CHAPTER 1 - BACKGROUND

1.1 Disease

1.1.1 Virus and transmission

Measles virus is an RNA virus and is a member of the genus *Morbillivirus* in the family *Paramyxoviridae*. The measles virus genome contains approximately 16,000 ribonucleotides. Measles has been considered to be an antigenically stable virus, but recent analyses of nucleotide sequences from measles isolates obtained from various regions of the world have found important genetic differences between isolates, especially in the areas of the genome which code for the haemagglutinin protein. This has resulted in 8 distinct genotypes being identified, including a genotype predominant on the African continent.

Measles is an ubiquitous, highly infectious disease affecting nearly every person in a given population by adolescence in the absence of immunisation programmes. Measles is transmitted primarily from person-to-person by large respiratory droplets, but can also be spread by the airborne route as aerosolized droplet nuclei.

1.1.2 Clinical aspects

Measles is most infectious during the prodrome. First there is localized infection of the respiratory epithelium of the nasopharynx and possibly the conjunctivae, with spread to regional lymphatics. Primary viraemia occurs 2 to 3 days following exposure, and an intense secondary viraemia occurs 3 to 4 days later. The secondary viraemia leads to infection of and further replication in the skin, conjunctivae, respiratory tract and other distant organs. The amount of virus in blood and infected tissues peaks 11 to 14 days after exposure and then falls off rapidly over the next 2 to 3 days.

**Prodrome and General symptoms**: Measles infection presents with a 2-3 day
prodrome of fever, malaise, cough, and a runny nose (coryza). Conjunctivitis and bronchitis are commonly present. Although there is no rash at the onset, the patient is highly contagious. A harsh, non-productive cough is present throughout the febrile period, persisting for 1 to 2 weeks in uncomplicated cases, and it is often the last symptom to disappear. Generalized lymphadenopathy commonly occurs in young children. Older children usually complain of photophobia and, occasionally, of arthralgia.

**Koplik's spots:** Koplik's spots may be seen on the buccal mucosa in over 80 percent of cases, if careful daily examinations are performed shortly before rash onset. The spots, however, may be confused with other vascular lesions and are present in other conditions. Koplik spots are slightly raised white dots 2 to 3 mm in diameter on an erythematous base. Initially, there are usually 1 to 5 of these lesions, but as rash onset approaches there may be as many as several hundred. They have been described as resembling “grains of salt sprinkled on a red background”. The lesions persist for only 1 to 3 days, and disappear soon after rash onset.

**Rash:** Within two to four days after the prodrome symptoms begin, a characteristic rash made up of large blotchy red areas usually appears behind the ears and on the face. At the same time a high fever occurs. In dark skinned children the rash may not be as evident. The rash peaks in 2 to 3 days, and becomes most concentrated on the trunk and upper extremities. The density of the rash varies; young infants may have rashes that cover the face and trunk. The rash lasts from 3 to 7 days and may be followed by a brawny or fine desquamation. Some children develop severe exfoliation, especially if they are malnourished or have vitamin deficiencies.
Differential Diagnosis: Many febrile illnesses are accompanied by a rash and a variety of non-specific symptoms (see adjacent box).

Mild or "modified" forms of measles with generally mild symptoms occur in persons with partial protection from maternal antibody, and rarely from vaccine failures.

1.1.3 Complications and permanent sequelae

Though usually a mild or moderately severe illness of childhood, measles can result in residual neurological impairment from encephalitis in approximately 5–10 cases per 10,000 and in death in approximately 1–3 cases per 1,000.4

Complications from measles include otitis media, pneumonia, diarrhoea, blindness and encephalitis. It is estimated that otitis media or pneumonia occur in 10 to 30% of infants and young children with measles.

Diarrhoeal Diseases: A large number of infants and children in developing countries develop diarrhoeal illness both during and following acute measles illness. Dehydration and the concomitant loss of Vitamin A may have disastrous consequences, raising the probability of dying from measles in these infants considerably.

Respiratory infections: Respiratory infections are the most common cause of significant morbidity and mortality in infants and children with measles. Pneumonia may be due to the measles virus alone or to secondary infection with
other viral agents, especially herpes simplex and adenoviruses, or bacterial organisms.

**Malnourished Children:** Measles infection is more severe among malnourished children. Diarrhoea is one of the major factors contributing to the adverse impact of measles on the nutritional status in children in developing countries. Measles may exacerbate malnutrition because of decreased food intake due to malaise, increased metabolic requirements in the presence of fever, or because parents and health practitioners inappropriately withhold a child's food during an acute illness. Undernutrition may in turn lead to vitamin A deficiency and keratitis, resulting in a high incidence of childhood blindness during measles outbreaks.

