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ISSUES FOR ACHIEVING THE 1995 MEASLES CONTROL TARGETS IN DEVELOPING COUNTRIES

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Issues for Achieving the 1995 Measles Control Targets in Developing Countries

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1995 Measles Control Targets:

"Reduction by 95 per cent in measles deaths and reduction by 90 per cent in measles cases compared to pre-immunization levels by 1995, as a major step to the global eradication of measles in the longer run"

from *Goals for Children and Development in the 1990's*

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Acronyms

AFRO	WHO Africa Regional Office
A.I.D.	Agency for International Development
ARI	Acute Respiratory Infections
CDD	Control of Diarrheal Diseases
CFR	Case Fatalities Ratios
DPT	Diphtheria/Pertussis/Tetanus Toxoid
EPI	Expanded Programme on Immunization
EZ	Edmonston-Zagreb strain of measles vaccine
HIV	Human Immunodeficiency Virus
IMR	Infant Mortality Rate
ORT	Oral Rehydration Therapy
SI	Surviving Infants
WHO	World Health Organization
VE	Vaccine Efficacy

SUMMARY

The World Health Organization has adopted targets of reducing measles cases by 90% and measles deaths by 95% from pre-immunization levels by 1995. These targets were endorsed by major international health agencies including U.S.A.I.D. at the World Summit for Children in 1990.

Global measles vaccine coverage was estimated to be 78% in 1990 and measles vaccine efficacy is now assumed to be 85% with the EPI recommended schedule. In 1990, 39.5 million cases of measles occurred globally with three-fifths of these cases in Africa and Asia. Reducing the incidence of measles by 90% from pre-immunization levels will require high rates of both vaccine coverage and vaccine efficacy. At high levels of coverage, low vaccine efficacy is the main impediment to reducing cases. To achieve 90% protection with a one-dose measles vaccine schedule, both coverage and efficacy must exceed 95%. With a two-dose schedule, 90% protection can be achieved with a coverage of 85%.

In 1990, there were an estimated 1.2 million deaths due to measles with three-fourths of deaths occurring in Africa and Asia. Measles mortality depends on susceptibility to measles and the case fatality ratio (CFR). WHO has estimated measles CFRs in developing countries to be 2-4%. At high levels of coverage, a high risk of death in cases is the most important impediment to reducing measles deaths. With 90% coverage, the CFR must be reduced among the remaining cases in order to achieve a 95% reduction in deaths. The overall CFR in the pre-immunization era was estimated to have been 5% in developing countries and the current rate is estimated to be about 3%. Reducing measles deaths by 95% could be achieved with 90% coverage with one dose and a 1% overall case fatality ratio. With a two-dose schedule and 85% coverage the goals could still be achieved with a CFR as high as 2.0%.

Reducing cases will depend on adopting control programs that are optimal for the country situation and goals. In many countries with low coverage, the key to success is better application of the current strategy of one dose at nine months of age through building infrastructure and improved management. In countries with an established EPI, alternative or additional strategies may be appropriate, including alternative vaccines, alternative schedules and two-dose strategies. Approaches to reducing deaths involve both decreasing the number of cases and improving case management. Vitamin A treatment of measles cases holds the greatest promise for reducing the CFR.

Measles surveillance is crucial to determining the success of existing programs and guiding new program initiatives.

I. INTRODUCTION

More than 25 years after the introduction of measles vaccines and 14 years after the start of the Expanded Program on Immunization (EPI), measles continues to be a significant health problem in many developing countries. Measles is the most important cause of vaccine preventable deaths in children, causing more deaths worldwide than all other childhood vaccine preventable diseases combined[1]. Because of low vaccine, coverage measles is a major problem in Africa.

In 1989, for the first time, the international community agreed on specific targets for the control of measles[2]. These targets are: 1) Increase measles vaccine coverage in children under one to 90% by 2000, 2) Decrease measles cases by 90% compared to pre-immunization levels by 1995 and 3) Decrease measles deaths by 95% compared to pre-immunization levels by 1995. These targets are intended to be the basis for "eradication of measles in the longer run." These targets were endorsed by major international health organizations including the World Health Organization, the Global Advisory Group of WHO/EPI, the Task Force for Child Survival and U.S.A.I.D.

Adoption of these targets represents a fundamental change in the focus of EPI from raising coverage to decreasing disease. At the beginning of EPI, the epidemiology of measles was sufficiently similar in all developing countries that a common strategy was appropriate. This strategy called for a single dose of standard measles vaccine to all infants at nine months of age. Given a policy based on service delivery, EPI has aimed to maximize coverage with little modification of policy based on the local epidemiology of the disease. However, the epidemiology of measles has been altered in most countries by immunization programs. The distribution of cases by age, time and place is now different from the pre-vaccination era. Immunization strategies that have been used to bring us to the current level of disease control may not be appropriate to achieve the new reduction targets or eradication goal. Local conditions must now be taken into consideration.

The purpose of this paper is to 1) clarify issues in defining and measuring the 1995 measles control targets, 2) identify strategies for improving measles control and 3) identify those areas where U.S.A.I.D. efforts can be most effective in measles control in developing countries.

This paper is not an exhaustive review of all issues in measles control. We have focused on those areas that could have a direct effect on development of policies and methods for achieving the measles control targets.

II. ESTIMATES OF THE CURRENT LEVEL OF MEASLES CONTROL

It has been difficult to determine accurately the current level of measles control because of limitations in the surveillance of disease. Routine surveillance for measles cases is inadequate in nearly all developing countries. In 1986, the last year for which reasonably complete reports are available, WHO received reports of 2.1 million cases of measles globally but estimated that over 50 million cases probably occurred, resulting a reporting completeness of less than 5%[4]. WHO/EPI does not routinely collect reports of measles deaths.

To estimate the impact of EPI on measles in the face of inadequate surveillance, WHO has developed a method of estimating measles cases and deaths. This method is based on estimates of immunization coverage, vaccine efficacy and case fatality ratios combined with the number of newborns and infant mortality rates. It will be used to assess the status of measles control, the expected effect of interventions and the operational requirements to meet the measles control targets.

A. The WHO Method for Determining Measles Cases and Deaths

The number of measles cases is estimated by WHO using the following expression:

$$Cases = Susceptibility \bullet Number\ of\ Surviving\ Infants \qquad (1)$$

This model assumes that protection is lifelong and that all unprotected people will get measles during their lifetime. Therefore, the number of measles cases per cohort will equal the number unprotected by immunization in that cohort. It is further assumed that the number of cases per year is equal to the number of infants unprotected by immunization in each cohort.

An infant is considered susceptible to measles if he/she was not effectively immunized. Immunization coverage overestimates the rate of protection as vaccination does not always result in immunity and some vaccine is administered to children who have already had measles. The ability of a vaccine to prevent disease is the vaccine efficacy (VE). The product of VE and coverage is the estimated rate of protection and the rate of susceptibility can be estimated from this expression;

$$Susceptibility = 1-(VE \bullet Coverage) \qquad (2)$$

An infant becomes susceptible to measles when maternally acquired antibody declines to a level that is low enough to allow for infection with the wild virus. The decline in maternal antibody to below protective levels varies but most infants are susceptible by the age of six months. Nearly all infants in developing countries are susceptible to measles by the age of 12 months. A "surviving infant" (SI) is one who survives to one year of age. Since about 75% of infant mortality occurs by the age of six

months[3], the estimated number of "surviving infants" will be assumed to equal the number of infants susceptible to measles (i.e., SI = 1-(.75*IMR). By combining the above equations, the number of measles cases is estimated by:

$$Cases = 1-(VE \bullet Coverage) \bullet SI \qquad (3)$$

The estimated number of measles deaths is the estimated number of cases multiplied by the estimated case fatality ratio:

$$Deaths = Cases \bullet CFR \qquad (4)$$

B. Estimates of Vaccine Coverage, Vaccine Efficacy and Case Fatality Ratios

Of the parameters in equations (3) and (4), measles vaccine coverage, vaccine efficacy, and measles case fatality ratios are those that are of primary interest for measles control. These parameters can be estimated from existing data.

1. Estimated Measles Vaccine Coverage

The trends in measles immunization coverage globally and from the WHO African Region (AFRO) from 1984-1990 are shown in Figure 1. In 1990, the global and AFRO coverage levels for measles vaccine reached 78% and 54%, respectively. These figures include recent accelerations to achieve the 1990 target of 80% coverage. These data show an increasing trend in coverage but with a widening gap between global and AFRO coverage. It should be noted that these figures are typically coverage figures for infants less than one year of age. Often, they do not reflect the results of immunizations in older children or a child who receives more than one dose of vaccine. In this paper, coverage estimates published by EPI will be assumed to represent the number of infants immunized by one year of age.

