wild virus *(Krugman et al. 1965).* Antibody loss is quicker after further attenuated vaccines than after the early vaccines (Figure 4). Some data suggest that the rate of

antibody decline is faster among persons who attain the highest antibody levels post-immunization, so that the range of levels narrows with time *(Uedu et al. 1974).*

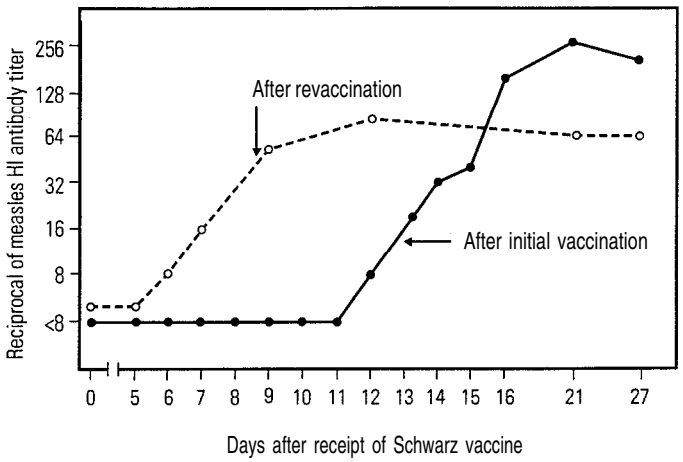
Antibody persists longer when there is boosting from exposure to circulating wild virus (Figure 5) *(Krugman 1983, Zhang & Su 1983).* However, even in isolated communities, antibodies have been shown to persist for at least 16 years after immunization *(Krugman 1983, Xiang & Chen 1983, Zhang & Su 1983).* The mechanism for maintenance of detectable antibody levels in the absence of reexposure is not known *(Black 1989).*

When measles antibody falls to low levels, re-exposure to measles virus (wild or vaccine virus) stimulates memory cells, which remain dormant after the initial infection and are primed to produce a measles-specific response. An anamnestic (secondary) immune response occurs, in which IgG levels rise rapidly and peak approximately 12 days after reinfection (Figure *6) (Krugrnan et al. 1965, Schluederberg et al. 1973).* If antibody levels are high prior to exposure, reinfection is prevented and a boost is rarely seen *(Krugman 1983, Zhang & Su 1983, Zhugi 1987).*

The choice of serological assay is important in evaluating the response to immunization. Because post-immunization antibody levels may be low, the sensitivity of the serological assay used is important. Both plaque neutralization (PN) assays (a modification of the neutralization assay described in Module 1 of this series) and ELISA assays are more sensitive than hemagglutination-inhibition (HI) assays *(Orenstein et al. 1987).* Although ELISA assays are quicker and cheaper to perform than PN assays, they may be less specific, depending on the manufacturer of the kit, the laboratory, and the type of antigen. ELISA assays often use supernatant fluid from measles virus-infected cultures as antigen, and hence measure the sum of antibodies to all structural and non-structural viral protein. Some ELISA tests use purified virus as antigen, and in this case, if the virus is not disrupted during the purification process, antibodies to the envelope proteins are measured.

Because of the inherent variation in assays, antibody levels measured in one laboratory may differ from those obtained in another laboratory. To assist in the standardization of serological assays, the Expanded Programme on Immunization (EPI) urges laboratories to test reference sera, calibrated against the International Standard for anti-measles serum, in parallel with the sera under study. One ampoule of International Standard serum contains 5 international units (IU). When the antibody content of the reconstituted standard is determined in the run together with that of the test serum, the test results can be converted to international units. An alternative to expressing antibody levels for the test sera in international units is to report the test and standard results separately *(Clements et al. 1988).*

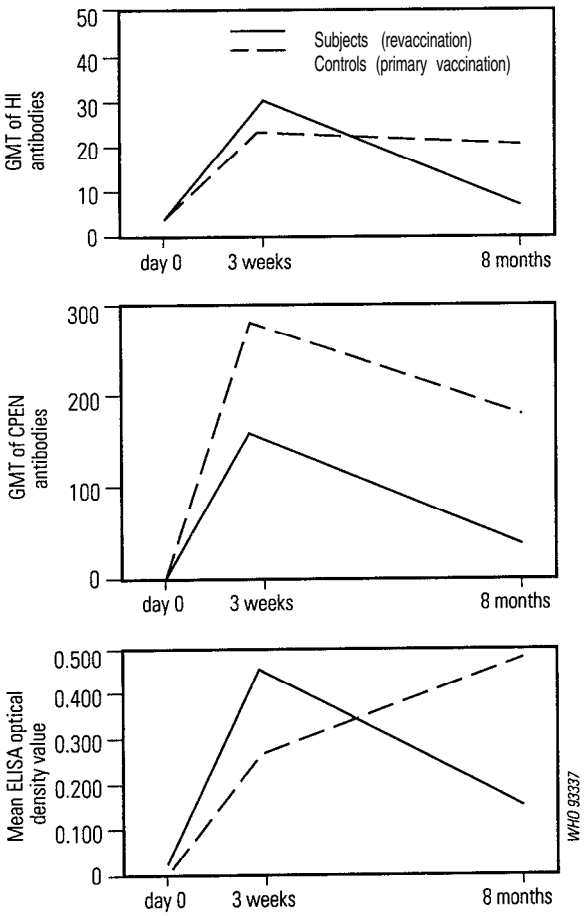
Figure 6. Antibody responses following vaccination and revaccination of children with non-detectable antibody levels pre-vaccination *(Krugman et al, 1965).*



Although use of the International Reference Serum will improve standardization, results from different assays may still be difficult to compare because they measure antibody to different measles antigens or epitopes *(Black 1989).* For example, a study in 1980 compared persistence of antibody after reimmunization of children first immunized at under 12 months of age with that in a control group whose primary immunization was at age 15 months *(Stetler et al. 1986).* Antibody levels in the control group were maintained according to the HI test, decreased almost in parallel with the study group by the neutralization test, and increased markedly by the ELISA assay (Figure 7).