**Neurological complications:** These occur in 1 to 4 of every 1,000 infected children. The most common manifestation is febrile convulsions, which are not usually associated with persistent residual sequelae. Encephalitis or postinfectious encephalopathy occurs in approximately 1 of every 1,000 infected children. Subacute sclerosing panencephalitis (SSPE) is a rare (incidence of approximately 1/100,000 measles cases) chronic degenerative neurological disorder associated with the persistence of the measles virus in the central nervous system. It may develop several years after a measles infection and is usually fatal within 7 years.

**Mortality:** Case fatality rates vary depending on the age of infection, intensity of exposure, nutritional status and availability of treatment. In developed countries the case-fatality rate for measles tends to be low (between 0.1 and 1.0 per 1,000 cases). In developing countries the overall case-fatality rate has been estimated at between 3 and 6%. The highest case-fatality rate occurs in infants 6 to 11 months of age. These rates may underestimate the true lethality of measles because of incomplete reporting of outcomes of measles illness, such as delayed deaths related to chronic diarrhea. In addition, some deaths may be
missed when death certificates are miscoded or hospital records are incomplete. In certain high-risk populations case-fatality rates as high as 20 or 30 percent have been reported in infants under 1 year of age.

1.1.4 Immunological response to natural infection and immunisation

In primary acute infection, T-cell and B-cell responses can be detected to most of the six measles virus proteins. Both IgG and IgM antibodies are initially produced, however IgM antibodies peak at 7 to 10 days after rash onset and fall rapidly, rarely being detectable more than 4 weeks after rash onset (Figure 1). Serum and secretory IgA are also produced but are usually transient.

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

IgG becomes detectable in the serum soon after rash onset, peaks within about 4 weeks and subsequently declines, but persists for life and therefore immunity after natural infection is usually lifelong.

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

Acute measles infection is associated with a wide range of immunological abnormalities, including depressed general cellular reactivity (manifest, for example,
in a depressed delayed hypersensitivity reaction to the tuberculin test\textsuperscript{(14)} and cytokine production abnormalities. Studies are in progress to elucidate further the mechanisms of immune disruption after measles and possible variation by age at infection.

Prior to the availability of measles vaccine, measles infection was virtually universal. Infants born to mothers with measles antibodies due to natural infection or vaccination are protected until 5-9 months of age. Some infants who are immunized before they are 9 months old may not develop detectable immunity due to interference by passively-acquired maternal antibody.

At present, no serological tests can distinguish between antibody, whether IgG or IgM, produced by measles infection and that produced by immunization. The levels of antibody induced by immunisation with attenuated measles virus vary with an approximately log-normal distribution, and reach lower peak levels than those induced by wild virus\textsuperscript{(15)}. Antibody loss is quicker after further attenuated vaccines than after the early vaccines. Some data suggest that the rate of antibody decline is faster among persons who attain the highest antibody levels post-immunization, so that the range of
levels narrows with time\textsuperscript{16}.

Antibody persists longer when there is boosting from exposure to circulating wild virus\textsuperscript{17,18}. However, even in isolated communities, antibodies have been shown to persist for at least 16 years after immunization\textsuperscript{17,18,19}. The mechanism for maintenance of detectable antibody levels in the absence of re-exposure is not known\textsuperscript{20}.

When measles antibody falls to low levels, re-exposure to measles virus (wild or vaccine virus) stimulates memory cells, which remain dormant after the initial infection and are primed to produce a measles-specific response. An anamnestic (secondary) immune response occurs, in which IgG levels rise rapidly and peak approximately 12 days after reinfection. If antibody levels are high prior to exposure, reinfection is prevented and a boost is rarely seen.

1.1.5 Treatment of measles and referral criteria

There is currently no specific treatment for measles infection. However, administration of Vitamin A to children at the time of measles diagnosis has been shown to decrease both the severity of disease and the case-fatality rate\textsuperscript{21}. The South African Standard Treatment Guideline indicates the following treatment at primary health care level:
If the patient is older than six months, well nourished and uncomplicated, treat at home with:

* paracetamol for fever or discomfort children: 10mg/kg every 4-6 hours
* if diarrhoea, rehydrate for 24 hours
* if bronchitis or otitis media, treat with appropriate antibiotic
* if purulent conjunctivitis, treat with tetracycline ophthalmic ointment
* all children with an acute attack of measles should be given retinol (vitamin A)

- 12 months: 100 000 IU Vitamin A orally as a single dose
- > 12 months: 200 000 IU Vitamin A orally as a single dose

In the following situations, refer the patient to hospital:

- younger than 6 months old;
- signs of severe or unresponsive bronchitis or pneumonia present;
- malnutrition (below 3rd percentile);
- dehydration;
- neurological signs or symptoms, for example confusion;
- associated illness such as AIDS, TB, asthma;
- immuno-compromised and severely ill adults.

