THE FUTURE OF MEASLES IN HIGHLY IMMUNIZED POPULATIONS - A MODELLING APPROACH

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science.

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ABSTRACT

A computer model was created to study the effect of the measles elimination program in the United States on the number of susceptibles in the population. The simulation revealed that in the prevaccine era approximately 10.6% of the population was susceptible to measles, most of whom were children less than ten years of age. With the institution of measles immunization, the proportion of susceptibles in the population fell to 3.1% in 1978 through 1981, but then began to rise by approximately 0.1% per year to reach about 10.9% in the year 2050. The susceptibles at this time were distributed evenly throughout all age groups. Despite short term success in eliminating measles in the United States, long range projectons demonstrate that the proportion of susceptibles in the year 2050 may be greater than in the prevaccine era. Vaccine technology and public health policy must be altered to deal with this eventuality.

Key words: future, measles, immunization, computer model.

RÉSUMÉ

Au moyen d'un modèle de simulation, cette étude examine les effets du programme d'éradication de la rougeole aux Etats-Unis en considérant dans la population générale le nombre de personnes susceptibles de la contacter. Ce modèle révèle qu'environ 10.6% de la population était susceptible de développer la rougeole avant l'introduction de la vaccination contre la rougeole. Cette proportion est tombée à 3.1% en 1978 et est demeurée stable à ce niveau jusqu'en 1981, date depuis laquelle un accroissement annuel de 0.1% est prédit. Cet accroissement laisse entrevoir une proportion d'environ 10.9% de personnes susceptibles à la rougeole d'ici l'an 2050.

Le modèle utilisé suggère que les candidats potential à la rougeole à cette date seront distribués à travers tous les groupes d'âge.

En dépit d'un succès apparent à court terme dans l'éradication de la rougeole, la proportion de personnes vulnérables en l'an 2050 pourrait être supérieure à celle existant avant l'introduction du vaccin contre la rougeole. Les politiques de santé publique ainsi que la technologie de vaccination devraient être modifiées afin de tenir compte de cette possibilité.

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To Dany, Kira, and Katie

INTRODUCTION

Measles (rubeola) has been close to the centre of the public health stage in the western world for the past twenty years. What was previously an ubiquitous childhood disease with significant mortality and morbidity is currently facing elimination in some countries, most notably the United States of America. The development of a safe and efficacious vaccine has prevented much disease and death. The World Health Organization is committed to global vaccination of children against measles (1), and the United States government has set October 1st 1982 as its target date for the elimination of indigenous measles (2).

Little is known about the effect of an intensive measles elimination program on the overall immune status of the population. The introduction of artificial immunity to measles by vaccine may alter the natural equilibrium between those susceptible and those immune (3,4). The purpose of this project is to define the relative proportion of the United States population that was immune and susceptible to measles in the prevaccine era and to describe the effects of an intensive vaccination program on this balance. This is accomplished by a computer model using modelling theory and

United States demographic data. Both the measles and measles modelling literature is reviewed. Finally, based on the findings, recommendations for public health policy are made.

CHAPTER ONE

MEASLES IN THE PREVACCINE ERA

1.1 - CLINICAL DESCRIPTION (5)

Measles is a highly contagious childhood illness that is worldwide in distribution. Its cause is a stable RNA virus from the paramyxovirus group. The manifestations of the disease are characteristic. With the primary viremia shortly after exposure, a short and mild illness may occur with a faint rash. Ten to twelve days after initial exposure the classical prodromal symptoms appear - fever, cough, coryza, keratoconjunctivitis, and occasional widespread lymphadenopathy and splenomegaly. At this time, Koplik's spots, the enanthema of measles, appear on the buccal mucosa. After three to five days of prodromal symptoms, approximately fourteen days after initial exposure, the maculopapular rash of measles appears around the hairline. Over the subsequent three days it spreads to involve the face, neck, trunk and extremities. Thereafter, the rash begins to fade and the fever falls; most children recover completely.

