II. REVIEW OF LITERATURE

I. HISTORICAL ASPECTS

Measles, also known as Rubeola, is known to mankind since antiquity (53). The ancient Indian physician Charak has tried to explain the disease 'Romantika' (measles), its aetiological and clinical aspects and treatment, which even today forms the basis of practices and popular beliefs of Indian people about the disease. Ancient Ayurvedic texts like 'Madhavnidan' (194) and 'Yogaratnakar' (357) also describe it.

The term measles probably derives its name from the Latin term 'Misellus' or 'Misella', itself a dimunitive of Latin 'miser', meaning miserable which described the inmate of a medieval leper house. In the anglicized form of 'Misella' namely measles, the word thenceforth became applied, not to the sufferer of the ill-defined skin lesion, but to the specific disease 'Morbilli'. The word is derived from the Latin word 'Morbus' which was introduced to distinguish minor rash disease, measles, from bubonic plague, 'Morbus', the major disease (346). Rubeola, an Arabic dimunitive, meaning red spots, was ascribed to bad blood - retained menstrual blood- during pregnancy entering the foetus and appearing later on as rash of measles (345).

No accurate information is available on the early history of measles. Measles was unknown to Hippocrates, and the tenth century Arabian physician from Baghdad, Rhazes (270), has generally been credited with describing the disease for the first time, distinguishing it from smallpox though he cited El Yehudi, a Hebrew physician, from the first century. But there is no doubt that Rhazes and the contemporary Arabian school generally regarded measles and smallpox as intimately associated with each other (13,346). Only during the 17th century, after studying the severe epidemics of measles, the observations of the physician and epidemiologist, Thomas Sydenham, finally cleared up what obscurity was left (346).

Measles hit the Roman civilization along with smallpox about 250 A.D. with devastating results. Similarly, following their introduction to the Americas from the old world by Columbus in 1492, the population of Central and South Americas of 130 million, dropped to 1.6 million over 100 years (213).

Measles has occurred regularly as epidemics everywhere in the world, except in very remote and isolated areas. It decimated the population of Fiji, Terradel, Fuego and various other virgin populations with catastrophic effects. The whole family was infected during this epidemic with no one left to carry food from the farm, bring water or cook, and starvation would then be added to an already grave situation (128). Major violent epidemics affecting people of all ages and mortality of 25-50% were experienced in Faroe islands, Estonia, Hudson's Bay, Cape Colony and Anden Spanish colonies in South America in the past centuries (37, 76, 251).

The first reported outbreak of measles in 1635 was followed by the description of its complications by Sydenham in 1670.

In the London epidemic of 1674, measles caused more deaths in the first six months than did smallpox (346).

From Edinburgh, Home in 1755 demonstrated viraemia and transmission of measles (129).

In 1846, Panum gave a classic report of epidemiologic analysis of measles epidemic in Faroe islands (227) highlighting the following features-

(i) Measles spreads by respiratory droplet infection.
(ii) There is a constant incubation period of two weeks.
(iii) Nearly 100% attack rate is seen in exposed susceptibles.
(iv) Life long immunity after a single attack is observed.

Koplik, in 1890, gave a detailed description of the enanthem (212).

It was known that traditional prophylaxis against measles was practised in ancient India (107).

Numerous attempts have been made to devise an effective and harmless means for artificial induction in man of immunity against measles.

Home, in 1749, experimented the principle of variolation which consisted of inoculating blood or secretions from upper respiratory tract of patients with measles by scarification of skin (morbillisation). However, this method never got general adoption (124).

Viral aetiology of measles was first suspected by Hektoen in 1905 and its filterable nature was demonstrated in 1911 by Anderson and Goldberger (11, 89, 113). Nicolle and Conseil in 1918 first described passive immunisation by inoculation by convalescent human serum containing neutralising antibodies. This was followed by the use of adult serum in 1921, placental preparation in 1933 and plasma globulin concentrates in 1944, as media of antibody preparations, under the presumption that as most adults have suffered from measles, pools of adult blood, therefore, contain specific antibodies (15).

In 1923, Savini, Caronia and Sidoni used Jennerian and Pasteurian principles of employing attenuated or inactivated virus as vaccine by inoculating children with heated blood from patients with measles or phenol-treated fluid from Noguchi type cultures believed to have supported the growth of measles virus. Protection offered by these vaccines was, however, not demonstrated (45).

Rake and Shaffer, in 1940, reported the adaptation of the virus to the chick embryos (261).

Enders and Peebles reported the isolation of measles virus from the blood and secretions of patients and inoculated them in human and simian cell cultures in 1954. The subsequent adaptation of the virus to growth in chick embryo and chick embryo tissue cultures by Enders, Katz and their colleagues in 1956, led to the development of measles virus strain

(80, 238) which was the keystone for the development of reliable diagnostic tests and vaccines, thus converting into reality the quiet confidence of a Hungarian physician who declared in 1755 in a book entitled, 'Tentamen de Inoculanda Peste', published in London, that "concerning me, there is no doubt at all that the experiment (inoculation) would be successful and it would be an extremely satisfying moment when this vaccine became a reality..." (319).

The first International Conference on Measles Immunisation was held at the National Institute of Health, Bethesda, Maryland, USA during November 7-9, 1961. This led to the licensing of measles vaccine in USA in 1963 (35, 105).

The impact of mass immunisation on the occurrence of the disease was so great that in the 1960s, the prospects of making measles a memory for mankind were discussed actively for the first time (35, 105).

Description of measles encephalitis as a clinical entity by Neil et al and Musoor et al (262) and recognition of the relation of subacute sclerosing panencephalitis (SSPE) to measles in 1965 gave a better understanding of the complications of measles (242).

During March 16-19, 1982, the International Symposium on Measles Immunisation was held in Washington, D.C., USA, which marked another step towards the eventual eradication of measles (13).

II. MEASLES EPIDEMIOLOGY

A. Agent : The Measles Virus

1. Classification

The measles virus belongs to the family 'Paramyxoviridae'. There is only one serotype. It is a single negative strand, RNA enveloped virus which together with canine distemper and rinderpest viruses forms the subgroup 'Morbillivirus'. These three viruses are quite similar antigenically, but only measles virus has haemagglutination activity.

The diseases caused by the morbilliviruses are similar, but the host species vary (212).

2. Morphological and Physical Properties

On electron microscopy, measles virions are pleomorphic but essentially circular with a diameter of 100-300 nm. Virions are composed of two structures; (a) an outer lipoprotein envelope, 10-20 nm thick, with short spike like projections and (b) an inner nucleocapsid core, 17 nm in diameter, which is a coiled helix of protein and RNA (212).

3. Antigenic Composition

Two proteins, haemagglutination (H) and fusion (F), are located within the envelope on the surface of the virion. The H protein, a glycoprotein with a molecular weight of about 80,000, is responsible for haemagglutination and haemadsorption of old world monkey red blood cells and adsorption of measles virus to permissive cells. The F protein is the second surface glycoprotein with a molecular weight of about 62,000 and is responsible for viral penetration into the cell and cell fusion (212).

There are four recognised proteins associated with nucleocapsid viz. nucleoprotein, phosphoprotein, large protein and matrix. The nucleoprotein is the major structural component of the nucleocapsid. The phosphoprotein is probably involved in transcription. The large protein is probably the viral transcriptase. The matrix is responsible for assembly of the nucleocapsid with membrane (envelope) during viral maturation preceding budding. It is likely that most, if not all, of the above mentioned antigens stimulate complement fixation antibody (212). Different strains of measles virus have antigenic homogenicity (80). No antigenic variation was seen among four wild strains, two vaccine strains, two laboratory strains and one strain isolated from a case of SSPE; when tested for H,F, nucleocapsid and polymerase proteins. But different strains showed extensive variation in their reactivity with the nine anti-monoclonal antibodies, which may be used as an epitopic marker in classification of measles virus strain (302).

4. Viral Infectivity

Infectivity requires the entire virion. Infectivity is lost but antigenicity remains after treatment with radiation, beta-propiolactone and formalin. The virus is stable at lowered temperatures, but is relatively labile at room and body temperatures; at 37°C, half of its infectivity is lost in 2 hours (27); a characteristic of major importance in the handling of vaccines and specimens collected for viral assay. The virus is usually destroyed when travelling 10-20 feet in ordinary atmosphere (74).

The disease is highly contagious with transmission by direct contact. During an epidemic, the secondary attack rate is 90%. New cases have developed in group situations, even when 80-90% of the population is immune. The prodromal stage is the most contagious period (12, 212).

5. Growth in Tissue Cultures

Measles virus was originally grown in primary human renal cells by Enders and Peebles in 1954. Now several types of primary and stable tissue culture cell lines can be used for propagation of the virus. Human and simian renal cells (Viro and CV-1, both African green monkey kidney continuous lines) and human amnion cell cultures are used for viral isolation and growth (212).

6. Host Range

Man is the only known natural host for measles virus. However, experimental measles can be produced in monkeys. Subacute sclerosing panencephalitis models have been developed in hamsters, mice and ferrets. Rabbits are a good source for production of serum antibody (212). Healthy carriers are unknown (7). However, subclinical, asymptomatic infection is known (242, 299).

7. Immunology

Measles virus infection in human stimulates the development of

(i) serum neutralisation (N),

(ii) haemagglutination inhibition (HAI), and
(iii) complement fixation (CF) antibodies.

The N and HAI antibodies closely parallel each other. They can be first demonstrated within 1 or 2 days after the appearance of the rash and reach peak titres 2-4 weeks later. The CF antibodies are usually delayed in appearance by a week or so, and peak later. The N and HAI antibodies persist for many years (probably lifelong), but tend to decline in titre. The CF antibody may disappear after 6 months to several years. The primary antibody response to measles is a mixture of IgM and IgG immunoglobulins, with a rapid disappearance of IgM by 21 days, but indefinite persistence of IgG. Reinfection, natural or with vaccination, leads to a prompt anamnestic humoral antibody response and results in an increased IgG level if the pre-exposure/pre-booster antibody level is low, within 1-7 days and peaks by 12 days (227).

In a 16 year long prospective study by Albrecht et al, all the 47 children who had natural measles and had high ($\geq$ 1:64) HAI antibody titre after one month of the disease, had detectable antibody after 16 years as well (175). It is doubtful whether the immunity resulting from an attack of any other disease is quite so strong and persistent (7).

Although not completely defined, cellular immunity must play a protective role. Patients who have humoral immune deficiencies and fail to respond to measles infection with detectable specific antibodies, do not become ill upon re-exposure; however, patients with cellular immune deficiencies do very poorly when they develop measles (212).

B. Host

1. Typical Measles

A close correlation between pathogenesis of the disease and clinical findings exists. Measles virus enters the body via the respiratory tract, or perhaps at times via the conjunctival sac, multiplies locally and spreads to regional lymphoid tissues. A primary viraemia follows, with dissemination and multiplication throughout the reticuloendothelial system.

A secondary viraemia then takes place, with widespread dissemination of the virus. As the incubation period ends, the virus has seeded into the respiratory tract and conjunctival sac and continues to multiply. Ultimately, the virus localises in the skin and/or organs (212).

The incubation period varies from 8 to 14 days. Measles typically is a 7-11 days illness consisting of a prodromal phase (2-4 days) followed by an eruptive stage (5-7 days). The prodromal period, probably related to the secondary viraemia, is ushered in by malaise and fever, followed within 24 hours by coryza, cough and conjunctivitis. Photophobia may be present. The Koplik spots first appear on the buccal mucosa opposite the lower molars 2 days before the onset of the rash. The period of greatest contagion is during the prodromal stage (212).

The rash appears about 2 weeks after exposure to the virus, at a time when the prodromal phase is at or close to a peak in severity. The maculopapular red rash first appears at the hairline of the forehead and behind the ears, and then spreads from face to arms to abdomen to legs and feet, within about 2 days. The fever often rises abruptly to 104-105°F as the rash appears, and then within 2-3 days the symptoms start subsiding rapidly along with fading of rash from face downwards (212).

Various factors affecting the outcome of measles are as follows-

(a) Sex

No significant difference is seen in the incidence of the disease in the two sexes though a slight male preponderence is reported.

However, due to socio-cultural maltreatment, females are at a higher risk of mortality than males (212, 296).

b) Age

Essentially all children will get measles eventually unless protected by vaccination.

The study of the age at measles disease is important because it helps in identifying the vulnerable population towards whom the preventive

programme can be preferentially directed. It also helps in deciding the earliest age at which active immunisation can be carried out.

Age at disease has also been found to be influencing the rate of complications, morbidity patterns and mortality.

Morley in his classic study reported measles at an earlier median age in the developing countries e.g. Nigeria - 16.5 months, Jordan - 18 months, Kenya and Uganda - 18.5 months, East Nigeria - 21.5 months, Ghana - 24.7 months and Zambia - 29.4 months as compared to 51.7 months in England and Wales (231).