Some paediatricians advise the use of chloramphenicol eye ointment instead of the tetracycline ointment mentioned above. In addition, the Manual on the Integrated Management of Childhood Illnesses (IMCI) which is currently being prepared includes a section on measles management. Following the general assessment of the child and the assessment for diarrhoeal disease, the manual proceeds to febrile illnesses. The following instructions are given in the case where the child has measles now or within the last 3 months:
1.2 Vaccine

1.2.1 Vaccine types

In South Africa, eleven measles containing vaccines are available (six measles only vaccine, one measles-mumps combination vaccine and four measles-mumps-rubella combination vaccines). Measles-mumps-rubella (MMR) vaccines are available in the private sector and are generally purchased by some parents for their children. Ignorance by parents and private health care providers of the importance of the cold chain have however occasionally led to the administration of MMR of dubious potency,
leading to "vaccine failures" in these children and subsequent outbreaks in "vaccinated" children. However, MMR vaccine that has been kept in appropriate conditions has been shown to be as efficacious as monovalent measles vaccine.

1.2.2 Vaccine stability, storage and supply

Prior to 1980, measles vaccines were extremely heat-labile, causing difficulty in their use in tropical and subtropical climates. The development of effective stabilizers and the formulation of the WHO requirements for heat stability for freeze-dried measles vaccine have considerably improved the quality of measles vaccines available since 1980, although there are still variations in the stability of vaccines produced by different manufacturers.

In the freeze-dried state, present measles vaccines which meet WHO requirements retain a minimum potency of at least $3.0 \log_{10}$ live virus particles per human dose after exposure to a temperature of $37^\circ C$ for at least one week, and the virus titre does not decrease by more than $1.0 \log_{10}$ during incubation. However, reconstituted measles vaccines quickly lose their potency at exposure to room temperatures. At $22^\circ C$ to $25^\circ C$, reconstituted measles vaccine suffer approximately 50% loss in potency in one hour. At temperatures over $37^\circ C$, it is inactivated within one hour. It is therefore extremely important to keep reconstituted measles vaccine cool (below $8^\circ C$) and protected from sunlight.

Measles vaccine is fragile. Breaks in the cold chain (temperatures greater than $10^\circ C$) may quickly render the reconstituted vaccine completely ineffective. Measles vaccine, MR, and MMR can however be frozen without loss of potency. When stored at 0 to $8^\circ C$, a minimum infective dose can be maintained in unreconstituted vaccine for 2 or more years. Reconstituted vaccine should be disposed of after 8 hours, regardless of the temperature maintained. Vaccine should never be left at room temperature. When used in the field, it should be transported on wet ice in isothermic containers.
Measles single antigen, MR, and MMR vaccine should be kept frozen at the national level. At the district and health facility level, vaccine should always be placed on the upper shelves of a storage refrigerator which is used only for vaccines.

Effective distribution of viable vaccine in sufficient quantities is critical to the success of the measles eradication program. All locations that provide immunization should have a sufficient vaccine supply on hand to last until the next consignment is likely to be received. Order frequency, stock control and other cold chain and vaccine operations issues are discussed in detail in the South African *Cold Chain & Immunisation Operations Manual*.

1.2.3 Vaccine efficacy

Not all persons given measles vaccine are necessarily protected against measles, since no vaccine is 100% effective. The appropriate way to evaluate whether the proportion of cases with a history of vaccination is high in an outbreak, is to estimate vaccine effectiveness. There are several approaches to calculating vaccine effectiveness. They include:

- use of coverage data, and
- outbreak investigation with case-control studies.

These methods are too detailed for presentation in this guide. If effectiveness is low (for example below 80%), this may indicate that there are problems either with the cold chain, age at vaccination, or with the vaccine's ability to produce protection as manufactured.
Table 1: Seroconversion rates in selected developing countries by age at measles immunisation (adapted from Halsey 198326; Source: WHO/EPI: Immunological basis for Immunization: Measles)

<table>
<thead>
<tr>
<th>Country</th>
<th>Seroconversion(%) by age in months</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Haiti</td>
<td>-</td>
<td>45</td>
</tr>
<tr>
<td>Kenya</td>
<td>&lt;50</td>
<td>40</td>
</tr>
<tr>
<td>Latin America</td>
<td>-</td>
<td>58</td>
</tr>
</tbody>
</table>

Serologic studies summarised in table 1 have demonstrated that measles vaccines induce seroconversion in 84 to 93 percent of recipients who are old enough to have lost all passively acquired maternal measles antibody (this usually occurs by 9 months of age). The development and persistence of serum antibodies following measles vaccination have been lower than, but parallel to the response following natural measles infection. Peak antibody responses occur 6 to 8 weeks after infection or vaccination.