The majority of side effects of typical measles involve the respiratory and/or central nervous systems. Tracheobronchitis and laryngitis commonly accompany the disease, as does a usually asymptomatic radiographic evidence of viral pneumonia in 20-60% of all cases. Secondary bacterial pneumonia, perhaps partially due to suppressive effects of viral infection on pulmonary antibacterial activity, is the leading cause of death. As well, giant cell pneumonia (Hecht's pneumonia) may be seen in immunocompromised hosts and is invariably fatal. Bacterial otitis media occurs in ten percent of children with typical measles.

The effects on the central nervous system are perhaps the most dramatic and feared. Acute symptomatic encephalitis occurs in 0.1% to 0.2% of cases. Fifty percent of the patients fully recover, 30-50% are left with mild to severe neurologic sequelae, and 5-10% of affected patients die. There also exists a very rare, late onset fatal encephalitis - subacute sclerosing panencephalitis (SSPE) which occurs four to seventeen years after initial infection.

Keratitis and conjunctivitis are classic features of the prodromal and early rash phase of the disease. Other less common outcomes are transient platelet count depression

that can infrequently evolve to thrombocytopenic purpura and a myocarditis and/or pericarditis that rarely induces clinical symptoms.

The severity of the disease depends upon the underlying health of the host. In developed countries the mortality rate is generally .01% to .02%. However, in the third world measles has always been and continues to be an important cause of childhood mortality. Mortality rates of 10% - 15% are common; in Zambia measles is the cause of 18% of all mortality under the age of five, and in the Cameroon, measles accounted for 25% of all child hospitalizations and one-half of all hospitalized infant deaths in 1975 (6).

Man and monkey are the only natural hosts of measles, but humans are the only natural reservoir for the virus (7). The disease is spread to susceptible individuals through direct contact with infected droplets or contaminated fomites. The upper respiratory tract and conjunctiva are probably the most important entry sites, and the period of communicability begins during the prodromal phase and lasts until four or five days after onset of the rash. Measles is extremely contagious and has an attack rate greater than 90% in susceptible hosts. Recovery confers solid, lifelong

immunity - reinfections are almost unknown. A long term infectious carrier state does not exist.

1.2 - PREVACCINE EPIDEMIOLOGY

Person

In the prevaccine era in the United States most children were infected with measles by the age of ten. Between 1960 and 1964 in four reporting areas of the United States, 90% of measles cases occured in children less than ten years old, and only 3.4% in persons 15 years of age and over (Table 1.1) (8). Some studies indicate that 95% of Americans were infected by age fifteen (9), and 99% of military recruits were shown to be immune by serologic survey (10). Infants less than six months of age are protected from disease because of passive transfer of maternal antibodies.

Between 1950 and 1959 an average of over 500,000 cases and almost 500 deaths due to measles were reported annually. Measles reporting in the prevaccine era, however, probably accounted for only about 10% of the cases. Such underreporting is supported for two reasons. First, since

virtually all children were infected, the real incidence rate should have been a crude reflection of the birth rate. Second, since deaths due to measles tended to be reported, a known case fatality ratio of 1 per thousand with five hundred annual deaths should mean the occurrence of about five million cases of measles per year (11).

From the years 1960-63, the case fatality rate for measles was between 0.85 and 1.02 per thousand reported cases, representing 1.93 to 2.37 deaths per million population (8). In 1963, of 364 deaths due to measles, 30 were attributed to measles encephalitis. Overall in that year there were 239 reported cases of measles encephalitis resulting in a death-to-case ratio for encephalitis of 12.6%.

The exact age-specific incidence of measles is difficult to determine. As seen in Table 1.1, in four reporting areas from 1960-64 most cases were in the 5-9 year age group. However, measles is traditionally reported by five-year age groupings and this tends to obscure the attack rate for a given one-year age group. Based on evidence from a household survey in Atlanta in 1961 conducted by the Epidemic Intelligence Service that reported measles cases by exact age, it appears that the peak of age of incidence of

measles in the prevaccine era was about three to four (Figure 1.1) (12,13,14). These data are in agreement with other American surveys (13).

In the prevaccine era the increasing population, birthrate, and urbanization seemed to affect the age distribution of measles infection (15). This phenomenon is demonstrated by the drastic reduction in incidence of measles in United States military recruits from World War I to World War II to the 1950's (16), and by the decreasing mean age of attack in Great Britain between 1956 and 1969 (15).