Many recent vaccine trials have evaluated the response to different measles vaccines in young infants who still have maternal measles antibody (see section 3.2.2). Measurements of maternal antibody by ELISA have correlated poorly with those from PN tests *(Sabin et al. 1984),* and the HI assay is relatively insensitive. Hence the PN assay is the assay of choice to evaluate the serological response to immunization in young infants. In the assessment of the response to immunization among infants with detectable pre-vaccination maternal antibody, the post-immunization antibody level is compared with the predicted level, after allowing for the estimated decay of maternal antibody over the interval between the pre- and post-immunization samples. The half-life of maternal measles antibody varies in different populations and individuals (see section 3.2.1), and reported estimates for the half-life of maternal antibodies have varied from 21 days *(Wilkins & Wehrle 1978)* to 45 days *(Black 1989).*

Figure 7. Geometric mean titers of hemagglutination inhibition (HI) and neutralization (CPEN) antibodies, and mean ELISA optical density values 8 months post-immunization or reimmunization *(Stetler et al. 1986).*



The immune response to inactivated vaccine was different from that to live virus. The immunogenicity of the F component was destroyed during the inactivation process, hence persons who received inactivated vaccines had a pronounced antibody response against the hemagglutinin protein but no anti-F component immunity. Virus infection, fusion of cells, and cell-to-cell spread could still occur because the F protein was not neutralized by antibody. Delayed-type hypersensitivity reactions occurred after exposure to wild virus, producing "atypical measles", characterized by headache, fever, myalgia, and a hemorrhagic or vesicular rash often accompanied by pneumonitis *(Annunziato et al. 1982).*

3.2 Determinants of response to immunization

3.2.1 Host factors

Age

The response to immunization increases up to the age at which all children have lost maternal antibody (Tables 1 and 2). The major reason for the age-dependent response appears to be the maternal antibody level pre-immunization.

Maternal antibody level

Early studies on the waning of maternal antibody used relatively insensitive HI tests, and it was initially thought that maternal antibodies were lost by 12 months of age in the USA *(Krugman et al. 1965)* and by age 6 months in developing countries *(MOH Kenya 1977).* Use of more sensitive tests subsequently showed that antibodies persisted in *some* children for several months longer and reduced the effectiveness of immunization *(Albrecht et al. 1977).*

Maternal antibody profiles of infants vary between geographic regions. The rate of loss of maternal antibody among different populations has been found to correlate inversely with socioeconomic status *(Black et al. 1986).* Reasons for earlier loss of maternal antibody in developing countries include lower antibody levels among mothers (particularly in southeast Asia), decreased efficiency of transplacental transfer of measles IgG, increased catabolism of passive antibody because of frequent infections in infancy, and loss of antibody into the intestinal lumen during diarrheal illness *(Black 1989).*

Until recently, even a low level of maternal antibodies has inhibited successful seroconversion after immunization *(MOH Kenya 1977, Wilkins & Wehrle 1979).* Recent studies have shown that seroconversion can be achieved in the presence of maternal antibody by using higher doses of certain vaccine strains (see section 3.2.2); however, seroconversion is still related to the level of maternal antibody (Figure 8). In many studies, including those using Edmonston Zagreb (EZ) vaccine, antibody levels have been lower after immunization in the presence of maternal antibody than after immunization of children without maternal antibody *(Markowitz et al. 1990c, Tidjani et al. 1989, Wilkins & Wehrle 1979).*

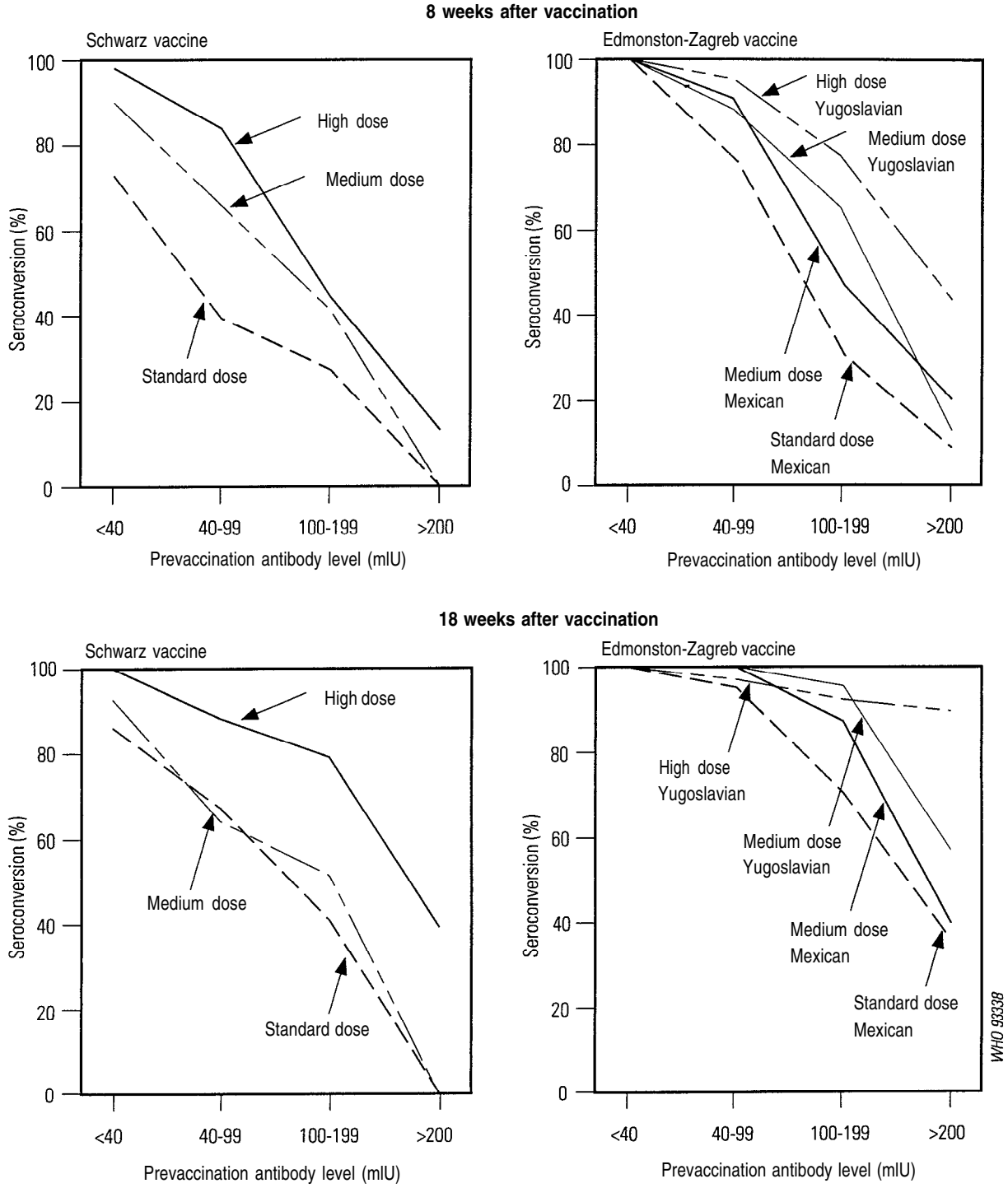
Nutritional status

Several studies have reported seroconversion rates at least as high in malnourished as in well-nourished children *(Halsey et al. 1985, PAHO 1982)* although Wesley et al. (1978) reported that the response to measles immunization was delayed among malnourished children. Because of the risk of severe disease and worsening nutritional status after measles, the EPI recommends that high priority be given to the immunization of malnourished children *(Expanded Programme on Immunization 1986).*