For combined vaccines (such as MMR), studies indicate that the antibody response to all antigens is equivalent to the response when each is administered separately, provided the vaccine has been handled correctly and has not lost its potency.

1.2.4 Adverse reactions and side effects29

The following comparative rates of serious adverse events in the case of measles disease and measles immunisation were found30 (Table 2).
Table 2: Estimated rates of adverse events following measles immunisation to complication rates of natural measles infection.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Measles disease (per 100,000 cases)</th>
<th>Measles immunisation (per 100,000 doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy/encephalitis</td>
<td>50 - 400</td>
<td>0.1</td>
</tr>
<tr>
<td>Convulsions</td>
<td>500 - 1,000</td>
<td>0.02 - 190</td>
</tr>
<tr>
<td>Death</td>
<td>10 - 10,000</td>
<td>0.02 - 0.03</td>
</tr>
</tbody>
</table>

More than 240 million doses of measles containing vaccine were distributed in the United States from 1963 through 1993. The vaccine has an excellent record of safety. Mild side effects include fever and between 5% and 15% of vaccinees may develop a temperature of greater than 39.4°C beginning 5 - 12 days after vaccination and usually lasting several days. Most persons with fever are otherwise asymptomatic. Transient rashes have been reported for approximately 5% of vaccinees. Central nervous system (CNS) conditions, including encephalitis and encephalopathy, have been reported with a frequency of less than one per million doses administered. The incidence of encephalitis or encephalopathy after measles vaccination of healthy children is lower than the observed incidence of encephalitis of unknown etiology. This finding suggests that the reported severe neurologic disorders temporally associated with measles vaccination were not caused by the vaccine. These adverse events should be anticipated only in susceptible vaccinees and do not appear to be age-related. After revaccination, most reactions should be expected to occur only among the small proportion of persons who failed to respond to the first dose.

Convulsions and febrile seizures

As with the administration of any agent that can produce fever, some children may have a febrile seizure. Although children with a personal or family history of seizures are at increased risk for developing idiopathic epilepsy, febrile seizures following vaccinations do not in themselves increase the probability of subsequent epilepsy or other neurologic disorders. Most convulsions following measles vaccination are simple febrile seizures, and they affect children without known risk factors. It should be stressed that
the likelihood of seizures during an attack of measles is far greater than seizures following measles vaccination.

An increased risk of these convulsions may occur among children with a prior history of convulsions or those with a history of convulsions in first-degree family members (i.e. siblings or parents)\textsuperscript{32}. Although the precise risk cannot be determined, it appears to be low.

Because the period for developing vaccine-induced fever occurs approximately 5-12 days after vaccination, prevention of febrile seizures is difficult. Prophylaxis with antipyretics has been suggested as one alternative, but these agents may not be effective if given after the onset of fever. To be effective, such agents would have to be initiated before the expected onset of fever and continued for 5-7 days. However, parents should be alert to the occurrence of fever after vaccination and should treat their children appropriately.

Children who are being treated with anticonvulsants should continue to take them after measles vaccination. Because protective levels of most currently available anticonvulsant drugs (e.g., phenobarbital) are not achieved for some time after therapy is initiated, prophylactic use of these drugs does not seem feasible.

The parents of children who have either a personal or family history of seizures should be advised of the small increased risk of seizures following measles vaccination. In particular, they should be told in advance what to do in the unlikely event that a seizure occurs. The permanent medical record should document that the small risk of postimmunization seizures and the benefits of vaccination have been discussed.

Subacute Sclerosing Panencephalitis (SSPE)

Measles vaccine significantly reduces the likelihood of developing SSPE, as evidenced by the near elimination of SSPE cases after widespread measles vaccination began in
the USA. SSPE has been reported rarely in children who do not have a history of natural measles infection but who have received measles vaccine. The available evidence suggests that at least some of these children may have had an unidentified measles infection before vaccination and that the SSPE probably resulted from the natural measles infection. The administration of live measles vaccine does not increase the risk for SSPE, regardless of whether the vaccinees has had measles infection or has previously received live measles vaccine\textsuperscript{33,34}.