TABLE 1.1

DISTRIBUTION AND MEAN ANNUAL INCIDENCE OF MEASLES CASES BY AGE GROUP, 4 REPORTING AREAS*, 1960-1964 (8)

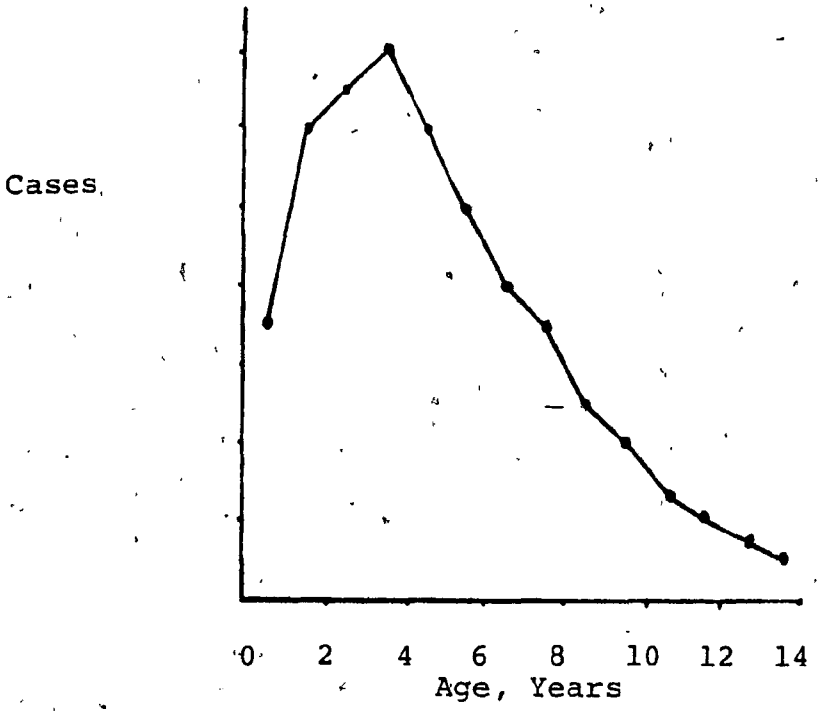
AGE GROUP YEARS	% TOTAL CASES	CASES/100,000
< 5	37.2	766.0
5 - 9	52.8	1,236.9
10 - 14	6.5	169:1
15 +	3.4	10.1

* New York City, District of Columbia, Illinois, and Massachusetts

From: Centers for Disease Control. Measles Surveillance Report No. 11, 1977-1981.

FIGURE 1.1

AGE SPECIFIC MEASLES INCIDENCE - EPIDEMIC INTELLIGENCE SERVICES SURVEY. ATLANTA, 1961 (13)



Adapted from: Paula CL, Bean JA, Burmeister LF, Isacson P. Postvaccine era measles epidemiology. JAMA 1979;241:1474-1476.

Place

Measles is a truly universal disease, being endemic on all continents (17). Local incidence is determined by birth rate, degree of urbanization, the number of susceptibles in the population, endemicity, and probability of introduction from other areas. It is likely that other less well defined factors are also important.

Fadeout, the absence of cases for a period of time longer than the generation time of the disease is a good indication of the endemicity of measles. Four weeks is usually used as the fadeout time for measles. If no cases have been reported in a given area in four weeks, the chain of transmission is presumed broken. Further cases imply introduction of the virus to that geographic area.

In the prevaccine period of 1956-1958, of 51 reporting areas is the United States, a maximum of six areas had a fadeout in any year, and 21-23 areas reported measles every week in each of the three years (11). Thus, prior to the vaccine era, measles was endemic throughout most of the United States.

Time

The incidence of measles varies in two distinct cycles; inter-annual and intra-annual (seasonal).