2. Estimated Vaccine Efficacy

The antibody response following vaccination is an indirect measure of the ability to prevent disease and serum antibodies have correlated with protection in several studies. Protection following immunization depends on the ability of a vaccine to prevent disease. Published studies of the serologic response to measles vaccination of nine-month-olds is presented in Table 1. These studies give an overestimate of vaccine performance as they have been done under controlled conditions of vaccine storage, transport, handling and administration. The median figure from these studies is 86%.

Protection against disease is directly measured by assessing field efficacy which is measured by comparing disease rates in immunized and unimmunized persons. Published studies of vaccine efficacy in developing countries is presented in Table 2. The median figure of vaccine efficacy in these studies is 72%. Several of the low efficacy rates reported in these studies were probably due to poor handling of vaccine or methodologic issues. With good immunization practices, the vaccine efficacy should approximate the serologic response rate. In this paper, it will be assumed that measles vaccine efficacy is 85%, the estimate currently used by EPI.

3. Estimated Case Fatality Ratios

A crucial factor in estimating the number of measles deaths is the need to estimate measles case fatality ratios (CFR). A sample of the published reports on age-specific case fatality ratios is shown in Table 3. Recent evidence suggests that measles can contribute to delayed excess mortality for up to two years following the acute illness.[5,6,7,8] The implications of delayed mortality are that deaths from measles may have been underestimated or attributed to other causes.

Widespread immunization could affect the CFR for measles in different directions. There may be an apparent increase in CFR as children who are at lower risk of death could be selectively immunized. Such factors as access to care, maternal education and socio-economic status, which are risk factors for non-immunization, also correlate with severe disease and mortality. As immunization coverage increases, proportionately more measles cases will occur among children who will have higher mortality following measles, resulting in an apparent rise in CFR.

There also could be a decrease in the CFR if immunization of some children results in decreased measles transmission and an increase in the average age of contracting measles as has occurred in some countries. Since the burden of disease shifted to an older age group, there was an overall decrease in the CFR although age-specific death rates remained constant. In several developing countries the CFRs are declining with increased coverage.

Two lines of argument suggest that the CFR from measles in the pre-immunization era was approximately 5%: 1) The average age of disease was 1-4 years where the CFR has been in the 5% range (Table 3). 2) The estimated infant mortality rate in the pre-immunization era was 15-20% and approximately one-fourth of infant deaths were attributable to measles in several studies. In recent years, EPI has used 3% as the overall CFR for measles in developing countries. This is probably an underestimate of the true CFR, but 3% may be a reasonable estimate for 1995. Over the period 1975 to 1995, we assume that the CFR may fall from 5% to 4% because of improvements in clinical care. With increased immunization coverage, the CFR could fall to 3% because of a shift in the age distribution of measles to older children.

C. Estimates of the Number of Measles Cases and Deaths

1. Estimated Number of Measles Cases

Without immunization it is assumed that the entire 1990 surviving global birth cohort of 117 million infants would acquire measles (Table 4). This estimate is slightly higher than WHO estimates as WHO assumes that only 90% of susceptible persons will acquire measles. Using the WHO method, 66% of the 1990 birth cohort is protected while 34% remain susceptible.* When this rate is applied to the 117.1 million surviving infants in 1990, there were 39.5 million unprotected infants who probably contracted measles. Most of the cases occurred in Africa and Asia because of large numbers of newborns combined with low coverage. In Africa and South East Asia the estimated number of measles cases is equal to about three-fifths of the birth cohort.

2. Estimated Number of Deaths

The number of measles deaths in 1990 was estimated by applying an estimated 3% CFR to the number of estimated cases (Table 4). Since 34% of the 1990 cohort was susceptible, the death rate in the cohort was ~1% (.34 • .03). If this death rate is applied to the 1990 birth cohort of 117 million infants, there were 1.2 million deaths from measles in 1990. Approximately three-fourths of all measles deaths occurred in Africa and Asia.

D. Operational Definition of the 1995 Measles Control Targets

An operational definition expresses the targets in terms of factors that can be influenced by the program. This section will define the measles control targets in terms of coverage, vaccine efficacy and case fatality rates.

1. Operational Definition of the Case Reduction Target

If we assume that all unprotected infants will get measles, then the measles case reduction target can be defined as protection of at least 90% of the birth cohort surviving beyond six months of age. Conversely, less than 10% of the cohort would be unprotected by one year of age. Figure 2 illustrates the progress toward the measles reduction target to date. The target will be achieved when the number of susceptible infants equals 10% of the surviving infants. As of 1990, 66% of the birth cohort was protected. To achieve 90% protection, 24% more of the cohort must be protected.

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*Protection = Vaccine Efficacy • Vaccine Coverage = .85 • .78 = .66

The protection from one and two-dose measles schedules is shown in Figure 3. The case reduction target is protection of 90% of children surviving to six months of age. With the current one-dose schedule and a vaccine efficacy of 85%, it is not possible to achieve the reduction target. The targets can be attained with a two-dose schedule with coverage of approximately 85% for the first dose (as described below).

2. Operational Definition of the Measles Death Reduction Target

Since the entire cohort of children surviving to six months of age developed measles in the pre-immunization era with an assumed CFR of 5%, approximately 5% of each surviving cohort died of measles. A 95% reduction from the pre-immunization level of 5% is 0.25% of each surviving cohort. Progress toward this goal is shown in Figure 4. A 95% reduction in the pre-immunization death rate applied to the 1995 birth cohort means that the 1995 target is less than 302,500 measles deaths (Table 5).

Two factors contribute to reduction in deaths from measles, reduction in cases and reduction in case fatality ratios. In most countries, there are simultaneous improvements in both CFR and coverage. A method for calculating the simultaneous effect of coverage and reduction in CFR is presented in the Appendix. The relationship between the two is presented in Figure 5. Both high levels of coverage and low levels of CFR must be achieved to reach the targets. At 90% coverage with a single dose of measles vaccine, the CFR must be reduced from 5% in the pre-immunization era to 0.85% in 1995. With a two-dose schedule at 85% coverage, the CFR must be reduced to only 2.0% to achieve the 1995 death reduction target.

III. STRATEGIES FOR MEASLES CONTROL

Achieving the targets for measles control will depend on extending protection to remaining susceptibles and reducing the risk of death in those who get measles. A variety of approaches are available to help reach these goals.

A. Increasing Coverage

Increasing coverage is the single most important activity for controlling measles. Activities to improve coverage are reducing missed opportunities for immunization, reducing drop-outs, and removing barriers to immunization. Achieving this will likely require improvements in the quality of routine services, extensive use of social marketing and decreasing barriers to immunization. This paper will focus on measles-specific activities that may need to be considered beyond the important improvements in the routine delivery system.

B. Improving Vaccine Efficacy

There are only two important sources of susceptibles to measles: unimmunized persons and immunized persons in whom the vaccine fails. As coverage increases, a higher percentage of cases is attributable to vaccine failure (Figure 6). At the current level of coverage (78%), over one third of susceptibles are attributable to vaccine failure. As coverage increases, the percent of susceptibles and subsequently cases due to vaccine failure will increase. If vaccine efficacy increased, the rate of cases due to vaccine failure would decrease.

1. Improved Vaccines

While improving program quality is a high priority, it is possible to improve vaccine efficacy even with the existing level of program quality. In areas of the world where protective maternal antibodies wane quickly, and where transmission is facilitated by crowding, measles has high morbidity and mortality in children under 9 months of age. High priority has been given to the development of vaccine strains that can overcome the interference of maternal antibodies and thus be efficacious in very young infants. Two such vaccine strains, the Edmonston-Zagreb and AIK-C, have shown promise in recent trials.[9-16] In some studies, high dose E-Z or standard dose AIK-C vaccine given at 6 moths of age induced seroconversion rates that are comparable to the standard Schwarz vaccine given at nine months of age. E-Z vaccine has been recommended for use in areas where measles before the age of nine months of age is an important cause of mortality. Whether the E-Z strain will remain effective at longer follow-up periods awaits further study. Also, problems have developed with

the availability of E-Z vaccine and questions have been raised about the long term safety of high titer vaccines. These issues need to be resolved before high titer vaccines can be accepted as providing a solution to these problems.