Thrombocytopenia

Surveillance of adverse reactions in the United States and other countries indicates that Measles/Mumps/Rubella (MMR) vaccine can, in rare circumstances, cause clinically apparent thrombocytopenia within the 2 months after vaccination. In prospective studies, the reported incidence of clinically apparent thrombocytopenia after MMR vaccination ranged from one case per 30,000 vaccinated children in Finland\textsuperscript{35} and Great Britain\textsuperscript{36} to one case per 40,000 in Sweden, with a temporal clustering of cases occurring 2-3 weeks after vaccination\textsuperscript{37}. With passive surveillance, the reported incidence was approximately one case per 100,000 vaccine doses distributed in Canada and France\textsuperscript{38}, and approximately one case per 1 million doses distributed in the United States\textsuperscript{38}. The clinical course of these cases was usually transient and benign, although haemorrhage occurred rarely\textsuperscript{33}. Furthermore, the risk for thrombocytopenia during rubella or measles infection is much greater than the risk after vaccination. Of 30,000 schoolchildren in one Pennsylvania county who had been infected with rubella during the 1963-64 measles epidemic, 10 children developed thrombocytopenic purpura (incidence: one case per 3,000 children)\textsuperscript{40}. Based on case reports, the risk for thrombocytopenia may be higher for persons who previously have had idiopathic thrombocytopenic purpura, particularly for those who had thrombocytopenic purpura after an earlier dose of MMR vaccine.

Revaccination Risks
There is no evidence of an increased risk for adverse reactions after administration of live measles vaccine to persons who are already immune to measles as a result of either previous vaccination or natural disease.

1.2.5 Contraindications and Precautions

Measles vaccine can be safely and effectively administered to children with mild acute illnesses. Malnutrition is a strong indication to vaccinate, not a contraindication. If a malnourished child is infected, the disease may aggravate his/her nutritional status and increase the chances of complications or death.

Pregnancy

Since measles and MMR vaccines are live viruses, they should theoretically not be administered to pregnant women. There is currently no evidence, however, to suggest that children born to pregnant women vaccinated with these vaccines during pregnancy will be adversely affected. This precaution is based on the theoretical risk of fetal infection, although no evidence substantiates this theoretical risk. Considering the importance of protecting adolescents and young adults against measles, asking women if they are pregnant, excluding those who are, and explaining the theoretical risks to the others before vaccination are sufficient precautions.

Allergic Reactions

Hypersensitivity reactions rarely occur after the administration of measles containing vaccines. Most of these reactions are minor and consist of a wheel and flare or urticaria at the injection site. Immediate, anaphylactic reactions to measles containing vaccine are extremely rare. Although >70 million of MMR vaccine have been distributed in the United States since the Vaccine Adverse Events Reporting System (VAERS) was implemented in 1990, only 33 cases of anaphylactic reactions that occurred after MMR vaccination have been reported. Furthermore, only 11 of these cases a) occurred
immediately after vaccination and b) occurred in persons who had symptoms consistent with anaphylaxis (CDC, unpublished data).

In the past, persons who had a history of anaphylactic reactions (i.e., hives, swelling of the mouth or throat, difficulty breathing, hypotension, and shock) following egg ingestion were considered to be at increased risk for serious reactions after receipt of measles-containing vaccines, which are produced in chick embryo fibroblasts. Protocols requiring caution were developed for skin testing and vaccinating persons who had had anaphylactic reactions after egg ingestion. However, the predictive value of such skin testing and the need for special protocols when vaccinating egg-allergic persons with measles-containing vaccines is uncertain. The results of recent studies suggest that anaphylactic reactions to measles-containing vaccines are not associated with hypersensitivity to egg antigens but with some other component of the vaccines. The risk for serious allergic reaction to these vaccines in egg-allergic patients is extremely low, and skin testing is not necessarily predictive of vaccine hypersensitivity. In South Africa, a measles vaccine grown on human diploid cells can be used if parents are greatly concerned about egg-allergy in their child.

Measles vaccine may contain trace amounts of neomycin as a precaution to bacterial growth. Although the amount present is less than that usually used for a skin test to determine hypersensitivity, persons who have experienced anaphylactic reactions to neomycin should not be given these vaccines. Most often, neomycin allergy is manifested by contact dermatitis rather than anaphylaxis. A history of contact dermatitis to neomycin is not a contraindication to receiving measles vaccine. Live measles virus vaccine does not contain penicillin.

Thrombocytopenia

Children who have a history of thrombocytopenic purpura or thrombocytopenia may be at increased risk for developing clinically significant thrombocytopenia after measles containing vaccination. The decision to vaccinate should depend on the benefits of
immunity to measles, mumps, and rubella and the risks for recurrence or exacerbation of thrombocytopenia after vaccination or during natural infections with measles or rubella. The benefits of immunization are usually greater than the potential risks, and administration of measles containing vaccine is justified - particularly with regard to the even greater risk for thrombocytopenia after measles or rubella disease. However, avoiding a subsequent dose might be prudent if the previous episode of thrombocytopenia occurred in close temporal proximity to (i.e., within 6 weeks after the previous vaccination). Serologic evidence of measles immunity in such persons may be sought in lieu of vaccination.