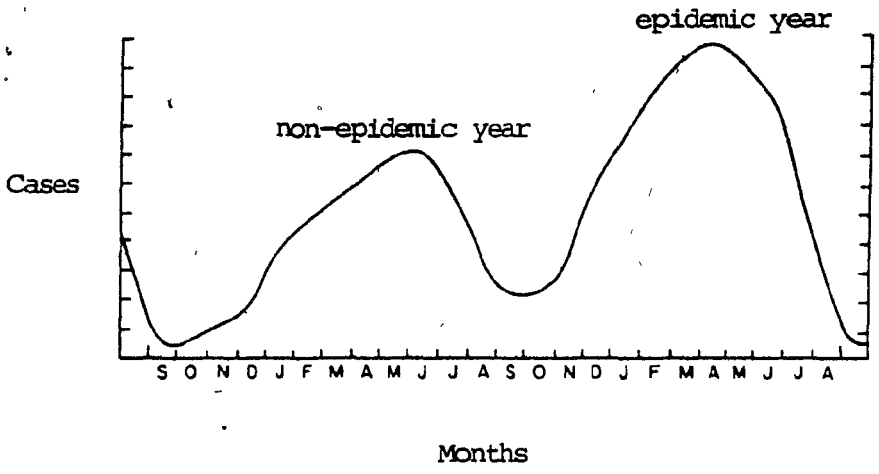
The first type of periodicity is on an inter-annual basis. In large cities in the prevaccine era it was a common observation that measles epidemics occurred every two years. As the community size decreased the inter-epidemic period lengthened. This was due to the decreased time a larger city needed to build up enough susceptibles in the population to exceed the threshold to trigger an epidemic. These observations were the basis for the development of mathematical models describing measles behaviour in populations and will be discussed in greater detail in Chapter Three.

The other periodic aspects of measles is seasonality. The peak incidence was between March and May with the lowest incidence from August to December (Figure 1.2). Data from Baltimore in 1928-1961 (18) show that only 1% of annual cases occurred in the months of low incidence, and this was unchanged in epidemic and non-epidemic years. The reasons for seasonality have never been clear, but Fine and Clarkson recently presented data which suggest that the beginning and ending of school terms were the most important factors (19).

The seasonal variation may also have had important effects on inter-annual epidemic intervals by independently creating conditions that could incite an epidemic in peak incidence months that might not have otherwise occurred, and by postponing an epidemic in low incidence months that could have occurred given a large enough number of susceptibles in the population. Thus, seasonality is what Yorke et al call the necessary "shove" to keep the epidemic pendulum swinging (18).

FIGURE 1.2

SCHEMATIC DIAGRAM OF THE SEASONALITY OF MEASLES IN AN URBAN CENTER (18)



Adapted from: Yorke JA, Nathanson N, Pianigiani G, Martin J. Seasonality and the requirements for perpetuation and eradication of viruses in populations. Am J Epidemiol 1979;109:103-123.

In summary, measles has a narrow clinical spectrum, is limited to humans with no known carrier state or third party transmission, induces lifetime immunity and has a stable antigenic structure. In the prevaccine era it caused much morbidity and mortality in the United States. The disease infected almost everyone in childhood and left virtually all adults immune for life.

The next chapter will describe the changing epidemiology of measles in the vaccine era.

CHAPTER 2

MEASLES IN THE VACCINE ERA

2.1 - THE VACCINE

In 1963 two measles vaccines were licensed in the United States - a live virus vaccine, the Edmonston B strain, and a killed (formalin inactivated) vaccine. In 1965 a further attenuated vaccine (Schwarz strain) was licensed and in 1968 the Enders' live virus (Moraten), an even more attenuated strain was marketed. This is the vaccine that is currently used alone, or in combination with the mumps and rubella vaccines.

At the time of the initial licensure it became evident that the febrile reactions caused by the live Edmonston B type virus were too frequent and severe, and consequently many physicians administered the vaccine with a simultaneous injection of gamma globulin(20). Others used killed vaccine or a killed-live virus combination. By 1967 it was apparent that the immunogenicity of the inactivated virus was less than sufficient. As well, atypical measles, most often a

result of prior immunization with the killed vaccine (but occasionally the live vaccine (21)) became recognized as a clinical entity. The killed vaccine was subsequently removed from sale, after about 1.8 million doses had been distributed (4).