2. Changing the Age of Vaccination

Determining the optimal age for vaccination is a trade-off between avoiding vaccine failures and avoiding early cases of measles. If the vaccine is given early in life, then interference from maternally acquired antibody will result in lower vaccine efficacy. If the vaccine is given later, then the infant is potentially exposed to measles infection for a longer period before vaccination. Increasing the age of administration will reduce vaccine failures attributable to interference from maternal antibodies. But, it also will allow more time for infants to be exposed and may increase the immunization drop-out rate. As high immunization coverage levels are achieved and an epidemiological shift to older ages occurs, raising the age of vaccination may become a reasonable approach. Those countries that have few cases below the age of 12 months might improve control in older age groups by increasing the age of immunization.

3. Two-Dose Schedule

A potentially effective method of overcoming limitations in vaccine efficacy is to give two doses of measles vaccine (Figure 3). Individuals who do not develop immunity after the first dose will be protected with a second dose. Since vaccine efficacy increases with age, the second dose will have a higher efficacy than the first dose. There are a variety of possible two-dose schedules. The schedules of interest to developing countries with high transmission rates give the first dose early in life (six to nine months of age) to prevent early disease and the second around the first birthday after maternal antibodies have waned.

Objections to a two-dose schedule are economic and programmatic. While the cost of vaccine is a burden to programs with limited resources, vaccine costs represent only a fraction of the total cost of immunizing children. If the second dose is incorporated into other visits, the additional cost is small. Research is needed on the true additional cost of adding a second dose.

Programmatically, there has been concern that insufficient numbers of infants would return to make the second dose worthwhile, that personnel would be diverted from emphasizing at least one dose for all children, and that parents would not return for second doses. Lower overall rates of protection would result from providing the first dose at under nine months of age. Research is needed to determine the rates of coverage with each dose, the factors that affect acceptance of the first and second dose, and the overall impact of the two dose strategy.

One example of a successful two-dose schedule is in Tunisia. The Tunisian EPI recommends the first dose at 9-12 months of age and the second dose 6 months later. In a 1991 program review, 96% of infants who correctly received the first dose received the second dose. This is similar to the program's drop out rate for DPT1 to DPT3. In addition, 68% of those who did not receive a dose at 9-12 months of age received a dose after 12 months of age. Based on this experience, it would appear that the second dose would reach the target population at an acceptable rate. Figure 3 compares the protection from one and two dose schedules. Because of the high efficacy of the second dose, higher protection can still be achieved despite the lower efficacy of the first dose.

C. Reducing Deaths

Measles vaccine can have a profound effect on reducing deaths (Table 6). In some studies, this reduction in deaths exceeds that which is usually attributable to measles. Part of this effect may be due to an underestimation of the long-term mortality of measles. A possible bias of these studies is that they were done in areas where there is crowding and low socioeconomic status, two factors that contribute to high measles CFR.

Several risk factors have been identified for death from measles including young age at infection, crowding, low socio-economic status, vitamin A deficiency, HIV infection and possibly malnutrition. While poverty and co-existing HIV infection are not addressable within EPI programs they remain strong risk factors for measles death. The risk of death in poor populations of industrialized countries in the late 1800s was similar to the rates observed in developing countries today.[17] The risk of death from measles was higher in low socioeconomic status groups as measured by household articles owned in rural Bangladesh and Haiti.[18,19] These are probably not biologic effects, but more likely related to poor nutrition, suboptimal medical care for secondary infections, and crowding.

Measles illness is severe in children with immunodeficiency disorders involving T-cell deficiency such as leukemia and HIV[20]. In Africa a trend toward higher measles CFRs was observed in older children with HIV antibodies.[21] Measles immunization may have a higher failure rate in HIV infected children, although the rates of adverse consequences have been similar to the rates in HIV uninfected children. WHO recommends that all children be vaccinated regardless of HIV status.

Some conditions that were previously thought to be risk factors for severe disease may be less important. Until recently, malnutrition has been considered an important cause of high measles CFR's. Malnutrition causes immunodeficiency, and malnourished children have prolonged excretion of measles virus compared with well nourished children.[22] Early hospital studies observed an association between low

weight and increased mortality; however, these studies did not take into account weight loss and dehydration during the measles incubation period and illness prior to admission. Recent studies that have looked for an association between pre-existing malnutrition and severe measles do not support the idea that malnutrition is a major risk factor for measles death (Table 7).

1. Access and Utilization of Health Care

Treatment of complications from measles can decrease the CFR. Many children with severe measles do not have access to or their parents do not seek curative health care. Analysis of large measles surveillance systems in Bangladesh showed that 91% of measles deaths occurred in the home and only 13% of the deaths were attended by a physician.[23] Only 12% of parents had consulted a medical doctor prior to death of the child and most medical contacts occurred only after first consulting a traditional healer. In an outbreak of measles in rural villages in South India, measles CFR in villages with health care services was 3.4%, compared with 16% in villages without health care services.[24] After the introduction of a medical care facility in a well vaccinated rural west African village, there were no deaths during a subsequent measles outbreak in children less than 5 years.[25]

2. Vitamin A Treatment of Measles Cases

Vitamin A has been shown to prevent deaths in children with measles in developing countries (Table 8). In a clinical trial in Tanzania, where xerophthalmia was prevalent, children who received vitamin A on admission for severe measles infection had decreased mortality as compared to controls.[26] Children hospitalized with measles in South Africa who were randomized to receive vitamin A upon admission had half the number of deaths, recovered more rapidly from diarrhea and pneumonia, and spent fewer days in the hospital than children who received placebo.[27] Interestingly, low weight for age and clinically apparent vitamin A deficiency were rare in this population. Few obstacles or risks to widespread use of Vitamin A in measles patients have been identified.

3. Treatment of Acute Respiratory Infections

Measles infection can affect all organ systems of the body and the respiratory epithelium is infected in 100% of cases. Respiratory infections are common complications from measles in both developing and developed countries. Community surveys in Latin America prior to measles immunization revealed pneumonia was the terminal event in 80% of deaths due to measles[3]. In a prospective study in Manila, measles was associated with 14% of pneumonia cases and 61% of pneumonia deaths.[28] In a study of children hospitalized with pneumonia in South Africa, measles was associated with 64% of admissions and 24% of all mortality.[29]

Measles-associated pneumonia occurs due to direct infection by the measles virus and secondary infections by other viruses and bacteria. An autopsy series of 21 children who died from pneumonia within 28 days of onset of measles rash showed 25% died early in the course with severe measles giant cell pneumonia[29]. After 2-3 weeks, viral and bacterial secondary infections were more frequently associated with deaths. Otitis media is the most common respiratory complication and pneumonia, bronchitis and croup occur as well[30,31].

The relative importance of these secondary infections varies according to the local epidemiology of measles and other acute respiratory infections. It is clear however, that measles control can reduce mortality due to respiratory infections and treatment of respiratory infections can probably reduce measles mortality.[51]

4. Diarrhea Treatment

Measles infection is commonly associated with diarrhea in developing countries. Some children have a protein-losing enteropathy and may lose 6-9 percent of their plasma protein in a single 24 hour period.[32] The loss of proteins and persistent diarrhea are major contributing factors in the development of malnutrition following measles. Other factors contributing to malnutrition include decreased food intake due to mouth sores, malaise and appetite loss, and increased metabolic demands due to fever. Morley showed that 50% of children required 8 or more weeks to return to their pre-illness weight.[33] Koster et al found that children who had measles complicated by prolonged diarrhea sustained a significant and persistent deficit in weight for height ratio of approximately 10%.[34]

There are few controlled studies that have assessed the role of secondary infections in measles-associated diarrhea. Cases of measles-associated diarrhea were compared with acute diarrhea without measles in an outpatient clinic in Bangkok.[35] Bacterial infections were isolated in 14% of cases and in 29% of controls. Rotavirus was absent in the measles diarrhea and occurred in 18% of controls. Greenberg et al [36], in a case control study of hospitalized children in Lima, Peru, found similar bacterial and protozoal pathogens in children who had diarrhea with or without measles.

Diarrheal disease as a consequence and contributory cause of death from measles occurred in 50.4% of measles deaths in 13 communities surveyed in Latin America during the years 1968-1972.[52] Measles complicated by diarrhea accounted for 19% of the admissions and was associated with a 24% mortality during the years 1973-1982 in a hospital survey in Ghana.[22] In this study, diarrhea was the most common complication associated with fatal cases. Measles mortality for children with diarrhea was 5.3 per cent compared with 2.1 per cent in children without diarrhea.