In India, in 1957, Silhar and Maru reported a hospital-based study wherein 80% of the cases had occurred below the age of 4 years and a peak was observed between the age of 1 and 2 years (303).

Ghosh and Dhatt from Delhi have also reported a higher incidence in the age group of 1 to 2 years with only 5.4% cases occurring above the age of 5 years (100).

Biviji et al have also reported that both incidence and morbidity were high in the age group of children below 2 years (26).

John and Devrajan, in an epidemiological investigation of an outbreak of measles in Ajivali- a remote, unapproachable village, have reported the occurrence of maximum cases between the age of 1 and 4 years, the median age being 24 months (139).

Similar results of an early onset of measles are available from other studies conducted in various developing countries. Koster et al from Bangladesh (167) and Zhang and Su from China (360) report 50% cases occurring by 4 years of age with maximum incidence between 2 and 4 years.

Various authors have reported 10-31% of children developing measles before reaching their first birthday (4,13,139,160,308).

The age group which is mainly affected is usually decided by various factors like overcrowding, practice of carrying child, prolonged excretion of virus by malnourished children and natural and artificial immunity

(234). Therefore, measles, an adolescent problem in a highly immunised community like the USA, mainly affects school children, 5-9 years of age, in developed countries without intensive immunisation, but affects preschool children in developing countries (13).

More infants are affected by measles in developing countries like India. Different Indian workers have reported an incidence of measles affliction among infants ranging from 15-30% (22,71,100,305).

Moreover, in India, the incidence of measles in ages less than 9 months is quite high. At 6-11 months of age, the incidence of measles was as high as 55.3 per thousand in a community-based study by Garai and Chakraborty (99). Fifty percent of all measles cases reported by Sinha occurred in 6-12 months of age, while 12% of the infants affected were less than 6 months old (305). Nearly 50% of cases in infancy are reported before 9 months of age by various authors (22,164,192,316).

In Kenya, Hayden found 2.3% cases under 6 months of age (112). Torigoe in a study from Ghana reported 45% of measles occurring in less than 1 year old children (321). From the fifth month onwards, the disease becomes increasingly frequent and in urban communities, by the age of 1 year, around a third of all children will have suffered from the disease, while before the third birthday, three quarters are likely to be infected (231).

Contacting measles between the age of 6 months and 2 years is considered a high risk factor as mortality is higher (215). In general, toddlers and infants are more likely to experience complications (22,164,316).

c) Interaction between nutrition and measles

Two separate evil forces join hands to the detriment of the child who is both malnourished and gets measles.

In the malnourished child, measles is more severe. A greater difference in severity is found in measles than in any other common childhood disease. The malnourished child may have a mortality 400 times higher than his well nourished counterpart with measles (231, 234).

The decline in mortality in measles in developed countries has antedated the introduction of better treatment of complications or of antibiotics, but it came at a time when improved methods of child feeding were being widely adopted as well as rapid industrialisation bringing in an era of prosperity (13).

The synergic detrimental effect of malnutrition and measles is important, for both contribute to an impairment in cellular immunity, leading to a greater incidence of complications (13).

The analysis of questionnaires from 600 doctors, in response to a request for survey by Morley revealed that measles was more common and more severe in countries where malnutrition was prevalent. In his analysis of many thousand weight charts of under-fives, Morley revealed that measles led to loss of weight more than any other childhood disease. In a longitudinal study, he has reported that 1.5% of children lost 20% or more weight, 25% lost about 10% of their weight, 66% lost 5% weight and 15% took over 3 months to regain their previous weight (229, 231, 232, 233, 234).

In a study from Afghanistan, Chaudhary et al reported significantly higher mortality rates (45.2%) amongst children with severe grades of malnutrition, whereas overall mortality was less (14.5%) (58). Depressed cell-mediated immunity to measles, resulting in a severe and prolonged attack of measles and higher mortality is also documented (78).

Studies from India show wide variation in the severity of measles. Ghosh and Dhatt reported higher incidence of measles complications in malnourished children (100, 170). However, studies by John et al (141) and Koster et al (167) suggest that nursing care during illness and availability of health care facilities appear to be more important in determining the course and outcome of measles rather than the nutritional status.

There are several reports confirming the adverse effects of measles on the nutritional status (141, 167). In a series followed by Krishnamurthy

et al, nearly 40% of the children developed grade 3 malnutrition following measles (170). Depressed immune status due to measles makes children susceptible to intercurrent infection and leads to malnutrition (78).

There are several reports indicating that serum vitamin A levels are depressed, either due to the effect of infection on intestinal absorption or release of vitamin A from the liver (136, 286). Corneal ulceration resembling keratomalacia is a frequent complication of measles in Nigerian (136, 286) and Asian (170) children. In Zambia, it has been established that 40% of the total blindness was due to corneal lesions caused by measles (14).

In India, Ghosh and Dhatt, during a hosptial-based study, reported that 84.5% complicated cases of measles were undernourished and 14.5% had reasonably well nutrition (100). Others have also reported similar observations (55,204,316).

Thus, prevention of measles will have a major impact not only on child survival but also on health and nutritional status (265).

Given the fate that measles is a setback to nutrition, prevention from measles by vaccination would be partial protection against malnutrition itself (324).

d) Socio-cultural aspects of measles

Till recently, the majority of the health workers felt that their responsibility did not stretch much further than the child patients in their wards and those who came to the clinics (231). Social and cultural factors not only affect patterns of morbidity and mortality, but also utilisation of medical and preventive care (195).

As Suchman puts it, "Social factors determine the response of society and individual to many health problems. The meaning of illness, its perception and definition, and behavioural responses to illness are basic factors influencing the reaction of public to any public health programme" (314).

For a thousand years in Europe, measles was thought to arise from the 'bad' blood of menstruation. As menstrual blood disappeared during pregnancy, it was believed that it entered the foetus and reappeared after birth as measles (13) and the universal belief is that the rash must be allowed or encouraged to 'come out' (231). Measles is considered 'God's disease', a classification which influenced adherence to traditional practices the world over as well as acceptability to modern medicines. The rash is believed to be important and to hasten the eruption of the rash, in Kenya, certain herbs are given to the child. Covering the child's head with an Akamba basket (Kyondo) is also believed to hasten the progress of the disease. Once the rash has appeared, it has to be cleaned. The most popular practice is to smear the child with mud taken from an anthill or with ashes from the fireplace mixed with certain herbs (231).

Milk, fat and meat are avoided for they are believed to prevent the rash from appearing on the surface (13).

In certain African countries, measles is managed by restricting the diet and even fluids during and immediately after the disease. In some communities, the child may be put in a dark portion of the house and covered entirely with blankets until the desquamation of the rash. The resulting hyperpyrexia and dehydration add to the already poor general condition of the patient. In South Americas, many of the old customs from Europe exist and there are reports of children being beaten with nettles to bring out the rash (13).

In Mali, the Bambaras consider the ultimate cause of measles to be spiritual and so diviners and marabouts decide the prevention and treatment of measles. In Gambia, though the western style of therapy is not adopted to treat measles, advocating the use of at least guinea corn meant that most nutritional needs were met. Many of the food preferences were sensible (3).

Morley, from West Africa, reports that measles is generally believed to be due to sorcery, though heat and eating certain foods such as snails

etc. are thought in some areas to be responsible. For treatment, all medicines, both traditional and scientific are avoided and injections which may prevent the rash 'coming out', feared. In the Zambesi valley, two dangerous customs are the restriction of fluids and the application of an astringent fluid made from roots and herbs (231).

In Asia, measles is often considered to be due to a malignant Goddess called 'Mata' (234).

Shahid et al (298), in a study done in rural Bangladesh, reveal that 45% of mothers believed that measles was caused by the 'Will of God'. Mothers who usually used Oral Rehydration Salt during diarrhoea as a routine, stopped using it for fear of stopping diarrhoea and consequent harm to the child.

In China, cleanliness is achieved by washing the child with plain water, purifactory herbs and herbal remedies (103).

In India, measles is considered as a visitation by a Goddess - 'Mata' in North India and 'Mariammai' in South India. Due to traditional beliefs, the child with measles is kept at home, isolated, hidden from neighbours and no medical care is sought even when complications set in (141, 296).

Failure to know and understand the attitudes and beliefs of the community limits effective care and increases the severity of the disease (199). The result is that the treatment given for the disease is as varied and diverse as religious taboos and attitudes prevailing in the community. The parents feel that it is useless and dangerous to bring a child suffering from measles to the hospital and promptly remove him from the hospital if he develops measles there (296).

Shah et al, during their survey in rural India, observed that most people resorted to dietary beliefs of giving milk, jaggery, etc., external application of bathing in 'neem' leaf solution and use of charms and 'mantras'. Though 43% of people took medical treatment, usually it was when illness failed to subside and complications had developed (296).

John et al observed that relief from symptoms was totally prohibited as it would anger the Goddess and lead to severe consequences. However, medical practitioners rejected these beliefs (141).

In Ayurvedic text books, measles is known as 'Romantika' and the description of its clinical features resembles that described in our text books. As per Ayurvedic medicine literature, measles usually affects children and is caused by air and water pollution, ingestion of 'opposite quality diet', overfeeding or starvation and by eating spoiled green leafy vegetables or hot and salty food. Treatment consists of eating unpolished rice, grams, fruits especially grapes and pomegrenates and fresh meat soup; isolation in cold, soothing and holy atmosphere surrounded by 'neem' leaves; doing 'japa' and worshipping Lord 'Shiva'. Hot, sour, heavy and oily foods are avoided and so are heavy physical exercises (53, 194, 359).

The following proverbs (231), though used in West Asia, suggest the respect in which measles is held all over the developing world -

- "A child that gets out of measles is a child that is reborn" (Arabic).
- "Count your children after the measles has passed" (Arabic).
- "Smallpox will make your child blind, measles will send him to his grave" (Farsee).

The doctor's knowledge of measles is influenced by the attitude of his own culture towards the disease, and if the traditional villagers do not bring the diseased to him and his experience is limited to his own children, he is unlikely to realise its severity. This attitude is now changing. The difficult piece of health education of pursuading the parents of Asia to bring their children with measles for medical care against their local cultural beliefs, now may become unnecessary. The mass scale introduction of measles vaccination should bring to an end this drama in which measles virus, poor nutrition and peoples' beliefs, have all played their part (231).

e) Herd immunity in measles

Although measles virus is ubiquitous and highly infective, its ability to perpetuate itself in human population is surprisingly fragile. A critical population size is required for its perpetuation (358).

That permanent immunity is established following mild measles infection can be seen in the data collected by Panum who described the 1846 epidemic in the Faroe islands. He observed that elderly residents who were infected during the previous epidemic in 1781, did not contract a second attack of measles (227).

Parameters which determine the perpetuation include-

(i) the size of the population,
(ii) the turnover of the population,
(iii) the proportion of immunes in the population,
(iv) the transmissibility of the infection, and
(v) generation time between sequential infections.

Estimates of the size of the susceptible population as a percentage of total are important because they determine both the minimum numbers required for perpetuation and the maximum reduction which might be achieved by immunisation (358).

Herd immunity of the population along with communicability determines the periodicity of the epidemic which varies from 12 years interval, which is now a rarity, to a peak every 2-3 years as reported in India (308). In the widely spread population in Africa, 'micro outbreaks' occur throughout the year (99).

However, the general concept of herd immunity is applicable only where outbreaks occur in randomly mixing populations. The requisite for occurrence of epidemics, namely, a large enough number of susceptibles in frequent contact with each other, exists virtually in all large populations, regardless of the total proportion of the population that is immune (96).

Unfortunately, in many developing areas, despite the fact that more than 90% of populations are immune, measles persists and annual outbreaks are associated with significant mortality among the susceptibles, most of whom are children under the age of 3 years. In Ibadan, Nigeria, after attaining measles mass campaign coverage of 92%, with a maintenance programme every 6 months for all children in the 0-3 years age group, new epidemics occurred after an interval of 18 months. Even in the United States, where vaccination is widely practised, measles has continued to occur in poorly immunised subgroups that are characterised by low educational level and economic status, very young children or imported measles (97).

Artificially high herd immunity achieved by mass measles vaccination campaign has shifted the high incidence to the 10-14 years age group in USA where preschool measles vaccination is mandatory against 5-9 years in Canada where vaccination coverage is not as impressive (69). Measles vaccine is safe in adolescence, without high incidence of adverse reactions (256).

Therefore, knowledge of distribution of susceptibles by age and numbers is essential to know about herd immunity and the timings of the epidemics.

f) Measles seasonality

It is observed that measles virus survives and maintains virulence in late winter and spring (358).

Seasonal prevalence of measles is seen in most communities, although the nearer to the equator the community lies, the less marked is the seasonal increase (234). Humidity, temperature and community movement play a key role with peak incidence seen in the months of February, March, April and May in India (296) and China (360) and in March in Bangladesh (167). Peak incidence in April is seen in Uganda, Kenya and Tanzania (167,231).