HIV-infected Persons

Because of the increased risk for severe complications associated with measles infection and the absence of serious adverse events after measles vaccination among HIV-infected persons, the Advisory Committee on Immunization Practices (ACIP) in the USA has recommended that measles containing vaccine be administered to all asymptomatic HIV-infected persons and that measles containing vaccine be considered for administration to all symptomatic HIV-infected persons who would otherwise be eligible for measles vaccine - even though the immune response may be attenuated in such persons. There is a theoretical risk for an increase (probably transient) in HIV viral load following measles vaccination because such effects have been observed with other vaccines.

ACIP continues to recommend measles containing vaccine for HIV-infected persons without evidence of measles immunity who are not severely immunocompromised. Severely immunocompromised and other symptomatic HIV-infected patients who are exposed to measles should receive immune globulin (IG), regardless of prior vaccination status. In addition, health-care providers should weigh the risks and benefits of measles vaccination or IG prophylaxis for severely immunocompromised HIV-infected patients who are at risk for measles exposure because of outbreaks or international travel.
Because the immunologic response to both live and killed antigen vaccines may decrease as HIV disease progresses, vaccination early in the course of HIV infection may be more likely to induce an immune response. Therefore, HIV-infected infants without severe immunosuppression should routinely receive measles vaccine as soon as possible within the routine immunisation schedule.

Even though HIV infection prevalence is high in South Africa, all infants and children should be immunized with the EPI antigens according to standard schedules. This also applies to individuals with asymptomatic HIV infection. Screening for HIV infection prior to vaccination should not be conducted. For persons with advanced HIV infection, the potential risks of measles vaccination must be compared with the potential risk of being exposed to circulating measles virus.
CHAPTER 2 - GLOBAL CONTEXT AND EXPERIENCES OF MEASLES ELIMINATION

2.1 Terminology

**Eradication** is defined as the interruption of measles transmission globally such that vaccination would not need to be continued. **Elimination** refers to interruption of transmission in a sizeable geographical area but, because of the continued threat of re-introduction of the virus, vaccination would need to be continued. Global eradication basically represents the sum of successful elimination efforts in all countries. Elimination has been achieved already in some areas for limited periods of time.

**Catch-up** campaign in measles elimination refers to a nationwide mass campaign targeting a broad age-group and designed to immunise measles susceptibles in the population and achieve a level of herd immunity sufficient to interrupt virus transmission.

**Follow-up** campaign refers to specific campaigns often targeted at a narrower age-group and designed to immunise susceptibles which have accumulated in the population since the catch-up campaign.

2.2 Global context and progress to elimination

In July 1996, a meeting was held in Atlanta, USA, to document the advances in global measles elimination. A summary of this meeting was published in the *Weekly Epidemiological Record*\(^\text{65}\) and is quoted in part here.

This consultative meeting represented a significant landmark in the history of measles control. The data presented demonstrated both the theoretical and technical feasibility of eliminating measles transmission for prolonged periods over wide geographical areas. The recent development of molecular tools to accurately identify individual strains of measles has supported these claims through the differentiation of indigenous
and imported viruses. In addition, global experience has now demonstrated that an important distinction must be made between the limited measles immunization campaigns that have targeted urban or poorly served areas in many countries, and the mass immunizing strategy which has been employed to interrupt transmission in the Americas and the United Kingdom. Geographically limited campaigns which target only young children may raise immunization coverage, but they will not be sufficient by themselves to interrupt transmission of the virus.

Of particular importance in the meeting were the country and regional presentations documenting the considerable political and public interest in the eradication of measles, particularly in developing countries. It has become increasingly evident, however, that an international consensus and commitment to measles eradication is essential as supplementary immunisation activities will be required in industrialized as well as developing countries. A global plan of action for the elimination/eradication of measles is needed to facilitate coordination between countries, donors, technical agencies and international organizations so as to ensure that activities are conducted in an efficient manner. At the same time there is an urgent need to strengthen poliomyelitis eradication efforts in countries and regions with endemic polio virus transmission to ensure that the introduction of measles elimination activities sustains rather than compromises the poliomyelitis eradication initiative.

The meeting found that, based on the success in controlling measles in the Americas and in the United Kingdom, global measles eradication is technically feasible with currently available vaccines. National, subregional, and regional elimination of measles can and should be accomplished. Although non-human primates can be infected with measles virus, it is very unlikely that non-human reservoirs could sustain measles transmission. Asymptomatic and non-classical cases of measles may occur in vaccinated persons but would not impede elimination or eradication of the virus. Waning immunity does not appear to play a major role in vaccine failure.

It was recommended that a goal of global measles eradication should be established,
with a target date within the next 10-15 years (i.e. between 2005 and 2010). Measles eradication is a logical addition and follow-on to the current poliomyelitis eradication initiative but needs to build on the success of poliomyelitis eradication. Because of the rapid accumulation of susceptibles to measles, the implementation phase of an eradication effort should be compressed into as brief a time as possible. Further research to understand molecular pathogenesis and the immune response to measles virus infection should be continued.