Intercurrent illness

Acute illness. Measles immunization of children with acute illnesses in developing countries has been shown to be safe and effective *(Halsey et al. 1985, Ndikuyeze et al. 1988).* A small study in the United

Figure 8. Sero conversion rates 8 and 18 weeks after immunization with Schwarz and Edmonston-Zagreb measles vaccines, according to maternal antibody level pre-immunization, determined by the plaque neutralization assay *(Markowitz et al. 1990c).*



States found lower seroconversion rates after measles-mumps-rubella (MMR) vaccine in 15 to 18 month old afebrile children with rhinorrhea compared to controls without rhinorrhea (37/47 and 50/51 infants, respectively, seroconverted at 6 to 8 weeks post-immunization) *(Krober et al. 1991).* These results are contrary to previous larger studies in Haiti (81% of infants with rhinorrhea and 78% of infants without rbinorrhea seroconverted) *(Halsey et al. 1985)* and Rwanda (81% of ill and 80% of well infants seroconverted) *(Ndikuyeze et al. 1988).* Preliminary data from recent larger studies in the United States have also shown no difference in seroconversion among children with upper respiratory tract infection compared to well children. Immunization of ill hospitalized children has considerably diminished the incidence of nosocomial measles in studies in South Africa *(Harris 1979)* and Costa Rica *(De Coto*

1983). WHO therefore recommends that measles immunization not be withheld from children with acute illness. Immunization of children who require hospitalization should be considered on a case-by-case basis, but eligible children should receive measles vaccine on admission wherever possible, and at a minimum, prior to discharge *(Expanded Programme on Immunization 1986).*

Immunosuppression. Because of the risk of serious adverse events, measles immunization is generally contraindicated in immunosuppressed persons *(ACIP 1989).* An exception is for children infected with human immunodeficiency virus (HIV). Active measles immunization of HIV-infected individuals has been evaluated, and although the antibody response is lower, there has been no apparent increase in adverse events after immunization at age 9 months in developing countries *(Oxtoby et al. 1989)* or at older ages in the USA *(Onorato et* al. *1988).*

WHO recommends the routine immunization of infants without screening for HIV status. For infants known to be HIV-infected, two doses of measles vaccine at age 6 and 9 months have been recommended to protect children as early as possible *(Global Programme on AIDS and Expanded Programme on Immunization 1989).* Recent experience with immunization of HIV-infected infants at age 6 months with EZ vaccine, (titer 5.6 $\log_{10}$) in Rwanda *{Lepage et al. 1992)* and Zaire *(Cutts et al. 1993)* has shown that a single dose of high titer EZ vaccine at age 6 months is as immunogenic as Schwarz vaccine at 9 months. Both studies found no significant difference in rates of acute adverse events after receipt of EZ vaccine among HIV-infected infants and controls. In Rwanda, seroconversion rates were equal among HIV-infected infants (91%) and controls (90%). In Zaire, seroconversion rates were lower among HIV-infected infants than controls (76% and 85%, respectively), but the rate among HIV-infected infants was similar to that in a previous study in the same site which used Schwarz vaccine at age 9 months *(Oxtoby et al. 1989).*

Table 1. HI antibody response to measles immunization by age, USA *(Wilkins & Wehrle 1979).*

Age (months)	Number studied	% of children with a post-immunization titer of:		
		<8	8	>=16
6 to 8	78	49	13	38
9 to 11	145	18	5	77
12 to 14	550	6	4.5	89
15+	78	9	5	86

3.2.2 Agent factors

The ability of a measles vaccine to induce an immune response, particularly in the presence of maternal antibody, varies according to the strain and the dose of vaccine.

Strain

Several studies have compared the effect of EZ and Schwarz vaccines by subcutaneous injection at the same dose and age, and found that EZ vaccine gave superior seroconversion rates to Schwarz (Table 3). Antibody levels after EZ have usually been similar to those after Schwarz vaccine when the vaccines have been given at similar doses and ages. However, levels after vaccines administered at 4 to 6 months of age are lower than after vaccines administered at 9 months of age *(Markowitz et al. 1990c, Tidjani et al. 1989, Whittle et al. 1988).*

One study compared AIK-C vaccine with EZ and Schwarz vaccines, and found that this vaccine was as

Table 2. Seroconversion rates in developing countries by age at measles immunization (adapted from *Halsey 1983).*

Country	Seroconversion (%) by age in months								Reference
	5	6	7	8	9	10	11	12	
Haiti		45	71	77	84	94	95	100	Halsey et al. 1985
Ivory Coast	–	–	84	–	–	–	95	–	Breman et al. 1975
Kenya	60	90	67	100	93	–	–	100	MOH Kenya 1977
Kenya	<50	40	93	90	93	94	100	100	EPI 1979
Latin America	–	58	69	82	85	92	89	92	PAHO 1982
Nigeria	–	–	64	–	–	–	89	–	Ruben et al. 1973
Rhodesia	–	71	–	–	94	–	–	–	Burrowes & Cruickshank 1976
South Africa	–	23	45	57	86[a]	71	86[a]	80[a]	Dick et al. 1975

[a] *Less than 10 children studied.*

Table 3. Effect of vaccine strain on serologic response to immunization by subcutaneous administration in infants aged 4 to 6 months *(Markowitz 1990b).*

Country	Age (months)	Dose (log^{10})		Antibody response (%)[c]		Reference
		EZ[a]	Schwarz[b]	EZ	Schwarz	
Bangladesh	4 to 6	3.7	3.8	60	37	Khanum et al. 1987
Gambia	4 to 6	4.6	4.6	92	46	Whittle et al. 1988
Haiti	6	5.6	5.3	83	66	Job et al. 1991
Mexico	6	5.6	5.3	93	79	Markowitz et al. 1990
Togo	4 to 5	5.6	5.4	91	43	Tidjani et al. 1989

[a] *EZ vaccine was obtained from the Institute of Immunology Zagreb for all studies.*

[b] *In Bangladesh and The Gambia, Schwarz vaccine was obtained from Institut Merieux, France. For the other studies Schwarz vaccine was obtained from SmithKline Beecham*

[c] *Different studies used different serological tests and different definitions of seroresponse.*

immunogenic as EZ vaccine in 5 month old infants *(Tidjani et al. 1989).*

Data from Mexico suggest that there may be a difference between measles vaccines of the same strain produced by different manufacturers *(Markowitz et al. 1990c).* EZ vaccine produced in Mexico was compared with that produced by the Institute of Immunology, Zagreb. Antibody levels after vaccination with the Mexican vaccine were lower than after the Zagreb vaccine.