Despite further attenuated vaccines, physicians still sporadically gave immune globulin with the vaccine, perhaps resulting in less protection (22). Furthermore, it was only after a few years that the practice of routinely vaccinating children as young as six or nine months was terminated because of high vaccine failure rates, presumably due to persisting passive maternal immunity.

Because of the problem of passive maternal immunity preventing seroconversion, the American Academy of Pediatrics in 1976 changed its policy from a twelve month to a fifteen month vaccination age. It also stipulated that all children having received vaccine at less than one year of age be revaccinated. There is still controversy regarding possible vaccine failure in the age group 12-15 months (23-38). A recent review recommends the fifteen month vaccination age without routinely recalling those immunized between twelve and fifteen months for revaccination (8).

On the whole, measles vaccine is extremely safe. The most common reaction, a febrile viral-like illness one week after vaccination, is typically mild and without consequence. The only serious side effect, post vaccine encephalitis, occurs at a rate of one case per million doses of vaccine (39). There is also a very small risk of subacute sclerosing panencephalitis following the measles vaccine (0.5-1.1 cases per million doses of vaccine), but this is less than the 5 to 10 cases per million resulting from infection with natural measles (40,41).

How good is the protection of the measles vaccine to those people vaccinated? Vaccine failure can come about in two ways. Primary failure describes the lack of initial seroconversion of the subject after vaccination, while secondary failure is the lost immunity in those subjects who had previously seroconverted (8).

Seroconversion, most commonly measured by the hemagglutination-inhibition (HI) antibody technique, occurs in 95% to 97% of vaccinees over twelve months of age (42,43). This seroconversion rate is typical of field trial conditions; in clinical practice it has been shown to be slightly less than 95% (32). Possible reasons for this

lower value include immunization of children less than one year of age, improper vaccination technique, poor vaccine storage, and/or varying quality of vaccine (44). Primary vaccine failure is estimated to occur in 3% to 8% of vaccinees (45).

Secondary vaccine failure, or waning immunity, occurred most commonly as a complication of the killed measles vaccine. Because of the limited number of doses distributed before removal from the market the killed vaccine will not be discussed further. Little data is available to describe waning immunity after seroconversion with the currently used live virus. This will be discussed later in this chapter.

Vaccine efficacy, a measure of the protection afforded by the vaccine is defined by the percent reduction in attack rate of the vaccinated subjects versus unvaccinated subjects:

$$\text{Vaccine Efficacy (VE)} = \frac{\text{Attack Rate in Unvaccinated} - \text{Attack Rate in Vaccinated}}{\text{Attack Rate in Unvaccinated}}$$

Vaccine efficacy is difficult to quantify. As seen from the equation the underlying vaccination level of the population must be known, and the vaccinated and unvaccinated groups must have equal exposure to disease (44,46-48). Nevertheless, studies of two outbreaks (33,49) suggest that in community settings vaccine efficacy is at least 90% and perhaps as high as 97%. This latter figure was derived by determining the vaccine efficacy from secondary attack rates in households.

2.2 - THE VACCINE ERA EPIDEMIOLOGY OF MEASLES

Although approximately 13 million doses of measles vaccine were distributed between 1963 and 1965, irregular vaccination practices made the impact difficult to measure. A systematic measles vaccination program began in the United States in 1966 with the passage of the Vaccine Assistance Act that permitted federal assistance to state programs for purchase of vaccine, and with the Centers for Disease Control national campaign to eliminate measles. This campaign emphasized community immunization programs, and included intensified surveillance of the disease, control of outbreaks, and the establishment of continuing immunization

programs for those children who were either one year of age or entering school. Furthermore, the Childhood Immunization Initiative was begun in 1977 by the Centers for Disease Control. One of its goals was to ensure that at least 90% of United States children received the necessary childhood vaccines.

In 1978, the Secretary of the Department of Health, Education, and Welfare, Joseph A. Califano Jr., encouraged by measles elimination progress announced that the United States was seeking to eliminate indigenous measles by October 1, 1982. This goal was to be achieved by a four point strategic program (9):

1) Achieve and maintain high levels of immunity - the aim was to have 90% of the nation's school children immunized by 1979;
2) Know where the susceptibles are - this included a one time assessment of susceptibility through the school years and the immunization of susceptibles;
3) Know where disease is - surveillance methods were improved, and
4) Prompt response to the occurrence of disease - the clinical criteria of fever of 38.3°C or greater, a rash of three or more days duration, and a cough, coryza or

conjunctivitis were used, which were later to be confirmed by laboratory data. Control measures included school exclusion, search for susceptibles, and immediate vaccination.