This seasonal variation in the incidence of measles may be related to humidity or temperature (231).

Religious festivals and other communal gatherings in a particular time of the year, by increasing the chance of spread by droplet infection, may lead to an epidemic (231). In the same community, transmissibility index is reported to increase linearly to the number of susceptible children in the family (299).

2. Severe Measles

Measles is a mild disease in healthy children and so is not a major public health problem in the developed countries. However, in the undernourished children, especially in the developing countries, it differs in its manifestations and presents clinically in a severe form (234).

The grade of malnutrition and more so, overcrowding, increase the risk of early infection and the severity of measles. In instances in which several children have measles simultaneously, the case fatality rate is significantly higher than in isolated cases. This is probably a result of the intensity of exposure. Even within the same house, secondary cases have a much higher age-specific case fatality rate than the index case. This is due to increased rates of intercurrent infection and/or a greater dose of infection. Since it is not only the malnourished children who die of measles, vaccination may have a greater importance for survival patterns than has been previously assumed (1).

a) Clinical manifestations

i) Skin changes : The Arabin physician, Rhazes, noticed and described in his original classic description of measles in the year 850 A.D. that, "Measles which are of a deep red and violet colour are of a bad and fatal kind" (270).

The progress of the rash and subsequent changes in the skin are different in the early stages of severe measles. In a proportion of children, the rash becomes confluent. In some, it darkens to a deep red colour which may even progress to a violet or purple hue, a change rarely seen in European children and termed as 'black measles' or 'haemorrhagic measles' (242). In severe haemorrhagic measles, there is a sudden onset

of hyperpyrexia associated with the prodromal stage leading to delirium, stupor, coma, convulsions, marked respiratory distress and extensive confluent haemorrhagic eruption of the skin and mucous membrances, which may be accompanied by bleeding from mouth, nose and bowel, sometimes disseminated intravascular coagulation, and it often proves fatal (177).

Variation in the type and appearance of skin rash may well be correlated with the changes in other epithelial surfaces, which in turn may account for the 'so-called' complications which have rightly been regarded as the cause of the majority of fatalities from the disease (234).

ii) Probable results of equivalent changes in other epithelial surfaces: There is a possibility of association between the severity of rash and the manifestations of the disease in other epithelial surfaces (234).

The commonest change in the mouth is the occurrence of a sore mouth in which the tongue and the buccal mucosa become dry and ulcerated or covered with sores leading to inability to suck/swallow and, therefore, rapid emaciation. Cancrum oris or noma can also occur (234).

Laryngotracheobronchitis, severe enough to necessitate tracheostomy, is another life threatening complication (234).

Viral bronchopneumonia with secondary infection due to Klebsiella and staphylococci is common (234).

The diarrhoea so frequently associated with measles is due to changes in the intestinal epithelium, which may take weeks to months for repair and recovery, leading to a chronic or relapsing course (234).

Corneal lesions and encephalitis are also frequent in children with severe measles (234).

Acute proliferative glomerulonephritis and acute renal failure following measles have been reported (185).

However, long term consequences or sequelae of measles are not known and require study (273).

There is an extensive immunosuppression during acute measles and elements of this persist for periods varying from 6 to 52 weeks. In a study on immunological events in acute measles, Coovadia et al have reported that those children who have persistent severe lymphopenia (less than 2000/mm^3) subsequently die or develop chronic chest disease. The reversal of immunoparesis is also slower in this group of children (63).

b) Measles mortality

Measles per se is seldom fatal. It is the associated complications which make it one of the very dangerous illnesses (300). Death due to measles is defined as any death occurring within a month of onset of the rash (1). The gravity of the problem is well summarised in a West Asian proverb quoted by Morley (234), "Count your children after measles has passed".

Few other diseases cause as much morbidity and mortality as measles does among young children in India and other developing countries (139).

Mortality due to measles complications ranks first in the list of EPI case fatalities in different diseases in a study by Sundaravalli (316)

	Disease	Case fatality rate
-	Measles	22.4%
-	Pertussis	17.45
-	Poliomyelitis	7.1%
-	Diphtheria	4.9%

Five possible factors are identified with high mortality rates in measles. These are -

(i) Age at infection : Average age of infection varies from 14 months in high population density areas to 24-60 months in low density areas.

For children under one year of age, age-specific mortality rates varying from 0.19% in the USA to 64% in West Africa have been reported (33, 131).

In Guatemala, case fatality rate of 11.5% in infants against 4.5% in older children has been reported (102).

In India, various researchers have reported infant case fatality rates ranging from 10-20% and have noted highest mortality in the later half of infancy (71, 95, 100, 316).

(ii) Nutritional status : Though 400 times mortality in severely undernourished children with reference to normal children has been reported (231) and a 66% fall in mortality due to measles has been attributed to improved diet (216), a few studies have challenged the role of nutrition in measles-related mortality. Aaby et al have reported a 25% case fatality rate from Guinea Bissau from amongst those with good nutrition but with overcrowding due to polygamous family structure (2). A recent case control study from rural Bangladesh also concludes that mortality in measles is not related to nutritional status (167). Mathews et al also report significant mortality amongst well nourished children (204). Within the same house, secondary cases have a much higher age-specific case fatality rate than the index case. This is believed to be due to increased intercurrent infection and a higher dose of the virus (1,2).

(iii) Duration of diarrhoea : Diarrhoea lasting more than seven days has been identified with measles-related mortality (167). Several studies have reported a high incidence of diarrhoea and diarrhoea-related complications in children suffering from measles (23, 141, 167).

(iv) Secondary infection : In India, many measles-related deaths have been attributed to secondary bacterial infection. In one study, secondary pulmonary pneumonia was reported to be responsible for half the mortality (260). In a study from Nagaland, 50% died of respiratory complications while another 35.71% died due to respiratory and gastrointestinal infections (23).

(v) Availability and utilisation of medical services : The easy accessibility and prompt utilisation of medical services helps in preventing secondary complications and thus undoubtedly reduces mortality (344).

3. Modified Measles (177).

This occurs in those infants or children who have been immunised with immune serum globulin after exposure to disease or in infants whose materal immunity levels have only partially waned.

It differs in the following ways-

(i) Incubation period is prolonged to 14-20 days.
(ii) Prodromal period is shortened to 1-2 days or is even absent.
(iii) Clinical features

- Koplik's spots may be absent.
- Coryza, conjunctivitis and cough may be minimal or absent.
- Fever is usually low grade.
- Rash is minimal, sparse and discrete.
- No or minimal complications due to measles.

4. Atypical Measles

This was seen in children who were previously immunised with inactivated measles virus vaccine and were subsequently exposed to natural measles (177, 237). It was characterised by high fever; unusual rash- urticarial, maculopapular, petechial, purpuric or occasionally vesicular with predilection for extremities; oedema of hands and feet; myalgia; severe hyperaesthesia of skin; pneumonitis and/or pneumonia with pleural effusion. These patients had very high HAI titres compared to those of typical measles (177).

5. Measles and the Central Nervous System

a) Acute measles encephalomyelitis

Post-infectious measles encephalomyelitis, an acute, perivenular inflammatory and demyelinating disease, is the most common neurologic complication of measles. It is rare in children under two years of age, but complicates about one in 1000 measles virus infections in older children. In contrast to measles virus dissemination in the malnourished and secondary infections, which constitute the major causes of death

in measles and are thought to be related to immunosuppression that is induced by measles virus, an autoimmune pathogenesis is suggested for measles encephalomyelitis. It usually occurs within one week of appearance of the rash, but rarely may occur prior to or few weeks after the rash. The mortality rate is 10-20% and the majority of survivors have neurologic sequelae (147).

In some cases, a direct evidence of invasion of the brain cells by measles virus, i.e. measles-like inclusion body in the brain cells, or isolation of measles virus from the CSF or cocultivation from brain tissue is reported (165).

b) Subacute sclerosing panencephalitis (SSPE)

This term is commonly applied to subacute or chronic forms of measles encephalitis characterised by an insidious onset of mental deterioration and later, motor dysfunction progressing to convulsions, coma and death usually within a year or two. There is a long latent period of about six years between measles infection and the onset of neurological signs. It is noteworthy that measles at an early age is common in children in whom SSPE later develops. In SSPE patients in South Africa, 43% had measles before the first birthday. Measles occurred in 46% of such patients in USA and 48% in UK before their second birthday (165, 242).

The disorder is characterised by widespread histological lesions throughout the white and grey matters of the brain, consisting of perivascular cuffing of the small blood vessels by lymphocytes and plasma cells and intranuclear and intracytoplasmic measles inclusion bodies. It is believed that the brain is seeded with measles virus during viraemia of the acute infection. It seems that the immune system of these patients is unable to clear the suppressed infection leading to continuing intracellular synthesis of measles components in the brain cells. Serum measles antibody titres of SSPE patients are usually very high (165, 221, 242).

c) Atypical measles encephalitis

There have been several reports of atypical forms of measles encephalitis which do not fall under the two categories described above.

A few cases of measles have been known to cause encephalitis in patients after immunosuppressive chemotherapy or in others where there is no evidence of immunosuppression.

They had a wide range of clinical manifestations but also had some clinical, serological, histological or virological information to assume that they had acute, subacute, or chronic measles inclusion-body encephalitis (165).

III. MEASLES VACCINES

A. Development

Over 35 years ago, in 1954, Enders and Peebles isolated the measles virus in human renal cell cultures from the blood of an 11 year old boy named David Edmonston, from Bethesda, Maryland, USA, in the early stages of classical measles (87). This experiment provided a tool for a fresh approach to the search for safe and effective means of inducing immunity against measles. This led to the development of measles vaccine by Enders, Katz and their colleagues which made the dream of control and prevention of measles a reality which had eluded researchers for about 200 years (Fig. 5).

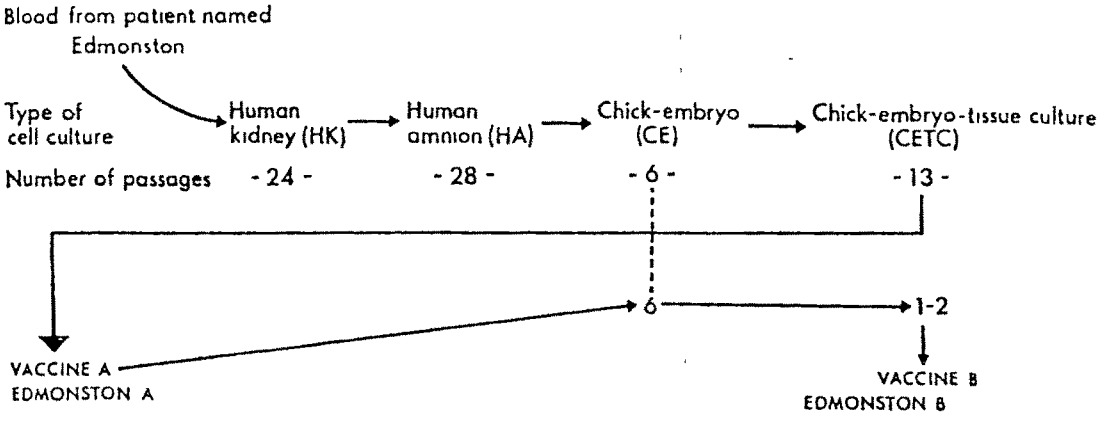
Twenty four serial passages of Edmonston strain in human renal cells were accompanied by no alteration in cytopathic effect or rate of viral replication.

Twenty eight further passages of the virus in primary amnion cell culture resulted in slower cytopathic changes and spindle cell transformation. The attenuation of measles virus brought about by multiplication and six passages of this strain in the chick embryo (CE) was a major breakthrough (152, 153, 179). After thirteen further passages in CE, the first batch of live measles vaccine was prepared for human inoculation, designated Edmonston-A, but was found to be too virulent

FIGURE-8

PASSAGE HISTORY OF EDMONSTON VACCINE STRAIN
AND OF VACCINES DERIVED FROM EDMONSTON A & B LINES

Vaccines Developed from Edmonston Strain



Beckenham 3C { 3 passages in CETC at 37° C.; 14 „ „ „ „ 33° C.

Vaccine 8 39 „ „ „

Vaccine L 5 „ „ „

Schwarz vaccine 77 passages in CETC

Glaxo vaccine „ „ „ „

Beckenham 4A 3 passages in CETC at 33° C.

16 { 3 „ „ „ „ 33° C.; 30 „ „ CE; 3 „ „ CETC „ 33° C

20 77 „ „ „ „ 33° C.

27 83 „ „ „ „ 33° C.