Dose

In the 1960s and early 1970s, the high cost of measles vaccine stimulated studies to determine whether the dose of vaccine could be reduced. Many studies used jet injectors. Results showed that, among children seronegative prior to immunization, doses of further attenuated vaccines as low as 200 $TCID_{50}$ induced seroconversion in over 90 percent of recipients *(Hendrickse & Montefiore 1968, Calafiore et al 1968).* However, reduction of the volume of vaccine injected was associated with lower seroconversion rates because of variation in the quantity of fluid expelled by the jet injector and poor skin penetration caused by vaccine frothing *(Stanfield & Bracken 1972).* Thermostability and potency of vaccine in vials recalled from the field also varied greatly *(Rosenbloom et al. 1970),* and the WHO requirement of a minimum titer of 1000 $TCID_{50}$ was maintained to allow for-potential poor vaccine handling in the field.

Recent trials conducted among infants who still have maternal antibody have shown increasing seroconversion rates with increasing dose, though the effect of dose was less marked for EZ than for Schwarz vaccine *(Markowitz et al. 1990c, Whittle et al. 1988).* In The Gambia, increasing the dose of EZ vaccine from 4.4 log_{10} to 5.1 log_{10} (titers corrected for results from the international reference preparation measured in parallel) gave higher seroconversion rates and antibody levels post-immunization.

3.2.3 Programme factors

Poor maintenance of the cold chain has been implicated as a cause of low vaccine efficacy *(Cutts et al. 1990, McIntyre et al. 1982).* Although new stabilizers have made the freeze-dried vaccine less heat-labile since 1979 *(Climie & Andre 1984),* reconstituted vaccine is still sensitive to heat and sunlight. Use of disinfectants to "sterilize" syringes and needles *(Cutts et al. 1990)* and variations in the dose of vaccine administered when using jet injectors *(Wassilak et al. 1985),* may also reduce efficacy.

3.2.4 Route of administration

Nonparenteral routes of administration of vaccines (e.g. intranasal, aerosol) could potentially allow vaccine virus to replicate locally on the respiratory epithelium without interference from maternal antibody, and may be more efficient in stimulating the formation of secretory IgA to provide local immunity against reinfection *(Ogra et al. 1980).* Administration of vaccine by aerosol has given equivalent seroconversion rates to the subcutaneous route in most studies *(Sabin et al. 1983, Whittle et al. 1984).* However, the aerosol route has often proved technically difficult and impractical *(Khanum et al. l987),* and there have been concerns about potential cross-contamination of the masks *(Whittle et al. 1984), so* that to date this route has not been recommended by the EPI. Countries in Latin America have used the aerosol route to administer measles vaccine during campaigns in response to recent epidemics, and the potential for a noninvasive, low cost method of administration is attractive.

Intranasal administration of vaccine gave good results in Yugoslavia *(Beck et al. 1986),* but very low seroconversion rates in a study in Kenya *(Kok et al.*

1983) and a small pilot study in Mexico *(J. Bennett, personal communication 1991).* At present, the subcutaneous route is recommended by the EPI, but further studies of alternative routes are in progress.

3.3 Protection after immunization

To evaluate the effectiveness of measles immunization, information is sought on the proportion of vaccinees who are protected from disease, and on the duration of protection.

3.3.1 Proportion of vaccinees who are protected

Protection from disease has been defined either in serological or epidemiological terms. In the former, seroconversion after immunization has been equated with protection from disease. In the latter, vaccine efficacy is estimated as the percentage reduction in disease incidence attributable to immunization, calculated by means of the following equation:

$$\text{Vaccine efficacy (\%)} = \frac{ARU - ARI}{ARU} \times 100 = (1-R) \times 100$$

ARU = attack rate in unimmunized population
ARI = attack rate in immunized population
R = relative risk = ARI/ARU

In the development of new vaccines, randomized controlled trials are used to determine vaccine efficacy. Such trials avoid the potential problem of bias and confounding by random allocation of subjects to study and control groups and double-blind designs, where both subjects and investigators are unaware of their status in the intervention under trial.

In routine immunization programmes randomized controlled trials are both impractical and unethical, hence observational studies are used, as described in detail by Orenstein et al. *(1985).*

Serological studies in developing countries have shown seroconversion rates after immunization at age 9 months of 80% to 90% *(Black et al. 1984, MOH Kenya 1977, Li-Min Huang et al. 1990, Ndikuyeze et al. 1988, Ruben et al. 1973).* Field studies of vaccine efficacy have given estimates of around 85% protection *(Hull et al. 1983),* except where poor immunization practices were identified and lower estimates were obtained *(Cutts et al. 1990).* These figures are lower than the 95% to 98% seroconversion rates *(Yeager et al. 1977)* and vaccine efficacy estimates *(Davis et al.* 1987) found in developed countries, where measles immunization can be delayed until all children have lost maternal antibody.

3.3.2 Protective level of antibodies

The development of very sensitive serological assays such as plaque neutralization tests has raised questions as to the clinical significance of low antibody levels, and some data suggest that levels below 200 mIU may not be protective. In an outbreak in the United States in 1985, all measles cases occurred among college students with pre-exposure antibody levels less than 200 mIU, although only one case had no detectable pre-exposure antibody. No cases occurred among 71 persons with pre-exposure titers greater than 200 mIU. The study also found that PN levels were significantly lower in those who reported some symptoms (e.g. fever, headache), than in those who remained completely asymptomatic, suggesting that immunity to measles may not be an all-or-none phenomenon *(Chen et al. 1990).*

The HI test is relatively insensitive, and it is likely that any detectable antibody by HI is protective. For the ELISA test, the cutoff OD value can be selected so that seropositivity as defined by the test correlates well with protection. Many studies have shown that children who are seropositive prior to exposure by ELISA assays have not had clinical measles during measles outbreaks *(Neumann et al. 1985).* However; in these studies, some of those classified as seronegative may have been protected, as only a small proportion of seronegatives acquired measles disease, although the exposure history of the seronegatives was not known.