It is not clear to what extent oral rehydration therapy (ORT) can Affect measles mortality. Measles-associated diarrhea may be prolonged and associated with a protein-losing enteropathy while ORT is most effective in acute secretory diarrheas. In addition, risk of non-immunization may correlate with lack of access to ORT.

5. Modify Age Distribution of Disease

Young age at infection is a risk factor for severe disease and death from measles (Table 3). Respiratory complication rates are inversely associated with age and directly contribute to the high age-specific CFRs in infants between 6-12 months of age. In the Ilesha Hospital in West Africa, during the years 1958-61, measles pneumonia was associated with a CFR of 30% in children less than two years versus 20% in those older than two[39]. In contrast, the CFRs from diarrhea were similar in all age groups.

Since measles CFR is inversely related to age, increasing the average age of measles infection should result in lower mortality. Mathematical modeling based on herd immunity assumptions predicts that introduction of mass vaccination produces a period of low incidence followed by a shift in the age distribution to older ages[40]. Measles transmission becomes more intermittent and infants will be less likely to be exposed to measles until they are older. The average age of disease has shifted to higher age groups in several countries following the introduction of measles vaccination programs.[41-43]

It is difficult to determine the critical level of immunization that affects the age distribution of disease. In developing countries the number of children in the lowest age stratum is relatively large with high rates of crowding and poor housing. Thus, frequent contact among pre-school children makes effective immunization before exposure difficult. In Kinshasa, Zaire 50-60% vaccine coverage was achieved but no significant shift in the age distribution of measles was observed.[44] In this densely populated urban community, higher rates of protection in young infants is probably needed to induce an age shift.

6. Modify Exposure

Crowding is a risk factor for severe disease and high mortality (Table 9). Even in areas in which the risk of exposure is low, such as rural villages, the intensity of that exposure is an important risk factor. In a typical rural African setting an index case may have only a brief exposure to measles in, for example, a marketplace while a secondary contact may have a prolonged exposure from the primary case by, for example, sleeping in the same bed. First described in studies by Aaby in Guinea-Bissau[45], several other investigations have noted similar findings of increased CFRs in secondary household cases compared with index cases[46-48]. The most probable biologic explanation for this is increased intensity of exposure within

households with higher inoculum of virus in secondary cases. The increased risks of death in the household contact compared to the index case range from 2-24. Removing the source of this risk factor (crowding) may be difficult.

In rural settings, there is an increased risk of death to the secondary contacts. In a crowded urban setting, there is an additional increased risk of death to the index case. In an urban area where measles may be endemic, exposure typically occurs early in life resulting in an earlier average age of disease. Early age of disease is the major risk factor for measles death.

D. Interrupting Transmission, the Caribbean Example

Measles remains a problem in the Caribbean region despite nearly 80% vaccination coverage since 1987. In May 1991, the English-speaking Caribbean countries embarked on a new measles elimination program, aimed at eliminating the indigenous transmission of measles in the region by 1995. The program began with an initial mass vaccination campaign targeting all persons 1-14 years of age regardless of prior immunization status. Intensified routine immunization services have been implemented to assure that all new susceptibles entering the population are immunized as soon as possible. Enhanced surveillance has been put in place to document each case of measles and to certify when cases are not occurring. The experience of these countries will be watched closely as the rest of the world intensifies measles control activities.

E. Surveillance

The EPI has set a goal of establishing routine surveillance for EPI diseases in all areas by 1995. Although nearly all developing countries have policies regarding measles surveillance, reporting is very poor in most areas.

Surveillance systems for measles control ideally should be able to answer the question: Is the current policy working to achieve the current goals? In this context, it is important to know whether the identified cases could have been prevented with the existing policy by classifying them as preventable or non-preventable[49]. Preventable cases occur in persons for whom vaccine was indicated. Non-preventable cases occur in persons for whom the vaccine was not indicated (typically younger than 9 months of age) or who had received vaccines and were vaccine failures. The distribution of cases in these categories will help provide the epidemiologic basis for evaluating measles policy.

In a hypothetical developing country, if 15% of cases occurred before 9 months of age and measles vaccine coverage was 80%, approximately 30% of the total number of cases would be vaccine failures and the remaining 55% of cases, occurring in older, non-vaccinated persons, would be preventable. A typical developing country should therefore expect more than 50% of all cases during outbreaks to be preventable. As coverage improves, there is likely to be a shift toward a higher percentage of cases being classified as non-preventable. When the majority of cases is found to be non-preventable and a high number of cases continues to occur, then further improvements in measles control may require a change in strategy. In 1988, after the U.S. experienced a shift of cases from those classified as unvaccinated to those classified as vaccine failures, the U.S. adopted a two-dose schedule. The U.S. decision to change to a two-dose schedule was based on routine measles surveillance and outbreak investigations. In developing countries, surveillance of measles cases and classification of cases by age and vaccination status should be the basis of decisions on changes in measles control strategies.

IV. CONCLUSIONS

Widespread use of measles vaccine under the EPI has resulted in the prevention of large numbers of measles cases and changed the epidemiology of measles in most areas.

The 1995 target of 90% reduction in measles cases cannot be achieved with the existing vaccine used in a single dose schedule because vaccine efficacy at that age is only 85%. The 1995 target for reducing measles deaths by 95% could be achieved with the existing vaccine if 90% coverage rates are reached and the case fatality ratio reduced to 1% or less. A two-dose schedule would be an effective means to improve vaccine efficacy and prevent cases that occur before the current age of administration. Mathematical modelling suggests that a strategy to give measles vaccine at 6 and 12 months of age, given 85% coverage and a CFR as high as 2.0%, could result in achieving both of the 1995 targets.

Current surveillance for measles is inadequate to monitor progress toward the 1995 targets. Improved surveillance systems should be developed and control strategies should be modified based upon surveillance reports.

V. RECOMMENDATIONS FOR A.I.D. ACTIVITIES IN SUPPORT OF MEASLES CONTROL

1. Improve surveillance for measles cases. Surveillance systems should be able to determine the current status of measles control, monitor its progress and provide sufficient information to decide between policy options.

2. Improvements in measles control will require national policies that reflect the local measles epidemiology. Decision-making for measles control strategies needs to be encouraged at the national level.

3. EPIs need to achieve and maintain at least 90% coverage with a single dose of measles vaccine at nine months of age.

4. In countries with coverage greater than 80%, two-dose measles vaccination schedules may be needed to reach the 1995 objectives. Two-dose schedules should be evaluated by pilot projects, operational research and cost effectiveness studies.

5. Case management of measles, including improved access to care, widespread use of vitamin A, and support from CDD and ARI programs should be improved.

6. The next several years will be a period of rapid change in measles control which will be enhanced by supporting policy development at W.H.O. Measles policy development needs to be supported at the global level.

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Appendix: Determining the necessary CFR at any given level of coverage to reach the 1995 measles control targets

Since all unprotected infants can be expected to acquire measles, in the absence of immunization the rate of death in the cohort is equal to the measles CFR:

Pre-Immunization Rate of Death = Pre-Immunization CFR = .05

The rate of measles deaths in the post-immunization era would be equal to the product of the rate of susceptibility (equal to 1-protection) and the new CFR:

Post-Immunization Rate of Death = (1-Protection) • CFR_{post}

In order for the rate of post-immunization deaths to be reduced by 95%, the ratio of the expected post-immunization era deaths to pre-immunization era deaths must be less than or equal to .05. Thus:

$$\frac{\text{Expected Deaths Post-immunization}}{\text{Estimated Deaths based on Pre-Immunization CFR}} \leq .05 \leq \frac{(1\text{-Protection}) \bullet CFR_{post}}{5\%}$$

Solving for CFR_{post} and adjusting for changes in the number of surviving infants in the two eras (121 million vs 97 million, respectively) gives an expression for the required level of CFR with any given level of coverage and vaccine efficacy to achieve a 95% reduction in deaths:

$$CFR_{post}\ (\%) \leq \frac{.05 \bullet 5\% \bullet (97/117)}{(1\text{-Protection})} \leq \frac{.2}{(1\text{-Protection})}$$

The protection from one and two-dose schedules is given in Figure 3. At 90% coverage, for one dose the protection is 76% which results in a $CFR_{post} \leq .83\%$. For a two-dose schedule the protection at 85% coverage is 90% and therefore the CFR_{post} can be as high as 2.0%.