31 85 „ „ „ „ 33° C

Milovanović vaccine 94 „ „ „

Canine kidney vaccine

Other Attenuated Measles Vaccines

Biken vaccine (Japan) 61 passages of Sugiyama strain of measles in chick-embryo amniotic membrane

Denken vaccine (Japan). Toyoshima strain isolated in monkey-kidney cultures → human conjunctival cells → bovine kidney cells

Fadeeva's vaccine (USSR) Strain USSR in HA → CETC

Smorodintsev's vaccine (USSR) Leningrad-4 strain in HK → HK(24) → HA(35) → CETC → guinea-pig renal cells

Smorodintsev's vaccine (USSR) Leningrad-16 strain in monolayer cultures of guinea-pig-kidney cells

for vaccination purposes. Using this as a seed virus, further passages in CE led to the development of Edmonston-B viral strain in 1959 (88). Initial vaccine trials were conducted by oral, intranasal or conjunctival route using Edmonston-A or B strain (159,188,290). Extensive studies using Edmonston-B vaccine revealed it to be highly immunogenic but unfortunately, adverse clinical reactions (high fever and rash) to the vaccine precluded its use. The simultaneous administration of measles human immunoglobulin was advocated to reduce the febrile reactions (207). Between 1960 and 1962, the first generation of inactivated vaccines came for the field trial. These were abandoned subsequently due to severe reactions (275).

Pursuing this need, many workers continued the further attenuation of Edmonston-B strain in CE culture till hyperattenuated vaccines emerged in 1960 (215).

The first International Conference on Measles Immunisation was held at the National Institute of Health (NIH), Maryland, USA, in November 1961. After one year of publication of its report in March 1963, the live measles vaccine was licensed for use in the USA (178).

B. Types

1. Inactivated Vaccines

Between 1960 and 1962, the first generation of inactivated vaccine appeared in the market. The initial formalin-killed vaccines were weakly immunogenic. Subsequently, concentrated and purified vaccines were prepared from the Edmonston strain in monkey kidney and chick embryo tissue cultures. Numerous inactivated vaccines were made available for clinical trials employing different protocols, using either inactivated vaccine or combining it with live measles vaccine (9,80,171,217,248).

However, the antibody response was poor and short-lived. It also did not induce secretory IgA (20,60,242). Documented seroconversion rates were 70% with two does and 90-95% with three doses. Antibodies declined over 6-12 months and became undetectable after 12 months (80). Unusual local or systemic reactions were seen when the recipients of

killed virus vaccine were later exposed to natural measles or were immunised with live attenuated vaccine. These reactions to live vaccine included severe local tenderness, swelling, erythema, haemorrhagic or vesicular lesions accompanied by malaise, fever and regional lymphadenopathy. Exposure to natural measles resulted in a severe atypical form of measles with high grade fever, oedema, pneumonia and toxicity, Such reactions do not follow repeated inoculation of live virus vaccine. The use of inactivated vaccines is not recommended (227, 242).

2. Live Attenuated Vaccines

Using the Edmonston-B virus as a seed virus, various further attenuated vaccines have been developed e.g. live attenuated Schwarz vaccine was derived by 77 additional passages in CE culture at a temperature of 32°C instead of 36°C or 37°C, while the Moraten vaccine was achieved by 40 additional passages (see Fig. 5). Most of these vaccines are highly effective. The original Edmonston strain (USA) and Beckenham strain (UK) are no longer used because of their toxicity. The third generation further attenuated vaccines now under use are highly effective. The immunity induced lasts at least 14 years and may be lifelong. There is a prompt humoral antibody response and subclinical infection on exposure to measles virus, even when the antibodies have become undetectable. Japanese CAM-Ex live measles vaccine has 90% seroconversion and induces low but persistent antibody levels (227). The Kitasato Insitute, Japan, has developed AIK-C strain (A=America, I=Iran, K=The Kitasato Institute and C=virus adapted to chick embryo cells), which showed an incidence of fever of one-half or one-third of that for other widely used live measles vaccines, and had sufficiently high immunogenicity (196).

C. Stability and Storage

During the past few years, the development of more heat stable vaccines has helped overcoming various cold chain maintenance problems which used to lead to considerable loss of the vaccine. Aqueous live vaccine had to be stored, frozen in sealed glass vials at -70°C temperature. The lyophilised freeze-dried products which contains less than 2% residual

moisture can be stored at 4°C for almost one year. Once reconstituted, it is stable for 8 hours at 4°C (91). In a study, where this vaccine was stored at 25°C for 7 days, the vaccine induced seroconversion in 92% of the children vaccinated (121). During the last few years, Rouvax (Merieux, France) and Attenuvax (SKF, USA) have become available which are claimed to be maintaining the minimum infectivity titre even after 14 days of storage at 37°C. Reconstituted Attenuvax maintains its potency at 25°C for 48 hours and at 37°C for seven hours (122). In general, the freeze-dried lyophilised vaccines now available are potent for -

- more than one year at 2-8°C
- four months at 20-25°C
- three weeks at 36-38°C (205).

In a trial conducted by Saha et al at Central Research Institute, Kasauli, India, to study the thermostability of live measles vaccines, it was observed that even after accidental exposure to high temperatures, the present generation further attenuated vaccines remain potent (284).

In another trial, Peetermans et al have reported that Schwarz measles strain vaccine is potent even after exposure to 41°C for a period of one week (252).

Similar proof of greater thermostability of measles vaccine was provided by Heymann et al in a study of second generation measles vaccines in Cameroon (122).

The increased heat stability of the vaccines does not eliminate the need for a well-monitored system of vaccine distribution but eases the cold storage requirements of conventional measles vaccines under the field conditions (122).

D. Dosage

To immunise a susceptible child, only 20 TCID 50 are required (43, 125). The recommended dose is 1000 TCID 50. The reduction of this dose would not be a satisfactory economic measure in measles compaigns as seroconversion decreases significantly (276).

However, Morley asserts that one-fifth of the standard dose vaccine can safely be given as long as extra precautions are taken once the vaccine has been reconstituted (234).

On recommendations of the WHO, all the vaccines now used have concentration of at least 1000 TCID 50 per dose (31, 125).

The live vaccines now in use are given as a single dose of 0.5 ml injection subcutaneously as early trials had established an all or none response to measles vaccine.

E. Route of Administration

Although intradermal route was found to be immunologically better (166), subcutaneous route advocated currently also gives a significant seroconversion (28). The wider use of administration of vaccine by using jet injectors (of 0.05 cc to 0.1 cc) by staff specifically trained to use them offers scope for economy (119, 233).

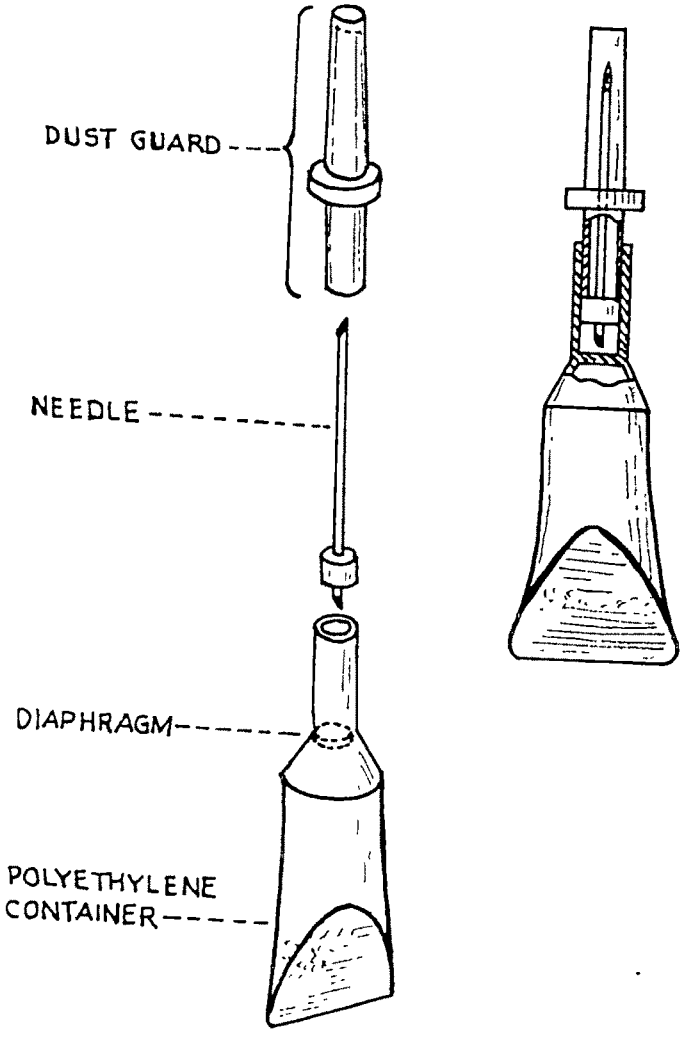
Recently, Edmonston-Zagreb (EZ) strain of measles virus has been developed which has been passaged through human diploid cells and is a safe and successful vaccine (133). Administration of tnis vaccine strain through the respiratory route has been successful because the virus replicates more readily in human lung fibroblasts than does the chick cell adapted Schwarz strain (201). Sabin in 1983 and Whittle in 1984 successfully immunised infants 4-6 months old with EZ vaccine given subcutaneously or by aerosol inhalation (279, 341).

A novel single dose delivery system (Fig. 6).

A novel system of administration of measles vaccine was licensed for general use by the Bureau of Biologics, Foods and Drugs Administration, USA, in 1978 (125). The system consists of a single dose inexpensive Ezect(R) (Merck, Sharp and Dohme) device developed to simplify the delivery of vaccine in single dose vials (124, 206). The vaccine is distributed in a single dose configuration that eliminates the impracticability and inconvenience of bringing a large number of children together at one time so that all the vaccine in a multi-dose package may be used. The

FIGURE-6

A SYRINGE\VIAL DESIGN FOR USE IN DELIVERY OF LIVE VIRUS VACCINE (EZEJECT ®)



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vaccine is dispersed and dried in a single plastic container that also serves as a syringe. For use, the needle is pushed downwards through the diaphragm. The puncturing of the diaphragm permits the intake of diluent for rehydration of the vaccine and the syringe is then ready for use for vaccination. The vaccine is expelled by squeezing the polythelene container. The syringes are made of a plastic that is acceptable for human use and are stored in foil containers. The clinical tests using this vaccine showed a seroconversion rate of 97-100%. The potency of the vaccine in the syringe was the same as that of vaccine dried in glass vials as was its antigenicity for humans (206).

With better understanding of immunology and appreciation of the fact that only IgG antibodies, and not IgA, are transferred transplacentally, the intranasal route has been tried and recent work by Sabin et al indicates that aerosol nasal vaccine at an early age is promising (279).

F. Reactions to Measles Vaccine

Reactions after measles vaccine are usually mild (101, 123, 180, 218, 222, 285, 291, 348).

Schwarz reported the following reactions in children receiving highly attenuated vaccine (291)-

Parameter	Vaccinated	Placebo inoculated
Mean maximum rectal temperature	100.8°F	100.4°F
Mean onset of fever ($\geqslant$ 100°F)	7.3 days	7.8 days
Mean duration of fever	3 days	3.2 days
Occurrence of rash	11.2%	3.6%
Mean onset of rash	9.3 days	9.5 days
Duration of rash	2.5 days	2.7 days

In a study by Meyer et al in 1964 with live attenuated vaccine, 42% of children developed rectal temperature of more than 39°C; 42% developed rash during 6th-14th day (one-fifth having a generalised rash and the rest having a detectable rash of limited distribution, usually over the head and shoulders); 16% had upper respiratory infection (222).

Hillman and associates in 1968 compared clinical reaction rates among three live attenuated vaccines - Moraten, Enders and Schwarz (123). The incidence of fever (oral temperature of more than 101°F) was 45.9%, 14.4% and 21.4% in recipients of Edmonston, Moraten and Schwarz vaccine respectively. The critical period of occurrence of fever was 5-12 days following vaccination. Other reactions observed were rash, local reaction, headache, irritability, malaise, upper respiratory illness and gastrointestinal symptoms.

In a study reported by Schwarz et al (292), 35.8% of the children who received Schwarz vaccine developed mild fever as against 62.5% of those receiving Edmonston vaccine. They also reported coryza (45.6%), cough (44.4%), pharyngotonsillitis (29.6%), conjuctivitis (16%) and diarrhoea (12.3%).

Ghosh from India (101) has reported fever (55.1%), rash (34.5%), coryza (34.5%) and other side effects (19%).

Meera (218) has observed upper respiratory infection (61.6%), fever (53.2%), diarrhoea (15%), rash (8%), Koplik spots (0.8%) and conjuctivitis (0.4%).

Katiyar, in 1985, in his study observed fever in 53.2%, diarrhoea in 41.9%, upper respiratory infection in 25.8%, cough in 19.4% and rash in 7.9%. The overall reaction was seen in 79% of vaccinated children as compared to 4.8% in the control group (151).