3.3.3 Duration of immunity

Several prospective studies of antibody persistence after measles immunization have identified antibodies in over 85% of vaccinees 8 to 16 years post-immunization *(Dai et al. 1991, Krugman 1983, Xiang & Chen 1983).* Most of these studies were conducted in open communities where boosting from exposure to wild virus was likely. In a prospective study in Zhuji County, China, where there was no exposure to wild measles, HI antibody declined during the first 4 years after immunization with Shanghai-191 measles vaccine, then remained stable. By 8 years post-immunization, 12.9% of vaccinees had no detectable HI antibodies *(Xiang & Chen 1983).* Similar results may be found after Schwarz vaccine: in another study in the same county, the rates of loss of HI antibodies were similar in persons who received Shanghai-191 or Schwarz vaccines produced in China. As measles control improves and circulation of wild virus decreases, the duration of detectable antibody may become shorter, although the clinical significance of this is not yet known.

Most persons who have successfully seroconverted after primary immunization will maintain antibody levels which protect against infection. Among those whose antibody levels fall to low or undetectable levels, reinfection and viral replication may occur after subsequent exposure to wild virus or challenge with vaccine virus. Although in the majority of these

persons, reinfection by wild virus will cause only a subclinical boost of antibody levels *(Krugman 1983, Zhuji 1987),* as Table 4 shows, cases of clinical measles have been documented in persons who had originally seroconverted after immunization (secondary vaccine failures) *(Mathias et al. 1989, Reyes et al. 1987, Zhuji 1987).* The initial post-immunization antibody level was not reported in these studies.

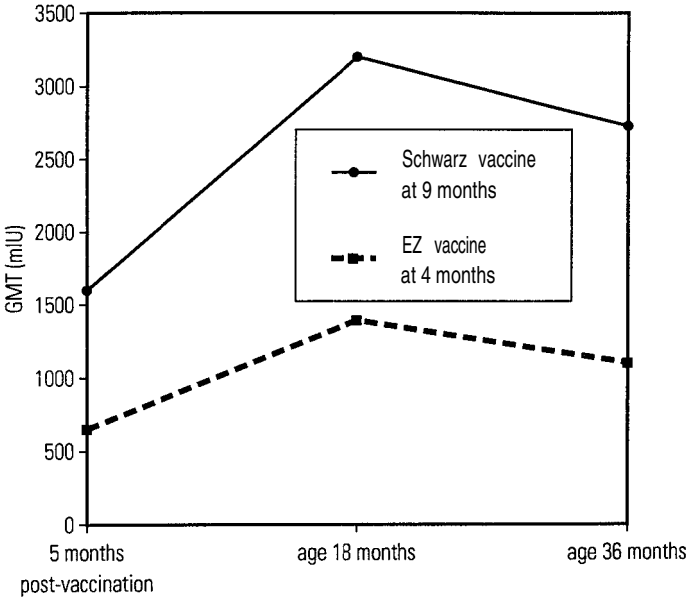
The proportion of secondary vaccine failures appears to be low: 2% in a study in China *(Zhuji 1987)* and 5% in a study in Canada *(Mathias et al. 1989).* In China, 172 persons who had been successfully immunized at around one year of age were in close contact with measles cases during an epidemic 12 years after immunization. Twenty-six had undetectable antibodies prior to exposure, but only 4 of these developed mild measles. Boosting of antibody levels occurring in the others without clinical symptoms.

Surveillance data and outbreak investigations also suggest that waning immunity is uncommon. If immunity waned in a substantial proportion of vaccinees, one would expect to see an increased incidence of vaccine failures with increasing time since immunization. In a large study in the United Kingdom, no such increase was seen among vaccinees, while measles incidence increased in unvaccinated persons *(Miller 1987).* In the Federal Republic of Germany, no increase in the number of vaccine failures was noted with time since immunization *(Fescharek et al. 1990).* However, in the United States, some outbreak investigations have shown a trend (often nonsignificant) towards increasing attack rates with increasing time since immunization, after controlling for age at immunization *(Hutchins et al. 1990, Robertson et al. 1992).* Interpretation of these outbreak investigation results is complicated by changes in vaccines and vaccine-handling practices over the years evaluated.

Secondary vaccine failure may be more common among persons who develop only low antibody levels after initial immunization. In the studies in China and Canada, the post-immunization antibody level of those who developed measles was lower than that of those who remained well. A large study in Hungary *(Nagy et al. 1984)* and two smaller studies in the United States *(Cherry et al. 1973, Smith et al. 1982)* reported that secondary vaccine failure was more common among children immunized at less than 12 months of age than at older ages.

Because secondary vaccine failure may be more likely when initial antibody levels are low, there are theoretical concerns about the duration of immunity after EZ immunization at 6 months of age. Although one study suggested poor persistence of antibody after early immunization with EZ vaccine *(Tidjani et al. 1989),* other studies have shown apparently good persistence. In The Gambia, 88% of children immunized at age 4 months and 95% of children immunized with Schwarz vaccine at age 9 months had antibody levels of at least 200 mIU, measured by PN, at age 36 months. Boosting, probably from exposure to wild virus, was suggested by an increase in antibody between 5 and 18 months after immunization (Figure 9). Though initial seroresponse was inversely related to maternal antibody level, by age 36 months the antibody level of infants immunized with either EZ vaccine at 4 months or Schwarz at 9 months was not related to pre-immunization maternal antibody level. In Mexico, children have been followed for 20 months post-immunization and antibody persistence has been good *(J. Diaz-Ortega personal communication 1991).*

Figure 9. Antibody persistence after vaccination with EZ or Schwarz vaccines, The Gambia, *(Whittle et al. 1990).*



In summary, immunity after measles immunization appears to be a continuum from full, lasting protection through partial or temporary protection through minimal or no protection. Some persons who develop low post-immunization levels may not have sustained protection. However, when measles cases do occur in immunized persons, many reports suggest that the disease is milder than in unimmunized persons *(Aaby et al. 1986, Cherry et al. 1973, Smith et al. 1982, Ueda et al. 1972).* The implications of the lower levels after immunization at age 6 months with EZ vaccine than after Schwarz vaccine at age 9 months are not yet known, but in countries where boosting from wild virus exposure occurs, immunity is likely to persist at least through the age of greatest mortality risk. More information is required on the persistence of antibody in populations without circulation of wild virus, particularly in developing countries.