This program was complimented by the enforcement of existing and the creation of new state legislation in all fifty states and the District of Columbia. Such legislation required children to furnish evidence of vaccination before entry to the school system. A 1978 review of immunization records of three million children revealed that 93% had been immunized against measles (11).

The effects of the immunization program have been dramatic, and are now described.

Person

From the over 500,000 reported annual average of cases in the United States between 1950 and 1959 (315.2 cases/100,000), the case number has been reduced to only 895 cases (0.4 cases/100,000) in the first twenty-six weeks of 1982 (50). Mortality from measles has dropped from 2.2 per million in 1962 to only 2 deaths in the entire country in 1981 (8).

There has also been a decline in the measles death-to-case ratio. In the period 1960-1972 the mean death-to-case ratio was 1.13 deaths per thousand cases and declined to 0.30 in 1976-1978 (8). The measles encephalitis-to-measles case ratio was 0.62 per thousand in 1963, and declined by 1979 to 0.22 per thousand (8). The most probable reason for these changes was the increased reporting of measles cases relative to the reporting of measles encephalitis and measles deaths (8).

Pneumonia and encephalitis still account for most of the measles deaths, with underlying chronic disease an important associated factor (51-53).

With the progression of the immunization program the age-specific incidence of disease has changed markedly. Whereas in the prevaccine era greater than 50% of cases were in children aged 5-9 (see Chapter Two), in 1980, the greatest caseload was in the 10-14 year old age group accounting for 28.4% of the cases (54). As can be seen from Table 2.1 (8) and Figure 2.1 (55), the age distribution has shifted to older age groups, although all age-specific incidences have fallen substantially.

The only deviation from this changing case distribution is the evolution of a peak of cases at less than fifteen months of age. For the year 1979, in 14

project areas which reported by individual age groups, only three cases were in children less than six months of age, and the number of cases increased with each month of age to peak at twelve months. Only at fifteen months of age did the cases begin to decrease substantially (Figure 2.2) (55). This observation can be related to the attenuation of maternal immunity beginning at six months of age and a vaccination policy which recommends vaccination at 15 months, leaving children susceptible between these ages. It can also explain the small rise in the relative percent of cases in the less than five year age group from 14.1% in 1977 to 20.5% in 1980 (54).

TABLE 2.1

DISTRIBUTION AND MEAN ANNUAL INCIDENCE OF MEASLES CASES BY AGE GROUP, 4 REPORTING AREAS*, 1960-1980 (8)

AGE GROUP YEARS	1960-1964		1976-1980		Percent decline in Incidence
	% of total cases	Cases/ 100,000†	% of total cases	Cases/ 100,000	
< 5	37.2	766.0	25.0	40.7	94.7
5 - 9	52.8	1,236.9	29.0	44.5	96.4
10 - 14	6.5	169.1	23.8	33.6	80.1
15 +	3.4	10.0	22.2	3.2	68.0