Another Indian author, Kumar (180), noticed 37.9% overall reaction in immunised children as against 29.9% in control group. His observations are as follows -

Nature of reaction	Immunised (%)	Time of onset (days)	Control (%)
Fever	27.7 7.8	0-7 8-30	7.8 10.2
Diarrhoea	11.6 12.1	0-7 8-30	12.1 10.7
Cough/Upper respiratory infection	3.9 1.9	0-7 8-30	5.3 9.2
Rash	0.5	0-7	-

In a WHO-sponsored field trial (348), using further attenuated Edmonston strain measles vaccine, an incidence of 15% of fever and 5% of rash was observed. When 0.2ml of gammaglobulin was injected along with the vaccine, the incidence of both reactions was only 3%.

Reactions reported by various workers with the use of further attenuated live measles vaccines are summarised in Table-1.

Local reactions to the vaccine are also known (135). Although both low serum antibody and high measles specific lymphocyte reactivity are associated with marked local reaction, findings suggest that exaggerated lymphocyte reactivity is of greater importance in the adverse clinical response (168). In a study from Australia, mottling of the skin 30 minutes after measles vaccination with complete recovery has been reported (208).

Allergic reactions to egg protein e.g generalised urticaria, angio-oedema and respiratory difficulty have been reported (120).

No statistically significant difference in side reactions has been observed in undernourished and healthy children (339).

The incidence of serious complications following measles vaccination is low. The risk of SSPE following vaccination is 0.05 to 0.1 cases/100,000 vaccinees. The comparison between the incidence of serious complications following disease and vaccination is summarised as follows (351) -

TABLE-1

REACTIONS WITH FURTHER ATTENUATED LIVE MEASLES VACCINE

Sr. No.	Source		Total %	Fever %	Rash %	U R I %	Diarrhoea %	Conjuncti-vitis %	C N S %	Other %
01.	M M W R	(49)	-	5.15	5.0	-	-	-	0.0001	-
02.	Jajoo et al	(135)	23.25	7.3	0.66	6.6	0.66	-	-	-
03.	Joseph et al	(149)	-	8.8	1.4	1.2	-	-	-	-
04.	Kaur et al	(158)	79.0	53.0	-	26.0	42.0	-	-	-
05.	Kumar et al	(180)	37.9	27.7	0.5	3.9	11.6	-	0.5	-
06.	Natu et al	(241)	-	18.5	2.3	9.4	12.8	-	0.8	0.8
07.	Phadke et al	(254)	-	93.7	0.6	71.6	-	11.3	-	-
08.	Rouvax	(275)	-	20.0	5.0	-	-	-	0.00008	-
09.	Sehgal et al	(294)	-	1.2	0.4	-	-	-	-	-
10.	Shah et al	(297)	20.7	1.3	-	-	-	-	-	-

Adverse reaction	Measles complications per 100,000 cases	Measles vaccine complications per 100,000 vaccinees	Background rate of of illness per 100,000 persons
Encephalitis/ encephalopathy	50-400	0.1	0-1-0.3
S S P E	0.5-2.0	0.05-01.	-
Pneumonia	3800-7300	-	-
Convulsions	500-1000	0.02-190	30
Death	10-10,000	0.02-0.3	-

In USA, the dramatic decline in measles following widespread immunisation is being reflected in a similar fall in the cases of SSPE. It appears that the overall effect of the vaccine is to protect against SSPE by preventing measles with its attendant higher risk of SSPE (165).

A rapid decline in the overall incidence of measles due to widespread use of measles vaccine was accompanied by an immediate decline in the incidence of encephalitis in USA (127).

The reported figures of measles cases, measles encephalitis cases and measles encephalitis deaths in USA after introduction of mass measles immunisation are given below (227) -

Year	Measles cases	Measles encephalitis cases	Measles encephalitis deaths
1963	3,85,156	239	30
1970	47,351	27	2
1975	24,374	17	5
1979	13,597	3	1

A depression of lymphocyte function (and not a depletion of functional lymphocytes) and temporary suppression of the delayed hypersensitivity response has been reported following MMR vaccination (235).

G. Contra-indications

Considering the importance of protecting against measles, medical personnel should use every opportunity to vaccinate susceptible children (49).

The absolute contra-indications to measles vaccine in children are leukemia and those receiving immuno-suppressive drugs, because of the risk of persistent progressive infection, such as giant cell pneumonia (242). However, in case of acute leukemia in remission, successful seroconversion without added risk has been obtained with cessation of chemotherapy one week before to one week after the administration of measles vaccine (275). A larger dose may be advisable in such cases (242).

A child with active tuberculosis should be receiving anti-tuberculosis treatment when live measles vaccine is administered. A tuberculin test prior to or concurrent with measles vaccination is desirable. Anergy to tuberculin may develop and persist for one month or longer after administration of the vaccine (242).

Asthma is not aggravated by and does not form a contra-indication to measles vaccination (160).

Convulsions or epilepsies are not absolute contra-indications, provided convulsions are under control (62,81).

Since the vaccine virus is grown on chick embryo fibroblast culture rather than in eggs, it can be given safely to children who are allergic to egg protein (242). However, anaphylactic type of reaction may occur and proper precautions should be taken (275), especially in those having neomycin sensitivity (50).

The response to vaccine is unpredictable if immunoglobulin has been administered in the 3 months preceding immunisation (242) or vaccine should precede immunoglobulin by at least two weeks (50).

Adequate immune response is found in severely malnourished patients receiving the vaccine, though it may be delayed. However, with a 50% case fatality rate following measles in these children, it forms the prime indication for measles vaccination (132, 257).

Use of live measles vaccine is not recommended for pregnant women (242) though low or no risk is found to the foetus (258).

Neurovirulence, in the form of measles vaccine virus encephalitis, is a possibility (17, 331).

H. Acceptance

Acceptance of measles vaccine by the uneducated rural poor is a cause of concern in the developing countries. As Morley quotes, "In developing countries, where children have frequent febrile illnesses, these symptoms (due to vaccine) are likely to go unnoticed and drawing attention to them may result in other intercurrent illnesses being blamed on the vaccine" (232). However, Assad states, " The experience with immunisation is rewarding; mothers who had previously accepted measles as an unavoidable risk, clamour for immunisation of their children once its effectiveness has been demonstrated" (13). Similarly even after warning mothers of adverse reactions, rural mothers readily accepted the vaccine irrespective of educational status and family size in a study reported by Shah et al (297).

I. Measles Vaccine with Multiple Antigens

Following measles, mumps and rubella (MMR) vaccination, seroconversion rates of about 98% for measles have been reported with side reactions being milder (315).

John has shown that measles and DPT vaccines can be mixed in one syringe just prior to administration (146). No difference in protection was observed, when measles and DPT were given with the same syringe or with different ones (210).

A combination of Schwarz vaccine with meningococcal A and menigococcal A + C vaccine can be used safely and effectively when given between the

ages of 8 months and 4 years. Seroconversion for both A and C meningococcal vaccines was 100% but that for measles vaccine was slightly depressed being 80% when measles vaccine was used in combination with meningococcal A vaccine and 69% when used with meningococcal A + C vaccine (6).

J. Safety

The WHO has outlined the present requirements for production of measles vaccine (348). Contamination of live vaccine with an adventitious agent or agents coming from the tissue cultures which may produce malignant tumour is a constant possibility; however, as yet there is no evidence that such contaminants have produced tumours in man, though the possibility of a very long incubation period, possibly decades, for oncogenic effects to surface cannot be ruled out (238).

K. Optimum Age for Vaccination

The issue of optimum age for measles vaccination is a controversial one, and has been the subject of discussion in recent years, especially in the developing countries like India. This is so because the determination of optimal age depends not only on factors like epidemiological data, seroconversion data and malnutrition but also on the type of test employed for measles antibody measurement, its sensitivity, design of study etc. (109).

As per a WHO study (349), three factors have to be primarily considered while determining the earliest possible age for vaccination against measles, viz.-

- the time of waning of maternal antibodies,
- the incidence of measles infection in the early months of life (reviewed earlier in Section II-B-1-b of this Chapter), and
- the seroconversion rates and the efficacy of vaccine given before one year of age.

Passively acquired maternal antibodies

Maternal IgG antibodies against measles, transmitted transplacentally, provide infants with protection against measles in the first few months

of life; at the same time interfering with the development of immunity to measles following vaccination (223). The level of these antibodies in the cord blood in the majority of cases is identical to that of maternal antibody levels (39,72,157,334). These antibodies then start waning gradually to undetectable and therefore non-protective levels.

Maternal antibody titre of 1:6 has been reported as interfering with successful immunisation against measles (349).

Various workers have reported different ages at which passively acquired antibodies wane in the majority of infants as shown below -

Worker	Reference	Year	Age (months) when in majority, measles antibodies not detected
Torigoe et al	(321)	1986	6
Stokes et al	(310)	1960	7
Strauss and Zeimen	(312)	1967	7
Ueda et al	(323)	1967	7
Reily et al	(266)	1969	7
Mehta et al	(219)	1972	7
Dave	(67)	1980	> 6
Sinha et al	(305)	1981	> 6
Man Mohan et al	(199)	1981	8
Krugman	(171)	1965	11
Albrecht et al	(7)	1977	>12
Yeager et al	(356)	1977	>12

Albrecht et al (7), using a sensitive neutralisation test, found that many children who failed to seroconvert had pre-existing maternal antibodies to measles virus, though found to be negative by the HAI test. Children with lower pre-existing antibody titres seroconverted but the resulting antibody titre was significantly lower than in children without

pre-existing antibody titres. The result of this study demonstrated a possible mechanism for vaccine failure under 12 months of age.

Katiyar (151) also demonstrated that the rate of seroconversion was inversely related to the level of prevaccination titre and with increasing prevaccination titres, the geometrical mean titre (GMT) of postvaccination samples decreased.

Krugman et al, in a longitudinal study, measured measles immunity during the first year of life by serial determination of measles HAI antibody by the method described by Rosen (171,274). The antibody titres of 51 one month old children ranged from less than 1:8 to 1:512 but 3 infants had no detectable antibody. By the fourth month of age, 53%, and by six months of age, none, had detectable passively acquired antibody. There was a good correlation between initial level of antibody and its persistence. However, using more sensitive methods as described by Norrby (246, 247), at least 20%, 12% and 8% of children had detectable antibody by the ages of 9, 10, and 11 months respectively.

In a collaborative study by the Ministry of Health of Kenya and WHO, the proportion of children having negative HAI antibody titre was found to increase sharply from 53.9% at 5 months to 73.2% at 6 months and to 90% at 9 months of age (349).

Some infants lose their antibodies and become susceptible to measles as early as 5 months of age (73, 230, 335). In other infants, low levels of maternal antibodies may persist until approximately 9 months of age (74,111,349). But, unfortunately, in many developing countries, frequent exposure to measles results in illness as soon as children have lost their maternal antibodies (13,24,31,73,231,233,335,349). Since the maternal antibodies are lost at different ages, there is no exact age for measles vaccination that will lead to prevention of disease in all children as shown by Griffith (104). However, a vaccine that could be given to younger children would be easier to deliver since younger infants tend to have more contact with health facilities. Nine months is a particularly awkward

age since children often are too heavy to be carried to vaccination sites, but they cannot yet walk (134).

Seroconversion

Any titre is a protective titre against measles disease (109). A fourfold increase in the existing titre is considered a successful seroconversion (158). Several serological studies (Table-2 and Table-3) have been carried out on seroconversion following measles vaccination since its introduction.

This variability depends not only on the type of vaccine used but also to a greater extent on methods employed to detect the antibodies and the types of antibodies. For example, the filter paper strip method used in some of the studies has its own limitation that it indicates HAI titre only when it is 1:16 or more. So, even if the post-vaccination titre has risen four-fold and is less than 1:16, this method fails to detect it. Similarly, in many of these studies, the measurable measles antibody titre had a lower limit of 1:20, 1:16, 1:12 or 1:10 (7,109, 187,269,289).

In some studies, where children were vaccinated in the presence of low levels of maternal antibodies, they developed lower levels of postvaccination titres than did the children without detectable maternal antibodies (7,187,225,269,289). In some studies, complement fixation antibodies were measured instead of HAI antibodies (73,228).

A small sample size can also contribute to the variable rates observed in many of these studies. Other factors possibly explaining the differences in studies include differences in the strains and dosage of the vaccine (109).

The first clinical trial with live measles vaccine was carried out in 1958, where 303 children were given Edmonston-A or B vaccine, 272 by the parenteral route and the remaining 31 by the oral, intranasal or conjunctival route. The response to the two vaccines was essentially

TABLE-2

SEROCONVERSION RATES (%) BY AGE AT VACCINATION (OTHER COUNTIRES)

Sr. No.	Worker		Country	Year	Age (months)/seroconversion (%)	
01.	Meyer et al	(222)		1964	7 90.0	
02.	Hendrickse	(117)	Nigeria	1966	9 86.7	
03.	Hendrickse	(118)	Nigeria	1968[C]	10 95.7	
04.	Krugman	(173)	U S A	1971	9-11 86.0	≥ 11 97.0
05.	Borgono et al	(32)		1971	8 94-99	
06.	Reynolds	(269)	U S A	1972	6-11 79.0	≥ 11 100.0
07.	Hyden	(111)	Kenya	1972[C]	6 98.0	
08.	Ruben	(276)	Nigeria	1973	7 63.6	11 84.4

TABLE - 2 : CONTD.