Table 4. Documented secondary measles vaccine failures *(Markowitz et al. 1990b).*

Age at first immunization	Time between first immunization and measles	Illness	Laboratory confirmation	Reference
10 years	5 years	Mild	–	van Mazijk et al. 1982
26 years	5 years	Mild	–	van Mazijk et al. 1982
28 years	5 years	Mild	–	van Mazijk et al. 1982
18 months	4 years	Mild	4-fold IgG rise	Herrman[a] 1992
20 months	2 years	Mild	viral isolation	Reyes et al. 1987
8 months[b]	11 years	Mild	4-fold IgG rise	Zhuji 1987
8 months	12 years	Mild	(1 case)	Zhuji 1987
11 months[b]	11 years	Mild	–	Zhuji 1987
16 months	12 years	Mild	–	Zhuji 1987
12 months (9 cases)	no data	no data	1 of 9 cases confirmed	Mathias et al. 1989

[a] *K. Herrmann, personal communication, 1992.*

[b] *These children were revaccinated 2 to 3 years after primary immunization.*

4. Current WHO Recommendations

4.1 The minimum age for measles immunization

To obtain the optimal immune response to immunization, measles vaccine should be administered at an age when all children have lost maternal antibodies. However, the immunological response must be balanced against the risk of measles at a given age, and this is reflected in measles immunization policies.

In developing countries, behavioral and demographic factors lead to high transmission rates and infection of children soon after they lose maternal antibodies. Thus, by the time all children in a developing country population have lost maternal antibodies, many will already have contracted measles. Measles immunization was accordingly recommended from 6 months of age in the early measles immunization programmes, however, low seroconversion rates were reported *(Halsey et al. 1985, Kimati et al. 1981).*

WHO used data on age-specific rates of seroconversion and age-specific incidence and mortality rates from measles to estimate the number of cases and deaths-which would be averted by immunization at different ages. From data in Kenya *(MOH Kenya 1977),* Latin America *(PAHO 1982),* and Haiti *(Halsey, et al. 1985),* it was shown that maximum benefit would be obtained by immunization at 8 to 10 months of age, and WHO recommended a single dose of measles vaccine at age 9 months *(Expanded Programme on Immunization 1986).* Exceptions were made for situations where the risk of measles morbidity and mortality in young children was particularly high, and immunization at age 6 months, with reimmunization at age 9 months or later, has been recommended in refugee camps and among HIV-infected individuals *(Global Programme on AIDS and Expanded Programme on Immunization 1989, Toole et al. 1989).*

Initially it was thought that increasing coverage in older children would decrease transmission to younger infants. However, large cities in Africa continued to report high measles morbidity and mortality in infants under 9 months of age, despite moderately high (around 60%) vaccine coverage. Much higher coverage (around 90%), as has been attained in some cities in southern Africa, may be needed before a marked reduction in incidence is seen in younger infants through herd immunity. A vaccine which would be effective before age 9 months would make it easier to control measles. Several studies in the last decade showed that higher than standard titer EZ vaccine at age 4 to 6 months gives equivalent seroconversion rates to Schwarz vaccine at age 9 months (Table 5), and data from The Gambia *(Whittle et al. 1988)* and Guinea Bissau *(Aaby et al. 1988)* suggested that the efficacy after EZ vaccine at 4 to 6 months was at least as high as after Schwarz vaccine at 9 months, although the numbers of measles cases in each study were small.

Based on these results, in 1989 the EPI Global Advisory Group recommended that high titer Edmonston Zagreb (EZ) vaccine be administered at

Table 5. Percentage of children with post-immunization antibody titers >= 200mIU, after EZ vaccine at 4 to 6 months or Schwarz vaccine at 9 months.

Country	Seroresponse (%)		GMT (mIU)		Reference
	EZ 4 to 6 months	Schwarz 9 months	EZ 4 to 6 months	Schwarz 9 months	
Gambia	88	95	1104	2728[a]	Whittle et al. 1990
Mexico	94	82	782 to 1350[b]	1260 to 1921[b]	Markowitz et al. 1990
Togo	91	73	Not reported	Not reported	Tidjani et al. 1989

[a] *36 months post-immunization,*

[b] *Range is for children with and without pre-existing maternal antibody.*

6 months of age or as soon as possible thereafter in countries in which measles before the age of 9 months is a significant cause of death *(Expanded Programme on Immunization 1990).* This recommendation was not implemented, however (see section 5). Current recommendations are therefore to continue to administer measles vaccine at age 9 months, except in special situations where younger infants are at high risk of exposure to measles (see section 5.2.1).

4.2 Simultaneous administration and combinations of measles with other vaccines

The EPI has recently reviewed the literature on simultaneous administration of vaccines *(Galazka 1990).* Measles vaccine has been shown to be effective when given simultaneously with DPT and/or polio vaccine *(Deforest A et al. 1988, McBean et al. 1978),* with yellow fever vaccine *(Lhuillier et al. 1989),* and with hepatitis B vaccine *(Li-Min Huang et al. 1990).* The EPI therefore recommends simultaneous administration of measles vaccine with other EPI antigens for which a child is eligible.

North America and many developed countries use combined measles-mumps-rubella (MMR) vaccine in place of measles vaccine in children over 12 months of age *(Preblud & Katz 1988).* Different measles vaccine strains are used in MMR vaccine: Moraten strain in the USA, AIR-C strain in Japan, Schwarz strain in much of Europe, EZ strain in Switzerland. MMR vaccine is equally effective as measles vaccine; however, it is important that very high coverage is assured before introducing MMR vaccine in areas where rubella infection currently occurs early in life. If coverage does not approach l00%, immunization may reduce the transmission of rubella virus while still leaving many unimmunized children. As a consequence, a higher proportion of rubella-susceptible children may reach adulthood, giving rise to higher rates of congenital rubella syndrome than existed prior to immunization *(Anderson & May 1983).* For this reason, most countries which use MMR either have high coverage, or complement childhood immunization with screening of girls entering the reproductive period and rubella immunization of seronegatives *(Galazka 1991).* Because these measures are beyond the resources of most developing countries, the EPI does not recommend the use of MMR vaccine in the childhood immunization schedule in developing countries which have not achieved and sustained coverage approaching 100%.