The major obstacles to measles eradication are perceptual, political, and financial. The full significance of measles is often not understood and it is frequently perceived as a illness of little consequence. Measles eradication will quickly pay for itself due to savings in vaccinations, hospitalisations and deaths prevented.

There is a need to educate parents, medical practitioners, and public health professionals about the global burden of disease due to measles.

2.3 Experiences in measles elimination

2.3.1 United States of America (USA)\textsuperscript{56}

Beginning in 1966, a federally supported effort to eradicate measles was undertaken and federally-supplied vaccine became available in the public sector as well. Federal funds supported purchase of vaccine, public information and education, surveillance and investigation, and coordination, but could not be used for actual delivery of immunisations. The eradication strategy had four main elements:

1) routine vaccination of infants at one year of age;
2) vaccination of all remaining susceptible children at the time of school entry (age 4-6);
3) improved surveillance of measles; and
4) prompt epidemic control when outbreaks are first recognised.
Over the next 3 years, considerable effort and resources were devoted to measles eradication, with the result that reported measles dropped to 22,231 cases by 1968, a more than 95% decline from the prevaccine era. Unfortunately, the effort was not sustained, and in 1969 major public sector emphasis shifted to rubella vaccine, which had just been licensed. As a result, the number of reported cases rose, reaching a peak of 75,290 cases in 1971. Cases remained in the 20-60,000 range throughout the mid-1970s.

Because of evidence of low immunisation levels in children and a resurgence of measles, in 1977 a national Childhood Immunization Initiative was announced with the aim of raising immunisation levels in the nation’s children to 90% and putting in place a system to maintain those levels thereafter. Major emphasis was placed on reviewing immunisation records of children in primary and secondary schools and on enacting and enforcing school entry immunisation laws. More than 28 million records were reviewed and children needing immunisations were given them. The result was that, since 1981, more than 96% of children entering school have had evidence of immunity to measles, defined as a record of having received measles vaccine on or after the first birthday, documentation of physician-diagnosed measles, or laboratory evidence of immunity. The early success of this effort led to the announcement, in October 1978, of an initiative aimed at eliminating indigenous measles from the USA by October 1, 1982. The main elements of this effort were threefold:

1) Achieve and maintain high levels of immunity;
2) Conduct effective surveillance for measles; and
3) Aggressive response to cases.

Elimination was defined as the absence of indigenous transmission, with the expectation that any reported case could be traced to a foreign source within two generations before its onset. It was anticipated there would probably be about 500 cases reported per year -100 importations and 4 spread cases for each, on average. Considerable effort was placed on this program, with every case being investigated,
and reported incidence declined to a record low of 1497 cases in 1983. This represented an incidence rate of <1/100,000 and a >99% decrease compared to the pre-vaccine era.

Although the USA had come close to the target of elimination, they had not achieved it. Analysis of the measles continuing to occur in the 1980s revealed 3 main patterns depending on the primary age involved - preschool, school-aged, and adult. Outbreaks in preschool-aged children tended to be small (median number of cases 13 in 1985/1986) and to occur primarily in children who had not been vaccinated; approximately ⅓ because they were too young for vaccination, and the remainder for a variety of reasons, usually not related to contraindications. Outbreaks in school-aged children were more numerous and larger (median 25 cases) with most cases occurring in children who had been vaccinated (i.e., were vaccine failures). As an indication of the infectiousness of measles, transmission was documented in a secondary school in Texas where documented vaccination levels were 99% and serological evidence of immunity was present in 96% of students! The third pattern, cases in adults, involved those who had never been vaccinated (many because they were "too old" to have received measles vaccine) as well as vaccine failures.

In 1989-1991 there was a major resurgence of measles, focused primarily in unimmunized pre-schoolaged children living in crowded inner city populations. The poor and members of racial and ethnic minorities were disproportionally represented. When President Clinton took office in early 1993, he markedly increased the level of support through a new Childhood Immunization Initiative, focused on getting infants and young children immunised on time. He also announced a new measles elimination target date for 1996. This initiative has had striking results, with nearly 90% of children now receiving individual antigens before their 2nd birthdays and 77% nationwide having received a basic 4 DTP, 3 OPV, and 1 MMR. Uptake with the more recently recommended hepatitis B and varicella vaccines is not as great.