Sr. No.	Worker		Country	Year	Age (months) Seroconversion (%)						
09.	Tianjin	(320)	China	1974	6-7	7-11	≥11				
					94.3	96.8	95.0				
10.	Hayden	(112)	Kenya	1974	6-9						
					92.0						
11.	Dick	(74)	S.Africa	1975	6	7	8	9[b]	10	11[b]	12[b]
					23.0	45.0	57.0	86.0	71.0	86.0	80.0
12.	krugman	(176)	U S A	1975	6-7	7-9	9-12				
					28.6	56.5	72.2				
13.	Breman	(36)	Ivory Coast	1975	7	11					
					84.3	94.7					
14.	Wallace	(336)	Nigeria	1976[c]	9						
					39.3-63.3						
15.	Burrowes	(42)	Rhodesia	1976[c]	6	9					
					71.4	93.9					

TABLE - 2 : CONTD.

Sr. No.	Worker		Country	Year	Age (months)/Seroconversion (%)							
16.	Ministry of Health and UNICEF	(92)	Tanzania	1977	5	6-7	7-9	9-11	≥11			
					17.0	44.0	63.0	24.0	68-91			
17.	Ministry of Health and WHO	(349)	Kenya	1977	5	6	7	8	9	12		
					60.0	90.3	66.6	100.0	92.5	100.0		
18.	Yeager	(356)	U S A	1977	>12							
					94.0							
19.	King	(164)	Tanzania	1978	5	8[c]	11					
					0	50.0	83.3					
20.	Medical Research Centre[a]	(90)	Kenya	1979	5	6	7	8	9	10	11	12
					24-48	40.0	93.0	90.0	93.0	94.0	100.0	100.0
21.	Wesley	(339)	S.Africa	1979	7							
					83.0							

TABLE - 2 . CONTD.

Sr. No.	Worker		Country	Year	Age (months)/Seroconversion (%)						
22.	McMurray	(211)	Columbia	1979	10 100.0						
23.	Ministry of Health and PAHO	(223)	Costa Rica Chile	1981[d]	6 58.9 80.7	7 69.3 91.1	8 83.7 92.5	9 87.1 93.9	10 93.4 89.6	11 94.2 95.5	12 97.1 85.7
24.	Lee YL et al	(183)	Equator	1983	7-9 98.7	9-12 100.0					

a = Some of the data for this study were obtained from Reference No. 341.

b = Less than 10 children studied.

c = Some of these children received reduced doses of vaccine.

d = Top row represents children weighing $\geq$ 85% of expected norms.
Bottom row represents children weighing $<$ 85% of expected norms.

TABLE-3

SEROCONVERSION RATES (%) BY AGE AT VACCINATION (INDIAN STUDIES)

Sr. No.	Worker		Year	Age (months)/seroconversion (%)									
01.	Ghosh et al	(101)	1977	6-12	13-18	19-24	> 24						
				59.0	50.0	50.0	33.3						
02.	Mittal et al	(228)	1979	6-9	10-12	13-18	19-24	25-36	37-60				
				66.7	72.8	28.5	40.0	0	40.0				
03.	Dave	(67)	1980	6-18									
				95.0									
04.	Bhatnagar et al	(24)	1981[a]	8	10	12	15						
				66.7	77.4	84.3	84.6						
05.	Sehgal et al	(294)	1983	6-12	12	18	24	30	36	42	48	54	60
				80.0	76.3	95.2	76.2	85.7	85.4	57.1	91.5	83.3	100.0
06.	Job et al	(138)	1984	6-8	9-11	12-15							
				87.0	94.0	98.0							
07.	Kantharia	(150)	1984	9-11	12-14	15-17	18-21	21-23					
				94.8	66.7	69.2	41.7	86.7					

TABLE - 3 : CONTD.

Sr. No.	Worker		Year	Age (months)/Seroconversion (%)						
08.	Saha et al	(283)	1985	< 9	9-12	13-15	16-20	21-25		
				78.9	95.5	88.5	96.1	82.8		
09.	Katiyar et al	(151)	1985	6	7	8	9-12	13-15		
				33.3	40.0	80.0	74.1	75.0		
10.	Bhaskaram et al	(22)	1986	9-12	13-15	15-36				
				82.9	57.9	98.0				
11.	Dholakia	(72)	1987	9-12	13-15	16-18	19-21	22-24	25-60	
				78.8	82.4	84.4	84.4	74.2	70.6	
12.	Agrawal	(5)	1988	6	7	8	9	10	11	12
				81.5	69.3	88.9	92.0	90.9	90.5	94.7

a = titre $\geq$ 1 :20

similar but with the nonparenteral routes, the results were not encouraging. Seroconversion occurred in 96.5% of the children vaccinated by the parenteral route (80).

WHO-sponsored field trials in different countries like Chile, India, Japan, South Africa, UK, USA, USSR and Yugoslavia gave the seroconversion rates varying from 90-95% except in case of Japan where using Biken vaccine, the seroconversion rate was 68-69% only (348).

With live Edmonston-B vaccine, Meyer in Upper Volta obtained rates of 50%, 76% and 90% seroconversion in children vaccinated at 5,6 and 7 months respectively (222).

Cinfecu et al in a study of 185 children in the age group of 1-6 years, using Schwarz vaccine, observed the seroconversion rate of 95.3% by the HAI technique (61).

In a study conducted by WHO in Kenya, seroconversion rate was 72% at 7 months and 98% at the age of 10 months (93).

Ifekwunigwe et al, on the basis of a seroconversion study on 241 children aged 6 months to 9 years, showed 94% of cases having HAI antibody titre equal to or more than 1:20 eight weeks after immunisation (132).

To evaluate the effectiveness of measles vaccine in reduced dosage, Schwarz vaccine was given in variable doses by jet injector to 967 seronegative children aged 7-30 months in rural villages in North-West state of Nigeria (336). For children over 12 months of age, when given the dose of 3000 TCID 50, there was 89.3% seroconversion, but dosage reduction of 40%, 60% and 80% led to seroconversion rates of 79%, 71.2% and 45.7% respectively. Reducing the volume of the inoculum below the standard of 0.5 ml also resulted in further reduction in seroconversion rates at each antigen dosage level. Wood et al, in 129 children, obtained seroconversion rates of 80% and 69% with a dose of 0.5 ml and 0.2 ml respectively (347).

In the future more and more child-bearing women will not have had natural measles, but either will have been immunised in childhood or will not have received vaccine. Transfer of little or no measles antibody could alter the susceptibility and it is conceivable that in future, an age earlier than 15 months may be recommended for immunisation even in the developed countries (98).

L. Malnutrition and Vaccination

As stressed upon earlier, malnutrition is a strong indication of the urgent need for immunisation as in these children, the disease tends to be more severe and more often associated with complications and mortality than in well nourished subjects (132,170,211,234). Mortality due to measles is reported to be 400 times higher in malnourished than in normal individuals (234).

Moreover, vaccine is safe in malnourished children and seroconversion rates are good (138,151,154,163,211) as is evident from the following observations (138) -

Age group (months)	Normal children		Malnourished children	
	% Seroconverted	GMT	% Seroconverted	GMT
06-08	87.2	40.7	81.8	54.9
09-11	97.0	47.5	85.7	61.6
12-15	100.0	80.0	94.1	54.4

The difference in seroconversion was not statistically significant in both the groups.

Katiyar (151) also demonstrated a highly significant rise in GMT in both malnourished and well nourished children and both pre - and postvaccination titres in the two groups were comparable as is evident from the following observations -

Nutritional status	Pre-immunisation GMT(log)	Post-immunisation GMT(log)
Well nourished	0.5695	1.1494
Undernourished	0.5382	1.3044

There is no significant increase in the number of side effects in malnourished children, as has been shown by the following workers -

Worker		Incidence of side effects (%)	
		Well nourished	Undernourished
Kumar	(180)	35.1	46.1
Katiyar	(151)	77.3	83.3
Meera	(218)	70.4	73.2

M. Vaccine Efficacy and Strategy

The levels of measles antibody following vaccination are comparable to, but are only 20% of those following natural measles infection (242). Measles vaccine produces a lower HAI-GMT of 15 after 8 years compared to a HAI-GMT of 50 in children with natural measles (172). Although quantitative differences in antibody titres between these two groups have been shown, qualitative differences such as have been suggested with rubella vaccine have not been demonstrated (172, 188, 255).

The persistence of postvaccine antibody response to live further attenuated vaccine was studied in 70 children for 16 years by Krugman et al. The HAI titre was equal to or more than 1:64 one month after immunisation in all 70 vaccinees. The antibody was detectable upto 1:2 in 91% after 12 years. Krugman further showed that the decline of HAI antibodies to undetectable levels, i.e. less than 1:2 in 13% of vaccinees. after 16 years of vaccination had no practical significance because of the rapid anamnestic reponse induced by re-exposure to the virus. Moreover,

there was a simultaneous detection of neutralising antibodies which was also considered responsible for the prevention of viraemia and subsequent disease (175).

Katz and Enders (153) showed that titres as low as 1:2 were associated with resistance to measles infection. Serological studies of measles vaccine have produced no evidence of waning immunity over a period of time (174,217,301,337,356).

Ekunwae (86) showed that seroconversion following measles immunisation per se is a direct measure of clinical protection against the disease regardless of the height of antibody titre.

Thus, there is a consensus that vaccine failure, and not waning antibody, requires re-immunisation (174,179,356).

Two patterns of persistence of antibodies are seen (188). In closed populations, there is a progressive decrease in antibody titres (41,172). There is a 16-fold decrease from peak post-vaccination titre over a period of 8 years. In open populations, the level of antibody remains high, presumably as a result of subclinical infection due to re-exposure to wild virus (172). However, a community serum survey of 858 first grade children in Cincinnati in 1972, one year after a major epidemic, showed that 10% of vaccinees had HAI antibody titres less than 1:10 (189).

It has also been shown that the disease, if occurs, in seroconverted children is milder (16, 186).

Impact of measles vaccine

In 1964, British Medical Council began a field trial of measles vaccines including over 36,000 children where two vaccine schedules were used -

(i) one dose of killed vaccine followed a month later by Schwarz vaccine and

(ii) one dose of Schwarz vaccine.

By 1968, they reported that live measles virus vaccine resulted in 84% reduction in the attack rate during the first 9 months and 94% during the subsequent two years which included two epidemics. The protection given by killed vaccine followed by live vaccine ranged from 85-89% (38). They further reported in 1971 that live measles vaccine had remained over 90% effective in the face of continuing epidemics of measles (333).

Since the licensure of measles vaccine in 1963 in USA and its widespread use, the reported cases of measles encephalitis and deaths due to measles are reduced remarkably as is evident from the following data (126)-

(a) Reported cases of measles in pre-and postvaccination era in USA

Age (Years)	Cases/100,000 population	
	Pre-vaccination 1960-64	Post-vaccination 1981
< 05	766.0	7.2
05-09	1236.9	3.8
10-14	169.1	3.1
≥15	10.1	2.5

(b) Reported cases of encephalitis and deaths due to measles in USA

Year	No. of reported cases per 100,000 population		
	Measles	Encephalitis due to measles	Death due to measles
1960	4,41,703	299	380
1963	3,85,156	239	364
1968	22,231	-	-
1971	75,290	-	-
1975	24,374	17	20
1979	13,597	3	6
1981	3,032	-	-

In 1968, the number of measles cases and mortality due to measles were reduced to about 5-10% of the prevaccine era. More extensive use of the vaccine thereafter led to a 97% decline in cases of measles by 1982 (50,177). According to one estimate, since 1963, about 48 million possible cases of measles have been averted, 4800 measles deaths prevented and 16,000 possible instances of mental retardation due to measles averted in USA. It is estimated that USA alone has a net profit of $\sim$500 million dollars per year from measles vaccination (126).

In Canada, the reported incidence of measles in 1981 was reduced by 97% from the average annual rates of the prevaccination period 1949-1958 (182).

In China, before the vaccine era, the annual incidence of measles was as high as 1000-5000 per one lakh population in epidemics which occurred every alternate year. After the introduction of measles vaccine in 1965, the incidence had dropped to 57 cases per one lakh population by 1980 (360).

In May 1967, Gambia became the first country in the world to interrupt the transmission of measles (344). The USA is the only country with widespread immunisation with a substantial fall in the incidence of measles and has nearly achieved elimination (332).

On the other hand, in France, where vaccine is licensed since 1968, the level of vaccination coverage is less than 20% with an incidence of 5.6-75 cases per 1000 population and a death rate of 0.56 per one million. The problem posed is grave enough to justify a national campaign, but as the disease is no longer feared, participation of people is poor (268).