Table 1. Serologic Response Rates Following Standard Measles Vaccines Administered to Infants Nine Months Old in Developing Countries

Country	Seroconversion Rate (%)
Nigeria, 1966	86.7%
South Africa, 1975	86%
Rhodesia, 1976	93.9%
Nigeria, 1976	39.3-63.3%
Kenya, 1977	92.5%
Kenya, 1979	93%
PAHO, 1981*	84.6%
Haiti, 1985	85%
Gambia, 1988	85-95%
Togo, 1989	73%
Uzbekistan, 1991	95%
South Africa, 1991	61%
Haiti, 1991	84%
Indonesia, 1991	96.8%
Mexico, 1990	82-87%
Mean = 86%	

*Brazil, Costa Rica, Chile, Ecuador in children weighing >85% of expected norm.

Table 2. A Sample of Reported Measles Vaccine Efficacy Rates

Country	Vaccine Efficacy
Micronesia, 1982	83.5%
Zaire, 1985	78-87%
Taiwan, 1985	40%
Guinea-Bissau, 1986	72%
Mozambique, 1986	66%
Kenya, 1986	18%
Kenya, 1987	70%
Kenya, 1988	67%
Mexico, 1987-88	63-89%
Mexico, 1988	~95%
Burundi, 1989	82%
Gambia, 1989	90.1%
Guinea-Bissau, 1990	<68%
Median = 72%	

Table 3. Reported Age-Specific Measles Case Fatality Ratios by Source of Patients

Study	Type	Age		
		<1	1-4	5-9
Copenhagen, 1915	Hospital	20	15	3
East Africa, 1967	Hospital	6.4	5.6	2.6
Ghana, 1982	Hospital	9	15	--
London, 1911-14	Hospital	13.9		--
Gambia, 1981	Clinic	77.8	6	3.5
Chile, 1960	Community	13.7	5.6	2.6
Burma, 1966	Community	6	3	1
Kenya, 1974	Community	6.4	8.5	0
Bangladesh, 1975	Community	4.4	4.2	--
India, 1977	Community	22	4.9	0
India, 1977	Community	22	17	0
Gambia, 1981	Community	64	16.7	4.4
Senegal, 1983	Community	11.5	9.2	1.2
India, 1986	Community	23.1	11.5	5.5
USA, 1975	Community	0.33	0.15	0.04
USA, ~1985	Community	0.0	0.17	0.10
USA, 1990	Community	0.42	0.46	0.21
Median, Community Studies, LDC		11.5	5.6	1.0

Adapted from Aaby and Clements, Measles immunization research: a review, *Bull World Health Organ*, 67(4):443-8, 1989.

Table 4. Estimated Number of Measles Cases in Developing Countries, 1990 (V.E.= 85%)

WHO Region	Surviving Infants (millions)	Vaccine Coverage	Fraction Protected	Measles Cases (millions)	Estimated CFR	Measles Deaths (millions)
African	25.2	54%	.46	13.6	.04	.54
American	12.1	73%	.62	4.6	.02	.09
East. Med.	14.8	73%	.62	5.6	.02	.11
European	1.4	80%	.68	.45	.001	.0004
S.E. Asian	36.9	81%	.69	11.4	.04	.46
West. Pacific	28.1	94%	.80	5.6	.02	.11
Global	117.1	78%	.66	39.5	.03	1.2

Table 5. Operational Requirements to Meet the 1995 Measles Control Targets

	1975 Estimated (% of SI*)	1990 Estimated (% of SI)	1995 Target (% of SI)	1995 Target in absolute numbers[1]	Operational Requirements to Achieve 1995 Target
Coverage	0%	78%	90%	~108.9 million	90% Coverage
Cases	100%	34%[2]	10%	~12.1 million	1) 95% Coverage and 95% Efficacy or 2)Two-doses, 85% Coverage[3]
Deaths	5%	1%[4]	0.25%[5]	<302,500	90% Coverage, 85% Efficacy and CFR ≤ 1%[6]

SI = Surviving Infants

[1]The estimated number of births in 1995 will be 128 million with an expected IMR of 7.2%. Surviving infants (to 6 months of age) = Total Births • (1 - .75 • IMR) = 121 million. (from UN World Population Prospects 1988)

[2]Assuming a vaccine efficacy of .85 and a coverage of .78, the proportion of infants un-protected is 1-(.85•.78) = .34.

[3]This two-dose schedule assumes vaccine efficacy of 65% at 6 months and 95% at 12 months of age. The return rate is similar to that achieved in Tunisia: of those who receive the first dose, 96% return for the second dose and of those who do not receive the first dose 68% receive a dose at 12 months of age.

[4]This is based on the estimated 1990 CFR of 3% applied to the estimated case rate of 34%; .03 • .34 = .01 or 1%. The number of measles deaths in 1990 is this 1% rate applied to the number of surviving infants; .01 • 121 million = 1.2 million.

[5]This represents a 95% reduction from the estimated death rates of 5% in the pre-immunization era; 5% • .05 = 0.25%.

[6]The goal is death in less that 0.25% of the cohort. 90% coverage with a VE of 85% will result in a 76.5% protection. In order to have an overall death rate of 0.25% in the entire cohort, the remaining susceptible 23.5% of the cohort must have a CFR of .25/.235 = 1.06%.

Table 6. Estimated Efficacy of Measles Vaccination for Prevention of Death

Study location	Age at vaccination (months)	Length of follow-up (months)	Efficacy against death
Nigeria, 1963	N/A	18	100%
Zaire, 1974	7-9	30	46-60%
Guinea-Bissau, 1984	7-24	24	63%
Haiti, 1985	6-13	21	85%
Bangladesh, 1982	9	51	36%
Bangladesh, 1982	9	51	46%

Table 7. Nutritional Status and Severity of Measles in Children Who Died From Measles and Controls

Study	Age (years)	Type of Index	Nutritional Status (% of Standards)		Ratio Cases/Controls
			Fatal cases	controls	
Bangladesh	<9	w/h	.86	.88	98%
	<2	w/h	.93	.86	98%
	3-9	w/h	.85	.88	97%
Guinea-Bissau	<4	w/a	.87	.90	97%
	<5	w/a	.92	.92	100%
	<5	h/a	.97	.97	100%
	<5	w/h	.97	.97	100%
	<1	w/a	.88	.89	99%
Kenya	no data	muac	.84	.86	98%
Gambia	no data	w/a	.29	>.29	>100%

From Aaby[50]

where

w/h = weight for height
w/a = weight for age
h/a = height for age
muac = mid-upper arm circumference

Table 8. Impact of Vitamin A Treatment on Mortality in Children Hospitalized With Measles

Study	Dose	% Reduction in Mortality
South Africa, 1990[27]	400,000 I.U.	-79%
Tanzania, 1987[26]	200,000 I.U.	-48%
London, 1932[53]	~50,000 I.U.	-57%

I.U. = international units

Table 9. Measles Case-Fatality Rates by Index vs Secondary cases in Households in Urban and Rural Settings

Study	Case Fatality Rates		Relative Risk of Death:
	Index cases	Secondary cases	
Urban Studies			
Guinea-Bissau, 1989[14]	.08	.30	3.8
Guinea-Bissau, 1988[6]	.03	.38	14.2
Guinea-Bissau, 1988[6]	.05	.17	3.8
England, 1986[49]	.08	.22	2.7
Copenhagen, 1915[6]	.11	.27	2.4
Rural Studies			
Guinea-Bissau, 1989[14]	.07	.38	5.8
Senegal, 1990[9]	.04	.14	3.4
Bangladesh, 1988[46]	.01	.03	1.8
Kenya, 1975[50]	.03	.07	2.5

Adapted from Aaby and Clements, Measles immunization research: a review, *Bull World Health Organ*, 67(4):443-8, 1989.