Research studies have been conducted on combinations of measles or MMR vaccines with other vaccines, in the same syringe. However, combinations of these vaccines are still in the research stage and results cannot be widely extrapolated. The EPI does not recommend mixing measles with other vaccines, such as DPT vaccine or yellow fever vaccine, in the same syringe for several reasons. In routine programmes, it would be difficult to ensure mixing of correct doses of suitable vaccines and keeping vaccines mixed together for only a short time before injection. Some preservatives reduce measles vaccine viability, and indiscriminate mixing of vaccines could reduce vaccine potency.

4.3 Two-dose schedules

A two-dose immunization schedule is used in two situations:

- when the first dose must be given at an age at which seroconversion is known to be suboptimal because the risk of early measles morbidity and mortality is high (for example, refugee camps, outbreaks);
- in countries with measles elimination goals, to help achieve the very high levels (approximately 98%) of herd immunity required.

In the past, there was concern that immunization of infants who still have maternal antibody modified the immune response such that the infant would not respond adequately to a second dose *(Black et al. 1984, Wilkins & Wehrle 1979).* However, most studies have shown that the overall proportion of children who are seropositive after primary immunization before 12 months of age and reimmunization at age 15 months or later is at least 95%, similar to that

Table 6. Effect of a second dose of measles or MMR vaccine in children first immunized at less than one year of age, compared to controls receiving a single dose of vaccine at age 15 months or later.

Age at second dose (months)	Antibody assay	Seropositivity after 3-5 weeks				Seropositivity after 3-17 months				Reference
		2 dose		Controls		2 dose		Controls		
		No.	%	No.	%	No.	%	No.	%	
>12[a]	HI	37	65	78	91	37	49	–	–	Wilkins & Wehrle 1979
24 to 47[a]	HI	25	100	–	–	42	64	–	–	Black et al. 1984
15 to 18	HI	52	94	21	95	–	–	–	–	McGraw 1986
14 to 23	ELISA	–	–	–	–	291	98	300	98	Murphy et al. 1984
≥ 15[b]	HI	121	96	127	99	254	76	129	98	Stetler et al. 1986
> 15[b]	CPEN	120	98	–	–	253	98	129	99	Stetler et al. 1986
≥ 15[b]	ELISA	102	98	–	–	234	92	118	99	Stetler et al. 1986

[a] *Children who received a 2nd dose were "non-responders" to the initial immunization*

[b] *Results at 3 to 5 weeks are for those seronegative prior to reimmunization, results at 3 to 17 months are for all children*

after initial immunization at age 15 months (Table 6). Antibody levels among the revaccinated groups have, however, tended to be lower than those among the control group *(Black et al. 1984, Stetler et al. 1986).* There are few data on the immune response to two doses of measles vaccine in the first year of life. However, in Brazil 83% of 480 children seroconverted after a two-dose schedule, with the first dose at age 7 months and the second at age 9 months, compared to 88% of 33 children given a single dose at age 9 months *(Soerensen et al. 1985)*

Epidemiological data support the efficacy of a second dose among those first immunized in the presence of maternal antibody. In an outbreak in the USA, among children first immunized below one year of age, measles occurred in 36% of 55 infants who had not been revaccinated, but in none of 49 infants who had been revaccinated after one year of age *(Shasby et al. 1977).* A small study in Brazil found that among children first vaccinated at a mean age of 8 months and revaccinated after age one year, 5 of 32 exposed children developed measles, similar to the proportion among those first vaccinated after age one year (7 cases among 21 exposed), and lower than that among children who received a single dose prior to 12 months (7 cases among 13 exposed) *(Lopes et al. 1989).*

Many European countries have instituted a two-dose MMR vaccine schedule with the aim of eliminating rubella and measles *(Bottiger et al. 1987).* The rationale for the second dose has been to protect those persons who did not seroconvert after the first dose (primary vaccine failures).

It is not known whether a second dose will reduce the incidence of secondary vaccine failure. Among persons who have high antibody levels before re-immunization, viral replication does not occur and a second dose has no demonstrable effect. Among persons with low or undetectable levels, reimmunization produces a rapid increase in antibody, but levels soon fall again. A study in China found that those children who had been seronegative before reimmunization were more likely to become seronegative again after a short period, suggesting that there is a subgroup of children whose immune responsiveness is poor, for as yet undetermined reasons *(Zhang & Su 1983).* A longitudinal study in China found that a total of 755 children had HI antibody titers ≤ 16 at 2 to 3 years after primary immunization. Of these, 420 children received a second dose of vaccine. Over the next 12 years, the proportion of children whose antibody fell below detectable levels (HI titer 12) was similar among children who received only the primary immunization and those who received a second dose of vaccine *(Dai et al. 1991).* A recent study in the United States also showed that boosting of antibody was short-lived among children who had seroconverted to the first dose of vaccine and were revaccinated several years later when antibody titers had waned *(Markowitz et al. 1992).*

Although there are few precise serological data on the effect of a second dose of vaccine among children first immunized after one year of age, epidemiological studies have shown that increased protection is obtained after a second dose. In outbreak investigations in the USA, attack rates were 30% to 60% lower in persons who received two doses of measles vaccine compared with single-dose vaccinees *(Davis et al. 1987, Hutchins et al. 1990).* In the US military, institution of a policy of universal immunization of recruits or serological screening and immunization of seronegatives has virtually eliminated measles *(Crawford & Gremillion 1981)* and Scandinavian countries which have up to 8 years experience with a

two-dose schedule have come close to measles elimination *(Bychenko & Dittmann 1986).*

For most developing countries, it is premature to adopt a routine two-dose schedule. Priority in resource allocation should be given to achieving universally high coverage rates with the first dose. In the meantime, it is important to evaluate the cost-effectiveness of the second dose in countries which have instituted two-dose schedules.

5. Future Prospects

5.1 The effect of immunization on the immune status of populations

The changes in measles epidemiology that occur as immunization programmes mature and their potential implications for measles immunization policy have recently been reviewed *(Cutts 1990).* The major changes which occur as high immunization coverage is achieved are an overall reduction in measles incidence rates, a shift in the age distribution to older persons, and an increase in the interepidemic interval which may lead to the occurrence of outbreaks after a long disease-free period.