Vaccine and herd immunity

Measles vaccination, like smallpox vaccination, should be especially vulnerable to the herd immunity effect. The basic concept of herd immunity should be directly applicable here as man is the only natural host within whom transmission occurs by relatively direct contact and induces lifelong

immunity. Furthermore, immunity, that is believed to be equal to that following natural infection, can be achieved safely and economically by vaccination. Epidemics arise only when measles virus invades a population containing susceptibles who make sufficient contact with one another for transfer of infection from each new case to, on an average, more than one susceptible (97).

Unfortunately, the level of immunisation coverage required to break this chain of epidemic transmission seems to be very high in case of measles. In Ibadan, Nigeria, in 1969, inspite of mass vaccination campaign coverage of 92% and maintenance coverage programme at 6 months intervals for all children in the age group of 0-3 years, a new epidemic occurred within a period of 18 months (97).

A quick review of the resurgence of measles in the highly immunised U.S. population illustrated that in free living populations, the susceptibles are not distributed homogenously but they tend to cluster in subgroups defined by age and by such factors as ethnicity and socio-economic status. Regardless of the total proportion of the population that is immune, large number of susceptibles in frequent contact with each other exist in almost all large populations. Therefore, the ultimate success of a systematic immunisation programme requires knowledge of distribution of susceptibles by age and by subgroups and properly timed annual mass vaccination programmes to reduce the concentration of susceptibles throughout the community to a level where the chain of transmission can not be sustained (96,97).

Vaccine strategy

Immunisation is the only way to protect the community when it is possible neither to inactivate or sterilise a disease at its source nor to interfere with its transmission. In measles, the patient is usually infectious before diagnosis can be made and its airborne transmission is notoriously difficult to prevent or control (7). So immunisation is the only way to eradicate measles.

Vaccine strategy has been, and continues to be, a controversial and hotly debated issue.

The WHO recommends that, where prevalence of measles has declined, measles vaccine should be given after 15 months of age to avoid any interference by residual maternal antibodies (350).

In developed countries, maternal antibodies have been shown to persist until more than 12 months of age in a small percentage of cases (7,176, 356). The American Academy of Pediatrics (AAP) and the Public Health Services Advisory Committee on Immunisation Practices (ACIP), in 1965, changed the earlier 9 months of age to 12 months of age for routine measles immunisation (46).

Recent studies by Yeager et al (356) demonstrated HAI titre less than 1:4 in 14.6% of children vaccinated at 12 months but only in 5.2% of those vaccinated at 13 months. Albrecht et al (7), Krugman et al (176) and Shasby et al (300) have indicated that children vaccinated at the age of 12 months have lower rates of seroconversion than those children vaccinated at an older age. Children vaccinated at $\geq$ 14 months of age had $\geq$ 93% seroconversion (223). These led to the recent change in the recommended age for routine measles vaccination from 12 months to 15 months both by AAP and ACIP (48). This recommendation is further supported by recent epidemiological and serological investigations which show reduced vaccine efficacy and relatively high attack rates for clinical measles in children vaccinated before their first birthday (40,47,57,340).

However, the situation is different in the developing countries where frequent exposures to wild measles virus result in illness at a very young age, soon after children have lost their maternal antibodies (13,31, (73,231,233,335,349). Some children lose their antibodies and become susceptible as early as 5 months of age (5,72,73,230,334,335). The highest incidence of death due to measles occurs in the first two years of life and 30% or more of these children will have already developed measles before their first birthday (231,233). Measles case fatality rates of more than 10% have been noted in children under 12 months of age,

especially in areas with a high prevalence of malnutrition (78,167,231, 233,259,288).

A WHO-assisted study in Kenya, in 1977, revealed that 92% of children above the age of 7½ months did not show detectable HAI antibodies and 92-100% of children showed seroconversion at this age (349), and recommended 7½ months onwards as age for immunisation. In Tanzania, measles vaccination schedule in force is to give vaccine to all children above the age of 6 months (318).

The WHO recommends that in highly endemic areas, the vaccine has to be given early to protect infants who are likely to contract severe and sometimes fatal disease (350). At the WHO seminar held in Ghana in 1974 on the expansion of the use of immunisation in developing countries, it was agreed that, at the time, 6 months was the earliest age at which measles vaccine could be offered but further studies were needed (349).

At the present time, we do not have sufficient epidemiological and immunological data to suggest the ideal age for measles immunisation for Indian children (297).

A few studies done in India reveal that rapidly declining maternal antibodies necessitate measles vaccination under the age of one year (138,140,143,199,293). The highest percentage of case prevention due to measles vaccination is at 9 months (64-86%) followed by 12 months (57-90%) (308).

As mentioned earlier, Dave, Mehta, Sinha, etc. have reported absence of detectable antibodies by the age of 6-7 months (5,67,219,305).

Dholakia from Vadodara has reported 73% seronegative children by the age of 6 months (72).

In India, 94% seroconversion has been reported after administration of measles vaccine between 9 and 12 months of age (308).

The Indian Academy of Pediatrics (IAP), EPI Directorate and the Government of India have adopted the recommendation that the ideal age

for measles vaccination in India should be 9 months (59, 140, 224).

In a study to understand priority status of 11 common vaccine-preventable diseases, John and Steinhoff have given highest priority to measles vaccination (142).

A study by Wilkins et al (343) suggested 'altered immune response' describing a low level immune response in infants, also known as inadequate immunity by some (30). They suggested that when the first measles immunisation is done prior to one year of age and it fails, subsequent re-immunisation either fails to make HAI antibodies or produces detectable antibodies only transiently, due to a permanent insult to the immature immune system of the infant. They have reported 37 infants identified as 'vaccine failure' following their inoculation at less than one year of age. With subsequent revaccination after the age of one year, 51% had no detectable HAI antibodies by 8 months after revaccination, in contrast to only 6.8% of vaccinees in whom the first inoculation was done after the age of one year (343).

It has been observed that children who fail to develop HAI antibodies following vaccination at 6-9 months of age, might not respond to the second dose (190, 343) as the first dose blocked the immune response to the second dose, leaving children susceptible to natural measles infection. More sensitive serological techniques, however, revealed that these children did have low levels of neutralising antibodies (109, 343). It is not known if these low levels of antibodies will provide durable immunity against measles.

However, various authors (181,209,236,309) have demonstrated a normal antibody response to measles immunisation in such infants and they state that infants who did not respond adequately to the first dose could still be successfully immunised. Shasby et al (300) also showed that children who were immunised at less than one year of age and were later revaccinated, were protected from the disease when exposed to measles infection.

To protect younger infants who lose maternal antibody protection early, the Committee of Infectious Diseases of AAP and ACIP had recommended

that infants after 6 months of age should receive measles vaccine when cases of measles are recognised in the community and all those who were inoculated before 12 months of age be reinoculated after the age of 15 months (48,214,343).

In 1980, both the National Advisory Committee on Immunisation and the Canadian Pediatric Society, recommended the goal of elimination of indigenous measles in Canada (226). The Committee also advised that all the children should be vaccinated against measles at 1 year of age or as soon as possible thereafter and all those children should be revaccinated who had previously been given -

(i) live measles vaccine before one year of age, or

(ii) killed measles vaccine, either alone or followed by live measles vaccine within 2 years, or

(iii) further live attenuated measles vaccine and human immunoglobulin simultaneously, or

(iv) live attenuated measles vaccine within 6 weeks of receiving immunoglobulin (240).

Until 1983, the age of measles immunisation in Iran was 9-12 months. Revaccination with live vaccine was encouraged for those children who were first immunised before 12 months of age. Considering the fact that some children older than 4-6 months may lack the maternal antibodies and become victims of the disease before their first birthday, a new vaccination schedule to vaccinate the infants at 6-9 months of age and to revaccinate them at 12-15 months of age has been introduced (226).

In Yugoslavia, Ikic et al proposed that the first dose of the vaccine be given at 8 months, the second dose in the second year and a third dose at 7 years in order to build up the percentage of vaccinees in the most susceptible segment of the population as quickly as possible with the eventual aim of eradication of measles (133).

A two-dose schedule has been recommended in the People's Republic of China, considering the vaccine failures due to problems of cold chain maintenance, vaccine stability and the shortcomings of administering a single dose of vaccine during the early months of life. The first dose is given between 8 and 12 months of age and the second before the age of 2 years. The seroconversion rate attained after 2 doses was 97.2% as compared to 90% after one dose (361). It is estimated that several million children have been revaccinated in China and so far, no reports of adverse reactions or sequelae to revaccination have been received (361).

A two-dose schedule introduced in Costa Rica since 1979, the first dose of measles vaccine between 6 and 11 months followed by a dose of combined measles-rubella, led to the lowest morbidity due to measles in the country's history, in 1981. There were no fatalities and not a single case of measles was admitted at the National Children's Hospital (70).

A community-based measles research project was started in Tanzania in 1977. The optimum age of vaccination was computed from the information on seroconversion rates among different age groups, the age-specific incidence of measles obtained retrospectively from the study and the age-specific fatality rates. The optimum age for single vaccination was found to be 9 months and for double vaccination, the first dose at 8-9 months and the second at 12 months (198).

The serological studies on antibody kinetics after revaccination carried out in the People's Republic of China (313, 354, 359, 362) showed that the success of revaccination was dependent on the antibody level prior to revaccination; 80% of those who had prevaccination titres of $\leq$1:16 had a successful postvaccination response. However, one year later, the antibody titre dropped by a large margin and approached that before revaccination. Thereafter, titres remained steady or declined slightly and some vaccinees even became seronegative (313). Those children whose immune responsiveness was poor, were likely to become seronegative again

after a short period although they had responded successfully to revaccination (352).

However, there are several potential problems associated with a two-dose measles vaccination schedule. Apart from the increased expenditure of resources, the increased rate of vaccine failure in children vaccinated at 6-8 months of age could result in mistrust in the vaccine programme and decreased participation by other families in the community. Data from Ivory Coast reveal that only 26% of the children vaccinated at less than 9 months of age received the recommended second dose of vaccine and most of the second doses were not given until the children were more than 24 months of age (109).

A decline in postvaccination titre to very low or undetectable levels does not necessarily mean loss of protection to natural infection since a rapid anamnestic response in such individuals has been demonstrated (179, 190, 269). The purpose of re-immunisation is not to boost the primary vaccination response but to protect the children who fail to respond to the first inoculation (174), especially those who receive this at 6-12 months of age.

Inspite of documented vaccination of 98%, outbreaks have been reported from USA (244). Areas of concern after successful immunisation are -

- International imported cases may establish a transmission chain.
- Congregation of susceptibles (vaccine failures cases), say in colleges (in some cases 20% or more), can lead to a measles outbreak.
- In absence of disease, community interest for measles immunisation will wane, leading to a major outbreak.

A sustained immunisation campaign and flexible vaccination strategy can help in controlling measles (85).

N. Aerosolised Vaccine

In many parts of the world, only a small portion of the children receive the subcutaneously (SC) administered vaccine (329, 330). A variable

and sometimes large proportion of cases of measles occur in children 6-12 months of age with maximum risks of complications (4,13,139,160, 308); and SC vaccination is ineffective in a good percentage of children due to the presence of maternal antibodies, interfering with successful immunisation (74,90,92,176).

Refractoriness to vaccine in the first year of life is principally mediated by humoral measles specific IgG acquired transplacentally. The subcutaneous inoculum is rapidly neutralised by these antibodies before sufficient viral replication can occur to produce a critical mass of measles antigen capable of intitiating host immune reponse (156).

Natural measles virus enters primarily via nasal respiratory mucosal route. Since infants do not receive IgA secretory antibodies transplacentally, deposition of natural measles virus in nasal mucosa and its local replication can overcome inhibition produced by waning, unmetabolised passively acquired IgG antibodies when the virus reaches the blood stream (156, 212).

On the same principle of this dissociation of humoral and local secretory immunity, the concept of aerosol measles vaccine was experimented (156).

During 1960-62, investigators in Japan (229, 250) and USA (28,169,207) reported that the partly attenuated measles vaccine available at that time, when given in small amounts as aerosolised inhalations, consistently produced immunogenic response in nearly all susceptible children (279).

In 1971, Soviet investigators reported the high immunogenic effectiveness of Schwarz and other similar highly attenuated Soviet strains of measles vaccine in 3,306 seronegative children who were exposed to an aerosol of these vaccines in large rooms or tents. No febrile or other clinical reactions were demonstrated Two years later, Danilov reported, "From this experiment, we may conclude that this method is harmless, and immunologically and epidemiologically effective" (66).

A clinical trial of inhaled aerosols of human diploid cell (HDC) and chick embryo fibroblast (CEF) vaccines was carried out in Mexico

(87% of 39 four to six months old children seroconverted) and the results of enzyme-linked immunosorbent assay (ELISA) (277), as reported by Sabin et al, revealed that inhalation of undiluted aerosolised measles vaccine was immunogenic in 100% of 4-6 months and older children with or without maternal antibodies when HDC vaccine containing Ikic (Edmonston-Zagreb) strain and 1% human albumin was used. There was no immediate clinical reaction in the 160 children who inhaled the vaccine. There were no contact infections (278).