Figure 1. Estimated Rates of Measles Immunization Coverage Globally and Africa, 1984-1990

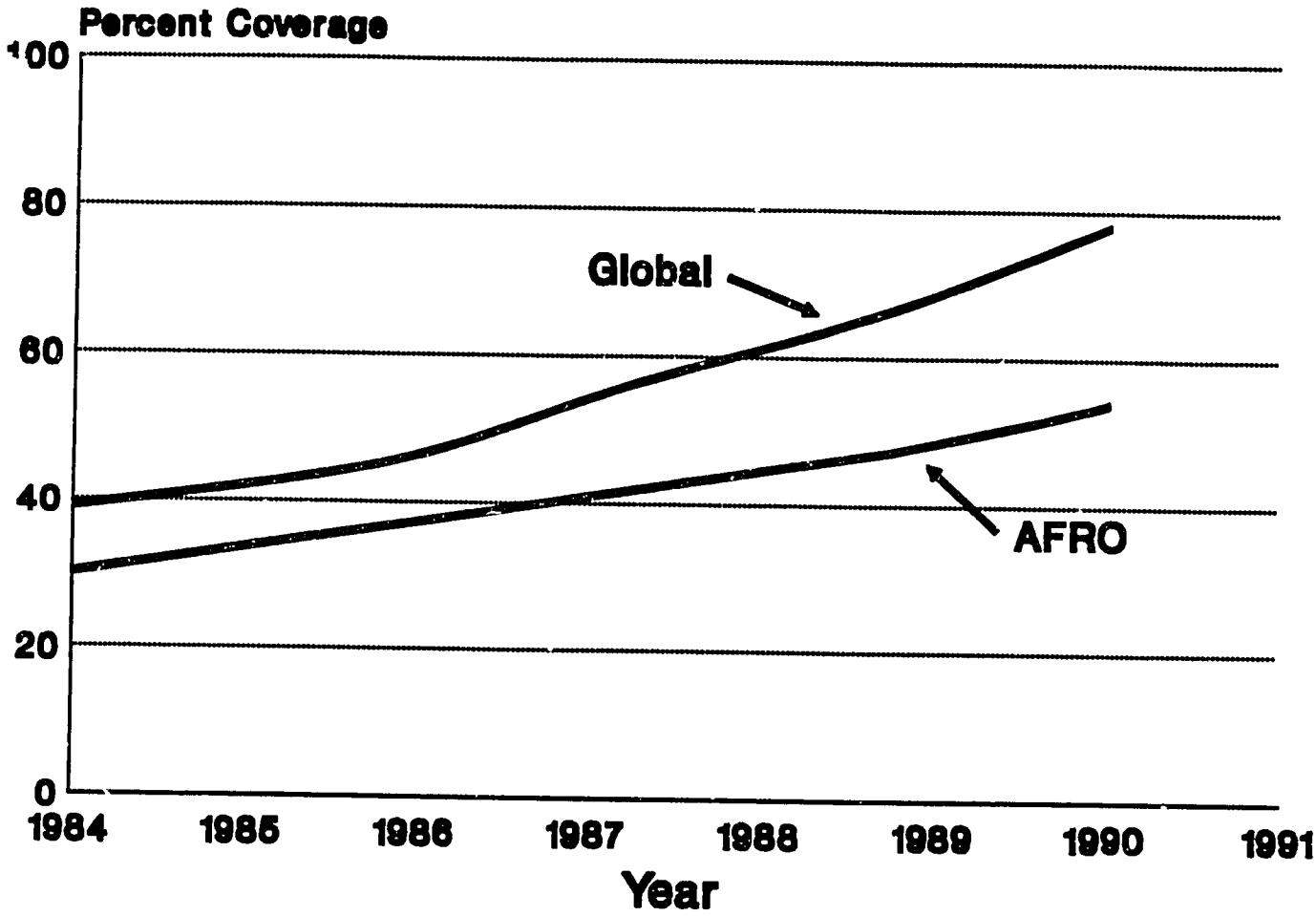
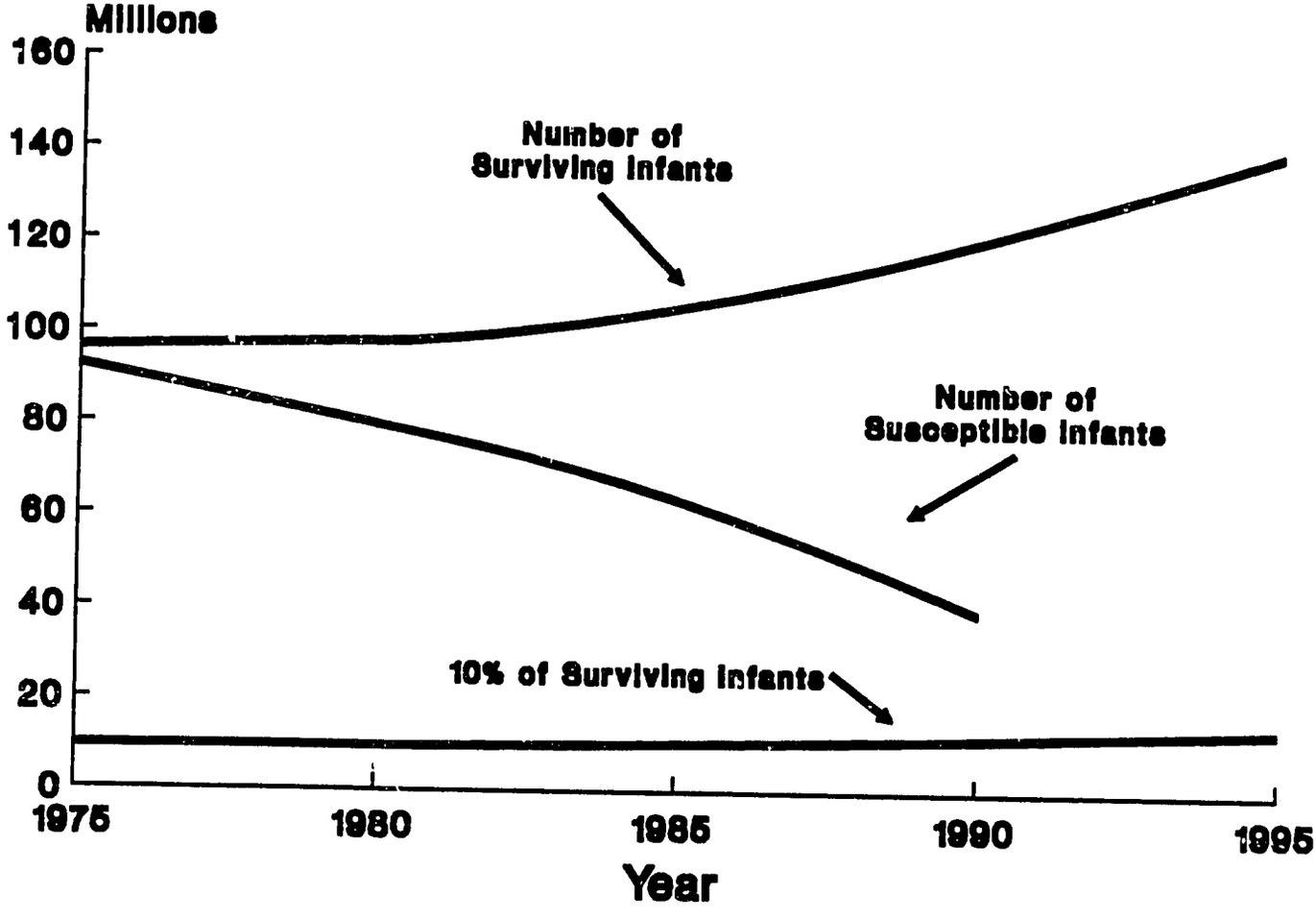
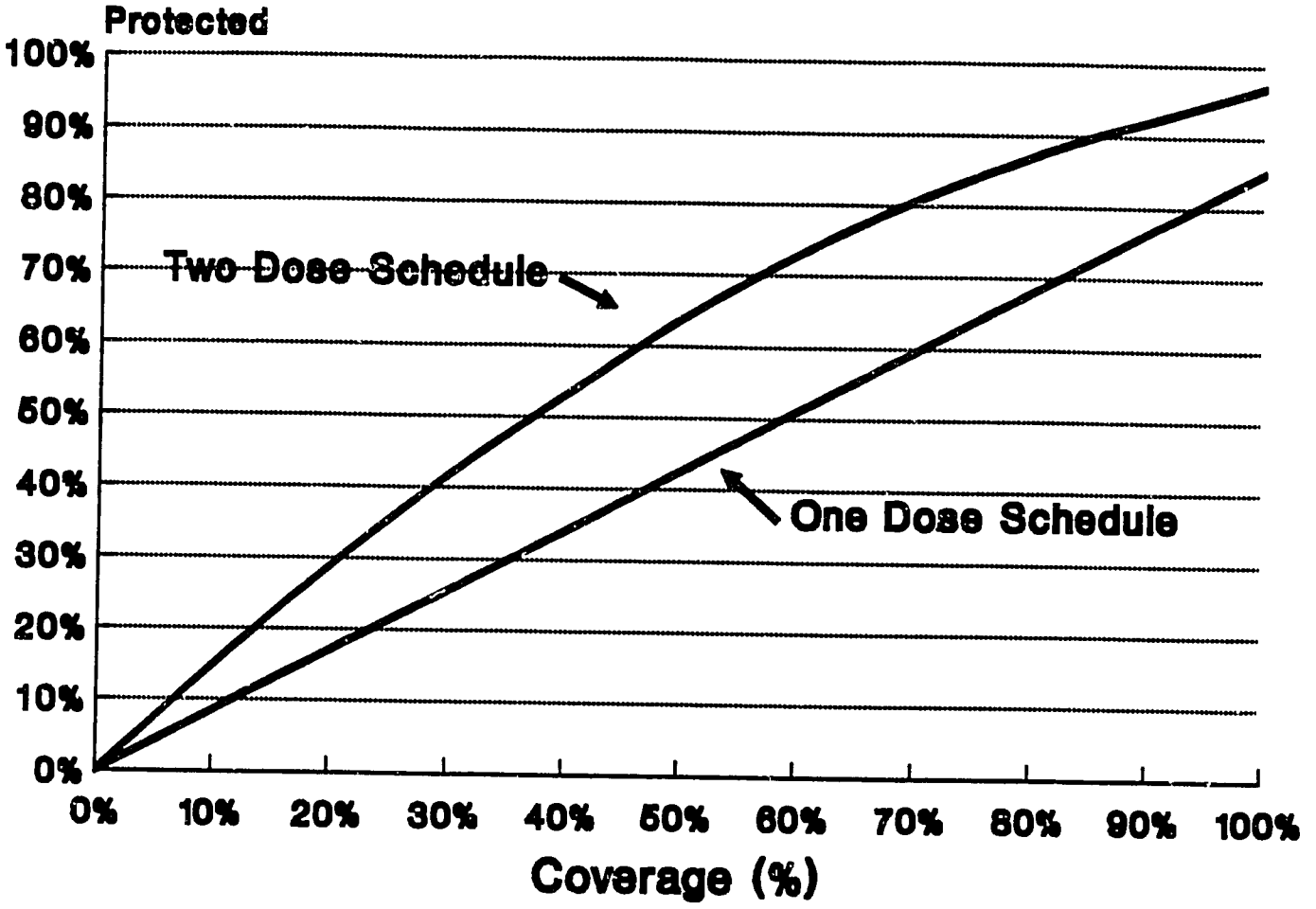