Measles incidence has fallen even further and only 309 cases were reported in 1995,
a record low. Both epidemiological and laboratory evidence indicates that indigenous transmission of measles was interrupted in 1993. During a 16 week period only 4 cases of measles were reported which were not clearly related to importation and these cases occurred in widely separated parts of the country. In addition, no isolates having the characteristics of strains circulating in the USA before 1993 have been isolated since then. All recent isolates have shared characteristics with viruses circulating in other countries, even in the instances in which no direct epidemiological link has been established. It is believed in the USA that their goal of interruption of indigenous transmission of measles was achieved. The challenge now is to ensure that imported cases do not re-establish transmission and maintain this status until global eradication can be achieved.

2.3.2 Cuba

In Cuba, measles vaccine was introduced at the beginning of the 1970s. Despite improved coverage, 2 large epidemics occurred with an interval of 4 years, in 1976-1977 and 1981-1982 (Figure 2). In 1986, since another epidemic was predicted, a catch-up campaign targeting all children from 1-14 years of age was organized. This vaccination campaign was completed over a 6-month period. A total of nearly 2.5
million children were immunized, achieving a 97.6% coverage.

After the campaign surveillance was enhanced and reported measles rapidly decreased to a 20-year low, with 858 cases reported in 1987 (a morbidity rate of 8.34 per 100,000 population). Since that time, cases have continued to decrease, with <20 reported cases occurring per year between 1989-1992, and the last confirmed case occurring in June 1993. Apparently transmission has been interrupted in Cuba. Because of accumulation of susceptible preschool-age children since the catch-up campaign, a follow-up campaign was conducted in 1993 targeting all children 2-6 years of age, regardless of prior measles immunization history. Over 880,000 children were vaccinated during this campaign, resulting in a 98% coverage. No confirmed measles cases were reported in 1994 and 1995 in spite of improved measles surveillance.

2.3.3 Chile

In Chile, measles vaccine was introduced in the mid-1960s and coverage rates gradually increased to reach a plateau around 90% from 1978. Measles incidence was

Figure 3: Measles in Chile (Source: PAHO)
reduced with the introduction of the vaccine but epidemics regularly occurred at 3-4 years intervals, in spite of high vaccination coverage. In 1982, with the intention of improving further measles control, a 2-dose measles schedule was implemented but discontinued after 3 years when an expected epidemic in 1985 was not avoided. Three years later, in 1988, a major measles outbreak occurred which represented the highest number of cases ever recorded in the post-vaccine era. To avoid the predicted measles outbreak in 1992, a catch-up mass campaign was carried out that year in May, the low measles endemicty period, targeting all children from 9 months to 14 years of age. The target comprised a total of 3.9 million children or 29% of the total population. Reported coverage rates for the campaign exceeded 99%.

Following the campaign, in 1992, a country-wide reporting system was established with the weekly reporting of suspected cases. During 1992-93, only 2 cases of measles were confirmed, both imported, and no secondary cases could be found in either case despite intensive epidemiological investigation. From then until to the end of 1995, no confirmed measles cases have been notified in spite of the implementation of intensified measles surveillance with laboratory testing of all suspected cases. Using vaccine coverage rates to estimate the build-up of susceptibles, a follow-up campaign was planned for May 1996.

2.3.4 Elsewhere in the Americas

Similar strategies have been implemented in all countries in Latin America. The circulation of measles has been interrupted in the

**Figure 4: Vaccination coverage and reported measles cases, Region of the Americas, 1960 - 1996**

![Chart showing vaccination coverage and reported measles cases from 1960 to 1996 in the Americas. The chart includes vaccination coverage rates and reported cases over time.]
English-speaking Caribbean islands since September 1991. In 1995, less than 5,000 cases were notified throughout the Americas, the lowest figure ever reported (Figure 4). Since Canada accounted for >50% of the cases reported in 1995, a similar strategy with the organization of a catch-up campaign was planned and implemented in Spring 1996. Based on this success, and following the declaration in 1994 that polio had been eradicated from the Americas, a goal of measles elimination from the Americas by the year 2000 was set.

2.3.5 United Kingdom (UK)

The UK embarked upon measles control in the 1980s, and estimated coverage reached 92% in 2 year-olds in 1988. This, coupled with a "catch-up" programme targeted at pre-school children, resulted in a marked reduction in the number of notified cases in all age groups. However, the reduced opportunity for unvaccinated older children to acquire immunity through natural infection was reflected in an increase in the proportion of school-children who were susceptible to measles and outbreaks occurred in secondary schools.

Predictions from mathematical models developed in the UK indicated that the accumulation of susceptible school children in recent years would be sufficient to cause a substantial resurgence of measles in older age-groups in the future. An estimated 100,000-200,000 measles cases, approximately half of whom would be secondary school-children, was predicted for 1994/95. An estimated 30-80 deaths would occur during the outbreak. Therefore, a catch-up campaign was conducted in 1994, which targeted children 5-16 years of age, and 92% coverage was achieved. Between January and September 1995, <100 measles cases were confirmed in the UK, with a high proportion traced as importations.