In Ghana (321), measles vaccine was given to children 5 months to 5 years of age using either SC or inhalation technique. The seroconversion rate with inhalation technique was only 59.1%. This happened probably as a nebuliser and not a mask was used directly for inhalation.

In a study in Bangladesh, while comparing seroconversion in the 4-6 months age group, following measles vaccination using Edmonston-Zagreb (EZ) strain and Schwarz strain, it was observed that seroconversion rates were 62% and 37% respectively when subcutaneous route was used, but only 35% and 34% respectively when aerosol by foot-pump-driven-nebuliser was used (161).

However, using higher potency of measles vaccine, Whittle has reported 100% seroconversion at the age of 5 months using 40,000 plaque forming units (PFU) of EZ strain. He has also reported almost 75% seroconversion using 40,000 PFU of Schwarz strain (342)

Although the observed risk of neurologic reactions to respiratory mucosal vaccination is zero, the actual risk cannot be known precisely at this time. Nevertheless, the risk would have to be more than 10,000 times higher than that for measles vaccine SC administered to offset the benefits of vaccination for infants in the developing world for whom the mortality rate due to natural measles infection is 3-40% (234).

Although it is clear that aerosolised vaccination against measles is technologically feasible, more information is needed about the safety, cost, ease of administration to large groups of infants and stability

in tropical climates of aerosolised vaccine before it can be incorporated into world-wide immunisation strategies (330).

If the high immunogenicity and complete lack of clinical reactions with the use of aerosolised vaccine could be obtained on a mass scale with the use of a practical, acceptable dose of the current CEF or HDC vaccine by means of an inexpensive hand-held nebuliser and if it would also be possible to immunise infants who have residual maternal antibodies, one would have a procedure for mass vaccination that could be applied by large numbers of non-professional personnel, which could be carried out in a short period, helping in rapid elimination of measles in both economically developed and underdeveloped countries of the world. The efforts to find out alternative methods of vaccine production (e.g. recombinant DNA) and of vaccine administration (e.g. aerosol, Ezeject^{R}) will help in achieving 'Make Measles a Memory' - our dream come true.

0. Indigenous Vaccine Production.

Today, measles vaccine is demonstrably the most cost-effective vaccine (245). In USA, $ 10.34 are saved for each dollar spent on measles immunisation (271). In Cameroon, the benefit-cost ratio has been reported as 23.3:1, the ratio increasing with the increase in number of vaccinees. In one agricultural region of USSR, 70,000 roubles per annum were saved (355).

The indigenous production of measles vaccine, though desirable, may not be a viable proposition for many developing countries. A plant with a production capacity of 800,000 vaccines per year costs 2.4 million dollars and takes upto 3 years to be commissioned, an amount which would take care of measles vaccines for 30 years at a cost of 10 cents per dose. Further, a population of 20 million or less would mean that the country will have to export 60% of its vaccine production (253).

In India, we require at least 20 million doses every year and most of it is imported (19). Serum Institute of India, Pune and Indian Virus Corporation Limited, by 1990-91, are expected to fulfill this demand and even export the surplus vaccine.

P. Future of Measles in Highly Immunised Populations-A Computer Modelling Approach

In USA, making measles a memory is a matter of time. With continuous vigorous implementation of the nation-wide indigenous measles elimination strategy and with additional measures to lessen the risk of importations, transmission of measles has been interrupted throughout most of the USA. Now, Canada has launched its own efforts towards elimination of measles (127,148).

Levy et al (184), using a computer model approach, have attempted to understand the strategy for measles immunisation and measles epidemiology in 2050.

In 1981, USA had a susceptible population of 3.1% (96% vaccine coverage in young susceptibles and 99% natural immunity in adult population). By 2050, due to progressive accumulation of susceptibles, 10.9% of the country's population will become susceptible to measles. Although the first battle for measles elimination has been won successfully in USA, the gain for today's young generation and generations of tomorrow will be preserved only if measles is eliminated globally or if the U.S. population is protected completely from reintroduction, so that the number of susceptibles, which otherwise can lead to an epidemic, becomes irrelevant due to absence of virus to incite the disease.

Q. Need for and Prospects of World-wide Measles Control

The global eradication of measles is desirable because the disease occurs almost universally, affects large number of children, can cause serious complications and is responsible for about 1.52 million deaths a year in developing countries (330). Measles, a disease of humans, having no animal reservoirs or insect vectors, fits the criteria defining an eradicable disease. After the successful eradication of smallpox, the global eradication of measles appears to be a theoretically feasible target given the commitment and resources. Because only one antigenic strain of virus exists, vaccine produced in any one country would be effective in all parts of the world year after year (82).

But the similarity between the two great killer diseases ends here. The example of smallpox eradication can not be applied directly to the measles problem. Attitudes towards measles are very different from those towards smallpox. Measles is a highly communicable disease compared to smallpox and is more difficult to diagnose by clinical observation. Measles vaccine is comparatively more expensive and is much less stable than the freeze-dried smallpox vaccine, requiring elaborate maintenance of the cold chain delivery system. The delivery system for measles vaccine - SC injection or jet injection - is also technically more complicated and cumbersome than the bifurcated needle for smallpox immunisation (272).

R. The Remaining Research Needs

Basic science investigators should address the identification of the genome of the measles virus and of those changes in the genome responsible for attenuation and should attempt to clone the genes responsible for the two major surface glycoprotein antigens - the haemagglutination and fusion proteins. Purification of these two proteins will facilitate studies of cell-mediated immunity for identification of the factors involved in the establishment and maintenance of persistent infections like SSPE and multiple sclerosis. Although no direct evidence implicates the attenuated vaccine virus in SSPE, this relationship should still be monitored (193).

More sensitive biochemical methods are needed for definition of the nature of the change in the viral genome that is responsible for attenuation (148).

Fortunately, an animal model is available that is capable of distinguishing differences in virulence of virus strains(8). Marmosets, the most susceptible primate hosts of measles virus reported to date, are a sensitive indicator of the viscerotropic and neurotropic properties of measles viruses. The marmoset model can therefore be used to distinguish between wild and vaccine viruses until specific genetic fingerprints are available (148).

Further improvements in heat stability of the vaccine would be beneficial. Continued improvement in cold chain technology is needed as is the development of simple and inexpensive means of production and delivery of vaccine. Research on the respiratory route of vaccine administration should be pursued. A rapid diagnostic serological test for measles antibody should be developed (193).

Another research area demanding utmost attention is genetically engineered measles vaccine, being developed at the Centre for Applied Microbiological Research, Porton Down, United Kingdom. This new vaccine which would have several advantages over the current vaccine, consists of two antigenic components - a haemagglutinin and a fusion protein - and is produced by recombinant DNA technique. The advantage of genetically engineered vaccines are -

- The antigen is non-disease-producing.
- No inactivation procedure is required.
- Production cost is less.
- As there is no pathogen involved, large scale safety trials are not required.
- Being more stable, transportation and storage costs are reduced (287).

Current technologies permit the purification, and even synthesis, of these (HA and F) antigens. Care should be taken to protect the antigenic stability of the F protein thus avoiding the failures and complications previously associated with formalin-inactivated measles vaccines (220).

The viral genome-encoded haemagglutinin and fusion surface antigens are the primary targets in the recognition and effector phases of the immune response to the virus, and it could be argued that these are the only components needed in an improved, inactivated vaccine that would be stable under adverse field conditions (21).

Operational strategies for delivery of vaccine and for improvement of vaccination through community participation also need attention.

Strategies are needed that would encourage attitudes of medical personnel and lay persons in support of measles vaccination. The optimal age for vaccination, particularly with respect to the presence of maternal antibody and the duration of vaccine-induced immunity should be clarified (193).

Behavioural and operational research must examine how best to extend measles immunisation throughout the world (115).

S. Current Measles Vaccination Strategy

The WHO launched a highly ambitious Expanded Programme on Immunisation (EPI) in 1974 with the aim of assisting all nations to immunise all children against 'the Big Six' major childhood diseases viz. measles, pertussis, diphtheria, tetanus, polio and tuberculosis, by 1990. Three years later, the World Health Assembly passed the resolution. The objective was to reduce the mortality and morbidity resulting from six vaccine-preventable diseases of childhood, and to help all nations to achieve self-sufficiency in production of vaccines. UNICEF became the world's largest supplier of vaccines and cold chain equipment (325).

In India, EPI was launched in January 1978.

On 25th October, 1985, as the United Nations entered its fifth decade, the Heads of States and senior officials of 21 Governments signed a declaration of their commitment to immunise all the world's children by the year 1990 (Universal Child Immunisation, 1990) (327). Ten months later, 74 Governments and more than 400 voluntary organisations signed the declaration. It is aimed at adding impetus to the Global Expanded Programme on Immunisation.

As a 'living memorial' to the late Prime Minister Mrs. Indira Gandhi, the Universal Immunisation Programme was launched in India on November 19, 1985.

In principle, 'Universal Immunisation' is that level of immunisation which is required to stop the transmission of EPI diseases in the country or community concerned. In practice, different countries have set different quantitative targets for 1990; where countries have not yet set their

own target, UNICEF uses 80% coverage for each antigen as a minimum indication of Universal Immunisation being achieved.

For India, the target for 1990 is -

(i) to immunise 100% of pregnant women with 2 primary doses (or one booster dose) of tetanus toxoid, and

(ii) to immunise 85% of children during their first year of life with - 3 doses of DPT
- 3 doses of OPV
- 1 dose of BCG
- 1 dose of Measles.

By 1988, 182 districts and all 106 medical colleges were participating in the Universal Immunisation campaign and the 'Technology mission on vaccination and immunisation of vulnerable population, specially children' has been set up to cover all aspects of immunisation (326, 327, 330.)

When WHO launched the EPI in 1974, fewer than 5% of children in the developing countries were immunised. By the end of the 1980s, vaccines are now saving at least 1.5 million children annually and there is now every prospect that 70-80% of babies born during 1990 in the developing world will be immunised by the age of 12 months (328, 329, 330).

Measles control would require widespread and logical application of vaccine so as to achieve and maintain a very high level of vaccination coverage, probably in excess of 90%. It has been suggested that in the developed countries like Western Europe and USA, 92-96% of children must be vaccinated to eliminate measles and pertussis, 84-88% to eliminate rubella and 88-92% to eliminate mumps (114, 130). In the developing countries where maternal protection wanes early and the average age of infection is as low as 1-2 years, something like 96% of each yearly cohort of children would have to be effectively immunised by the age of one year to attain measles elimination (12), against 50% coverage required for smallpox eradication (130). This will require more overt commitment to measles control; and the motivation issues and major management problems

related to the structure of primary health care delivery systems are as important as the technologic ones (155).

Moderate to low levels of coverage, however, are beneficial. They raise the average age at infection and thereby lengthen the age 'window' in which vaccine can be administered, and reduce morbidity and mortality (130).

Although it may initially be advisable to immunise infants younger than one year of age - at six to nine months - to reduce epidemic transmission and disease, eventual vaccination at or after the first birthday shall have to be done. If the aerosol experiments are proved successful and widespread use made feasible, this restriction could be removed and immunisation in very early infancy or even in the neonatal period could be recommended (155).

For those vaccinated after the first birthday, second doses of vaccine should be regarded not as boosters, but as 'fill-ins' for those 5-10% of recipients who may have failed to respond to the initial exposures, giving due consideration to the economics of a given programme. The need and desirability of a second dose should be carefully assessed and followed with proper clinical, serologic and epidemiologic surveillance (155).

In conclusion, the time is appropriate for consideration of the initial goal of measles control - from national control to global control - but the eventual goal must be that of global measles eradication (82,155,272).

IV. JUSTIFICATION FOR THE PRESENT STUDY

The above review reveals that measles is a major public health problem in India. Despite the availability of a safe, thermostable and effective vaccine, measles vaccination coverage continues to be poor. In the expanding, crowded and turbulent cities, the impact of measles is underassessed. Very few studies have been carried out in the urban slums to understand the epidemiology of measles in the community. One major factor which influences the age at the time of vaccination is the incidence of measles and its complications in the early months of life. The time of waning of maternal measles antibody and the seroconversion rates at various ages are the other two factors which determine the optimum age for measles vaccination. Due to technical limitations, various studies conducted in India had variable (1:20, 1:12, 1:10, 1:6) lowest measurable levels of measles HAI antibody titres and

had, therefore, considered a number of observations under the category of inconclusive results.

In view of the absence of regional data, the present work is a comprehensive study in an attempt to understand the epidemiology of measles in the urban slums of Vadodara; and to determine the waning of maternal protection and the seroconversion rates at different ages by using HAI technique which has a lowest measurable antibody titre of 1:2.