Figure 2. Progress Towards the 1995 Measles Reduction Target: Number of Surviving Infants and Susceptible Infants



This figure is based on UN population estimates, EPI coverage estimates and an assumed vaccine efficacy of 85%. As coverage improves, there are fewer susceptible infants. In 1990, 34% of the birth cohort was not protected by vaccination and was therefore susceptible to measles.

Figure 3. Protection from One- and Two-Dose Schedules



One dose schedule:

Protection from one dose = $VE_9 \bullet Cov$.

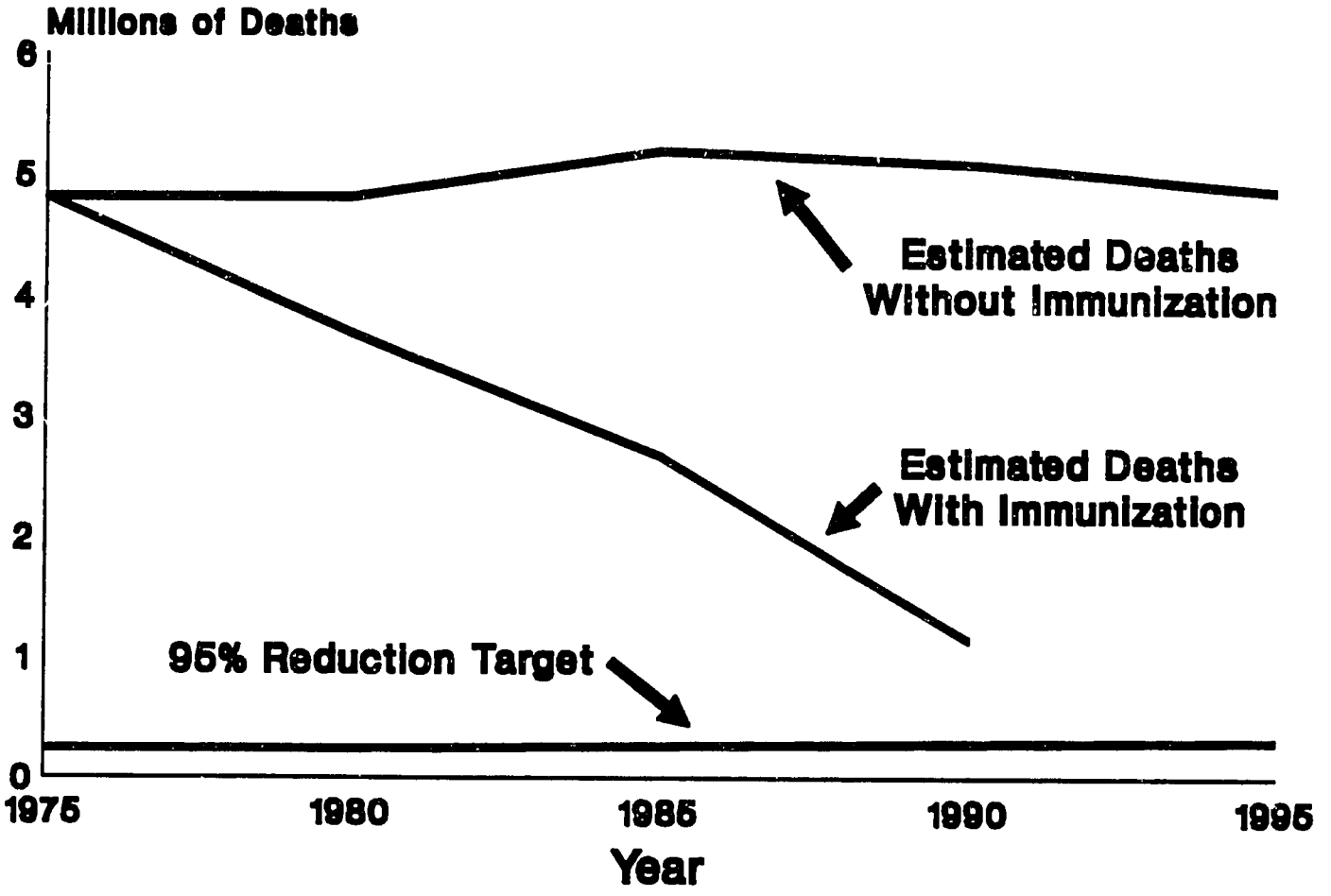
For two doses protection is the sum of:

Protection from 1st dose = $VE_6 \bullet Cov$
Protection from 2nd dose in Unvaccinated by 1st dose = $(1\text{-}Cov) \bullet Cov \bullet VE_{12} \bullet IR_{Unvac}$
Protection from 2nd dose in 1st dose failures = $(Cov - Cov \bullet VE_6) \bullet VE_{12} \bullet RR_{Vac}$

Where, VE at 6 months (VE_6), 9 months (VE_9) and 12 months (VE_{12}) is 65%, 85% and 95%, respectively.