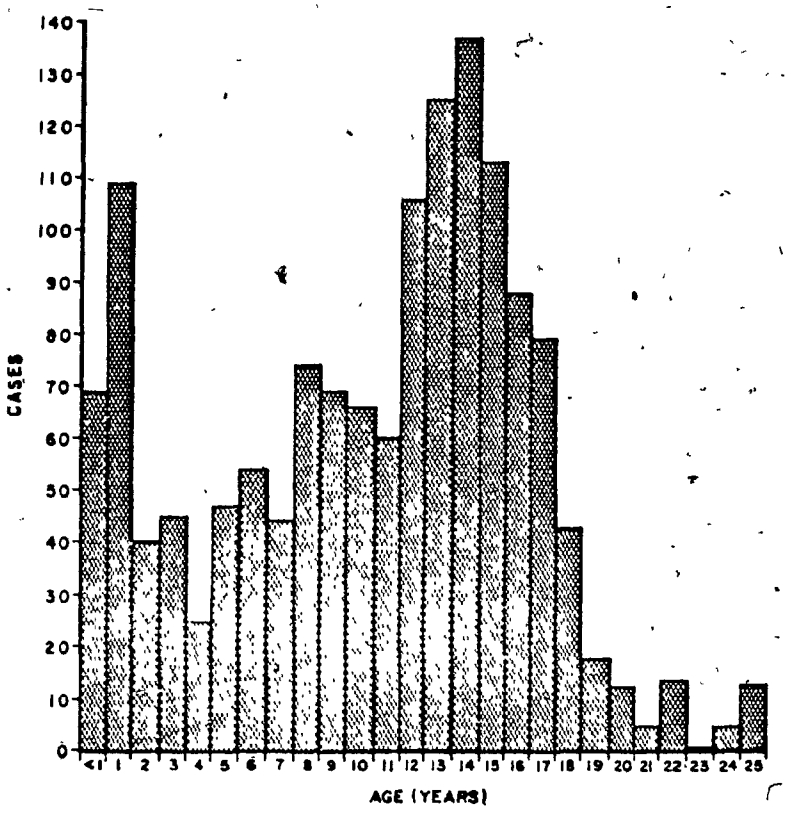
* New York City, District of Columbia, Illinois, and Massachusetts

† Yearly average for each interval

Adapted from: Centers for Disease Control. Measles Surveillance Report No. 11, 1977-1981.

FIGURE 2.1

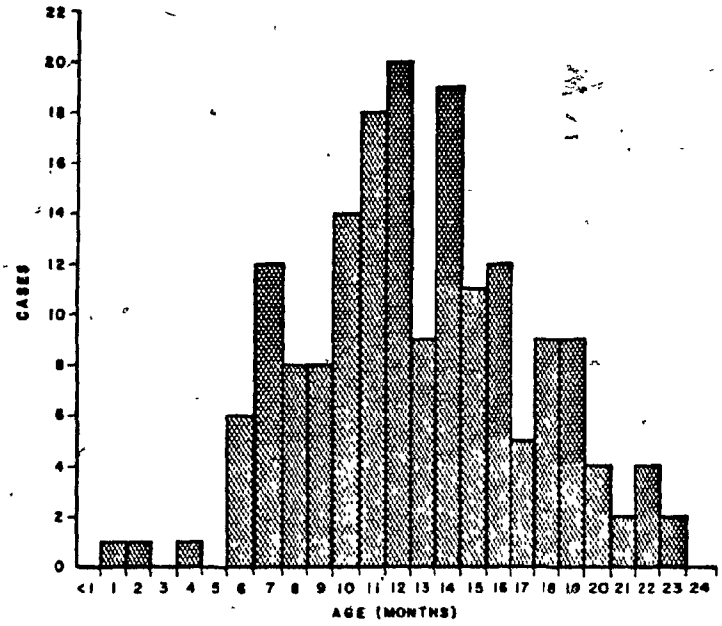
MEASLES CASES IN 14 PROJECT AREAS, BY AGE (YEARS), JANUARY THROUGH OCTOBER 1979 (55)



From: Centers for Disease Control. Age Characteristics of Measles Cases - United States. Morbid Mortal Weekly Rep 1980;29:526-528.

FIGURE 2.2

MEASLES CASES IN 14 PROJECT AREAS IN CHILDREN UNDER 2 YEARS OLD, BY AGE (MONTHS), JANUARY THROUGH OCTOBER 1979 (55)



From: Centers for Disease Control. Age Characteristics of Measles Cases - United States. Morbid Mortal Weekly Rep 1980;29:526-528.

Place

Fadeout was present in 44 out of 51 reporting areas in 1981, as compared to a maximum of six out of 51 reporting areas in 1956-1958. In the first 26 weeks of 1982 a total of 47 areas had reported fadeout (11,50). Highest measles incidence in 1981 occurred in California (2.27/100,000), Kansas (1.51/100,000), New York (0.78/100,000), Washington (0.59/100,000) and Michigan (0.42/100,000). In 1981, 23 states reported no measles cases at all (50).