As high coverage of young children is reached and sustained, measles transmission decreases. Cohorts of unimmunized children from previous years can then reach older ages without contracting measles. The number of susceptible older children gradually builds up so that there is a potential for outbreaks among these children. Measures such as school-entry screening and immunization, one-time immunization campaigns among older persons, and routine two-dose schedules have been implemented to address the relative increase in cases among older persons. Mass immunization of all children aged 9 months to 14 years has been conducted in countries in the Caribbean and Brazil, with dramatic impact on measles incidence. Many other Latin American countries are currently implementing this strategy and surveillance is being enhanced to evaluate its long-term impact. The decision to institute such measures will depend on the resources available to the country and the goal of the immunization programme (elimination or control). In all instances, the priority is to achieve maximum coverage as soon as possible after the age at which maternal antibody is lost.

Other potential changes may have implications for immunization policy. Because antibody levels attained after immunization with further attenuated vaccines are lower than those after measles disease, the antibody levels of women of reproductive age are lower in the post-immunization than in the pre-immunization era *(Jenks et al. 1988, Lennon & Black 1986).* Thus, maternal antibody may wane sooner in infants born in the "vaccine era", allowing lowering of the minimum age for measles immunization.

The persistence of antibody may be reduced when measles virus is controlled and circulation of wild measles decreases, because of less boosting of antibody in immunized persons from exposure to wild virus. Antibody persistence seems to be lower in isolated populations which are not exposed to wild virus. As discussed in section 3.3.3, most persons whose antibody levels are low respond to challenge with a subclinical boost, but there could be an increased potential for secondary vaccine failure. It is not known whether routine reimmunization of these populations would result in sustained immunity.

5.2 Implications for immunization programmes

5.2.1 Measles immunization schedules

The global recommendation for measles immunization in developing countries is to apply a single dose of standard titer measles vaccine at age 9 months or as soon as possible thereafter. In countries or regions where measles is a significant cause of death in infants younger than 9 months, in 1989 a single dose of high titer EZ vaccine was recommended at age 6 months or as soon as possible thereafter. High titer EZ vaccine was also recommended in refugee camps and for HIV-infected children. However, high titer vaccine proved to be more costly than expected. In addition, some subsequent studies have reported lower immunogenicity than was seen in early trials. Furthermore, while the high titer vaccines had initially appeared to be safe, some field studies conducted in areas with high background infant mortality unexpectedly found decreased survival among infants who received high titer measles vaccine at age 5 to 6 months compared to those who received standard titer vaccine at age 9 months *(Garenne et al. 1991, Expanded Programme on Immunization 1992).* A complete reevaluation of the immunogenicity, efficacy and safety of measles vaccines for use at age less than 9 months of age was conducted in 1992, and led WHO to recommend that the use of high-titer measles vaccines in routine immunization programmes be stopped *(Expanded Programme on Immunization 1992).*

The EPI does not currently recommend a routine two-dose measles vaccine schedule in developing countries. Two doses of standard measles vaccine at ages 6 months and 9 months are currently recommended in high risk situations such as refugee camps, hospital outbreaks of measles, and for HIV-infected children *(Expanded Programme on Immunization 1993).*

In all countries, the priority is to immunize children as soon as possible after maternal antibody is lost. Thus, in developing countries, the priority target age group is children age 9 to 11 months. However; older children presenting to health facilities who have not previously been immunized should be given measles vaccine.

5.2.2 Use all contacts to administer measles vaccine

All contacts with health facilities should be used to immunize children against measles. Measles vaccine should be administered simultaneously with other vaccines if a child old enough to receive measles vaccine presents late for the other EPI vaccines. Measles vaccine is safe and effective in children with most acute illnesses. A general rule is to give measles vaccine (and other vaccines) unless the child is so ill as to require hospitalization, when the decision to administer vaccine should be taken on an individual basis after reviewing the child's condition. Hospitalized children should receive measles vaccine as soon as their general condition allows, to reduce nosocomial transmission, and at a minimum, should receive measles vaccine prior to discharge. HIV-infection is not a contraindication to measles vaccine.

5.3 Research Needs

Countries which have achieved high coverage with a single dose of currently available measles vaccine strains at age 9 months have substantially reduced measles morbidity and mortality. Achievement of high coverage with a single dose of measles vaccine remains the major strategy for measles control. However, in the long term, WHO has the goal of measles elimination, and for this, additional strategies will be required.

Other studies are needed to evaluate potential additional strategies for measles control, particularly evaluation of the cost-effectiveness of mass campaigns, as used in the Americas, of two-dose measles vaccine schedules, and of the optimum age for the first and second dose in different epidemiological situations.

A rapid diagnostic test for measles that can be used in field conditions is required to improve disease surveillance and outbreak investigation and control. For example, a recent measles outbreak in the United States led to control activities costing $1 million; it was subsequently found that many cases had been falsely diagnosed and the outbreak was not as extensive as had been thought *(Robertson et al. 1992).*

While measles control can be achieved by high coverage with standard vaccines at age 9 months, and supplemental strategies such as mass campaigns or a routine two-dose schedule have enabled some countries to come close to measles elimination, the development of new measles vaccines which would be effective at an earlier age would facilitate measles control in developing countries. The reasons for differences in immunogenicity, efficacy, and safety of different measles vaccines when administered to children who still have maternal antibody need further study and clarification. Further studies are in progress on these issues, as are studies of immune function after measles disease, which will help to identify criteria for the evaluation of the safety and effectiveness of potential new vaccines. Novel measles vaccines are currently in the early stages of development, using new approaches such as vectored vaccines which express clonal genes of the measles virus into bacterial or viral vectors.

When measles vaccine trials are conducted, to allow comparison of results from different trials, it is essential to standardize potency measurements and methods used to measure the immune response to vaccine. Use of international reference preparations will assist in standardization, but more data are needed on the comparability of different serological tests. The immune response induced by various vaccine strains should be measured ideally both by cell-mediated immune responses and the levels of antibodies induced to specific epitopes.

These laboratory and epidemiological studies should provide more precise data on which to determine future measles immunization policies and to select optimal measles vaccines to achieve the long-term goal of measles elimination.

Abbreviations

CFR	case fatality rate
CPE	cytopathic effect
ELISA	enzyme-linked immunosorbent assay
EZ	Edmonston-Zagreb strain of measles vaccine
HI	hemagglutination-inhibition test
IU	international units
MMR	measles-mumps-rubella vaccine
OD	optical density
PFU	plaque forming units
PN	plaque neutralization test
SSPE	subacute sclerosing panencephalitis
$TCID_{50}$	dose which infects 50% of tissue cultures

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