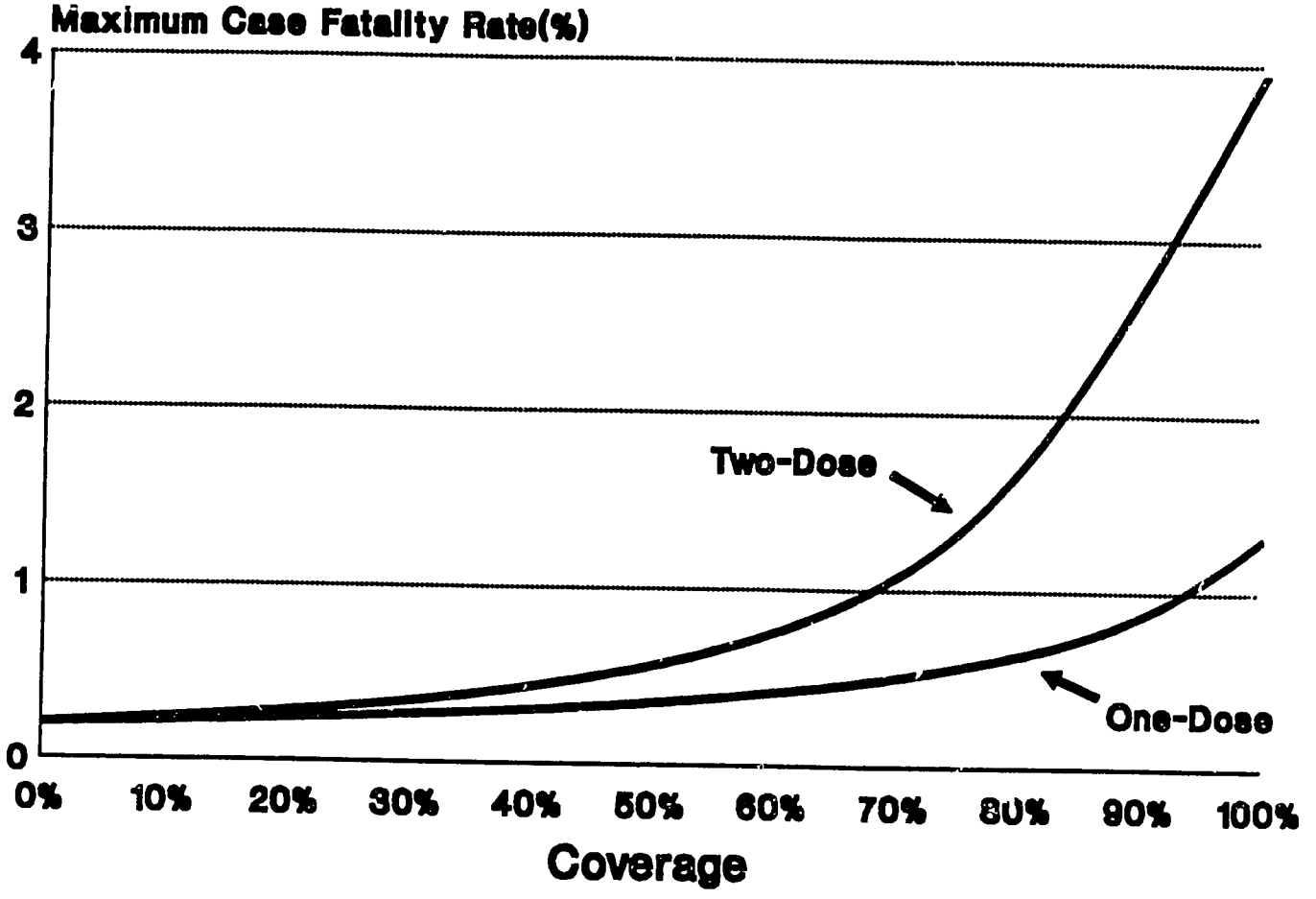
For the second dose, the immunization rates are based on figures from Tunisia in 1990. For those unvaccinated by the first dose, IR_{Unvac}, is 68% and for those vaccinated by the first dose, RR_{Vac}, is 96%.

Figure 4. Progress Towards the 1995 Measles Deaths Reduction Target: Number of Measles Deaths, Pre- and Post-immunization and 95% Reduction Target (VE = .85)



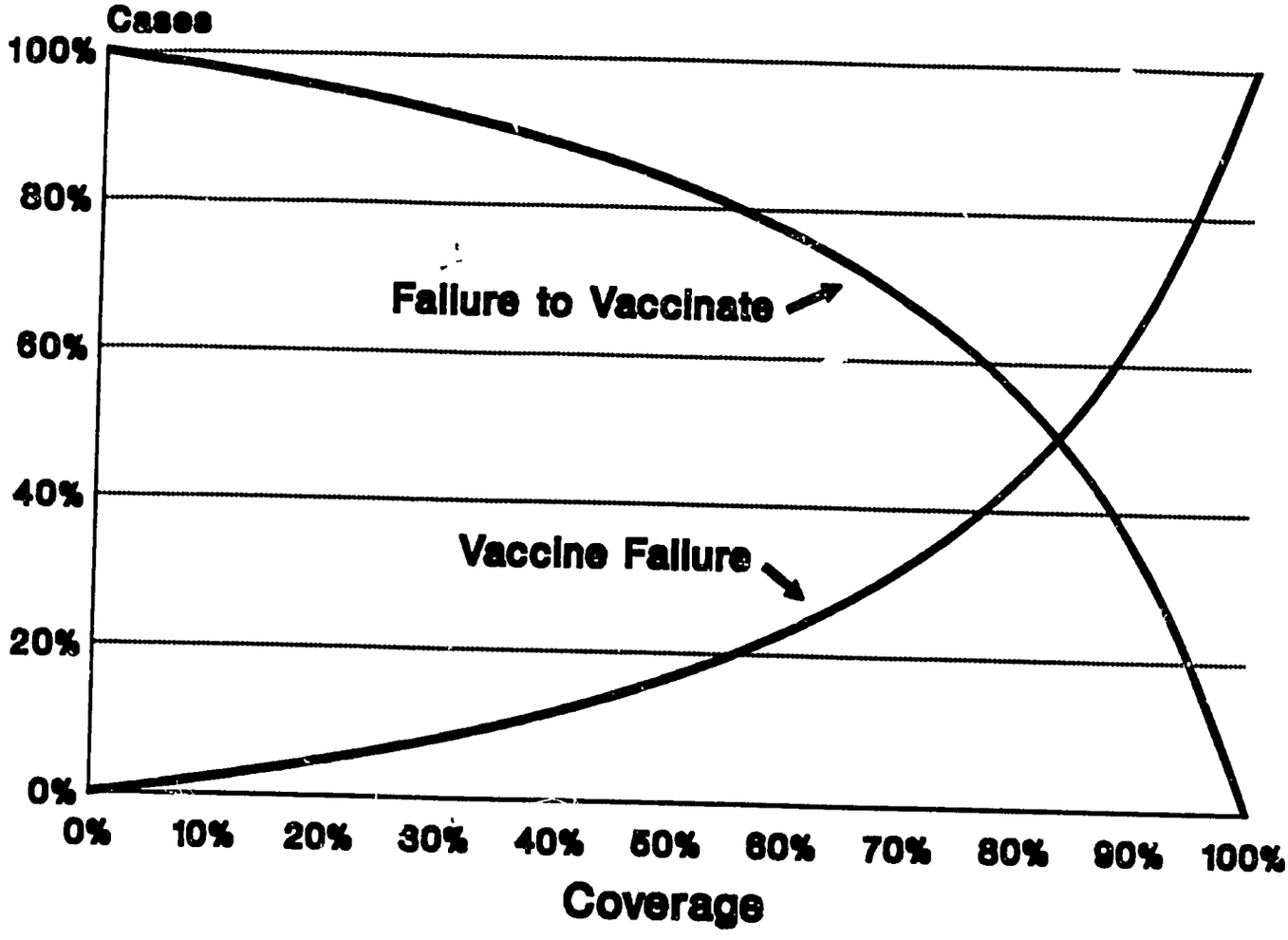
This figure is based on UN population estimates, EPI coverage estimates and an assumed vaccine efficacy of 85%. CFR in 1975 is presumed to be 5% which falls to 4% by 1985 in the absence of immunization. With immunization, the CFR declines to 3% by 1990. By 1990, measles deaths had fallen to 20% of what they would have been in the absence of immunization.

Figure 5. The Maximum Measles Case Fatality Ratio (CFR) permissible to Achieve 95% Reduction in Deaths by Measles Vaccine Coverage and Schedule



This figure is based on the assumptions in Figure 3 and the Appendix.

Figure 6. Cases Due to Vaccine Failure by Coverage Level



This model assumes a vaccine efficacy of 85% and that no cases occur before the age of vaccination. The percent of the population which can be expected to be vaccine failures = coverage - (coverage x VE). The percent of the population that is unvaccinated is = 1 - coverage. The fraction of cases due to vaccine failure = [Coverage - (Coverage x VE)]/[(1 - Coverage) + Coverage - (Coverage x VE)]. At 80% coverage, 38% of the cases are due to vaccine failure. If cases occur before the age of vaccination, then a smaller proportion of total cases would be attributable to vaccine failure.