Time

The two year epidemic cycle of measles was eliminated within just a few years after licensure of the measles vaccine. This effect was directly attributable to the large reduction of new susceptibles entering the population pool.

The seasonality of measles has persisted but only in a very residual form. In the spring of 1982 the peak was almost non-discernible.

The benefits to society of the immunization program have greatly outweighed its cost. In 1975 Witte and Axnick (56) summarized the health benefits and resource savings due to measles immunizations in the United States for the years 1963-1972. This was updated by the Centers for Disease Control in 1982 as follows (8):

. Cases averted	48,420,000
. Lives saved	4,840
. Cases of retardation averted	16,100
. Additional years of normal and productive life by preventing premature death and retardation	1,439,000
. School days saved	159,309,000
. Physician visits saved	24,880,000
. Hospital days saved	2,762,000
. Net benefits achieved	4,448,000,000

The achievements of the vaccine program have been immense, and for all intents and purposes, at this writing, endemic measles has all but disappeared from American society. One must now turn to the future and potential problems that may be generated as a consequence of the vaccine era.

2.3 - PROBLEMS IN THE VACCINE ERA

Although the gains from the present measles program have been remarkable, it is important to consider the potential problems that the program may generate. Two major areas are considered - the creation of new susceptible population subgroups, and the problem of waning immunity.

New Susceptible Population Subgroups

This problem arises from the fact that a vaccine efficacy of about 95% combined with a vaccine rate of 95% leaves an effective vaccine coverage of children entering school of about 90% (.95 x .95). Prior to the vaccine era virtually all people susceptible to measles were between the ages of six months and fifteen years, with only 1% or less remaining susceptible at the age of twenty. With artificial immunity given to 90% of these susceptible children, the number of people in the population susceptible to measles should fall and fadeout should result. After the occurrence of fadeout, those remaining susceptible to measles would remain disease free as long as the virus was not reintroduced into the population. They would thus be

protected by the overall high level of immunity in the population - herd immunity. However, the persistence of fadeout due to the herd immunity effect of vaccination could theoretically lead to a situation where susceptibility to measles might persist or be created in previously unseen age groups. These new population subgroups would be i) adult men and women, ten percent of whom may be left susceptible in the long run because of the effective vaccine coverage of only 90%; ii) children between the ages of six to fifteen months, all of whom would become susceptible to measles prior to immunization at fifteen months of age; iii) all infants born to the ten percent of adult susceptible women who in the prevaccine era would have otherwise passively transferred immunity to their offspring. These three groups will be discussed separately.

i) Adult men and women - The prolongation of susceptibility by the herd immunity effect has been discussed by Cherry (4). That this theoretical possibility has been proven true is shown by the changing age distribution of measles described earlier. Since the onset of measles vaccination, epidemics have occurred in older age groups and unusual settings such as high schools, colleges, and military bases (48,57-65).

ii) Children between six and fifteen months of age - This subgroup has also proven to be at risk. The peak of cases in children less than fifteen months of age in 1979 in 14 project areas (55) has been described earlier in this chapter.

iii) Infants not passively immunized by their mothers - In the future this subgroup may represent up to 10% of all newborns. The longstanding observation of very few cases less than six months of age has led to the suggestion of autarcesis against measles in early infancy (66). Cases less than six months of age, however, are occasionally recorded (67-69) even though the distribution in 14 project areas surveyed by the Center for Disease Control showed only three cases less than six months of age. Antibody and cell mediated immunity studies do not clarify the role of maternal immunity versus autarcesis as a cause for the fewer than expected cases of measles in infants. Thus the risk of these babies for infection with measles is still theoretical and unproven.

The impact of a different age distribution of people susceptible to measles is only as important as the potential change in mortality and morbidity in these new age groups. In 1963, Miller (67) studied the frequency of complications

and hospitalizations of over 53,000 cases of measles in England and Wales. As can be seen from Tables 2.2 and 2.3, the complication and hospitalization rates were much higher in the less than one year and greater than twenty year age groups.

Another way of assessing the impact of measles on unusual age groups is to examine epidemics in "virgin" populations, ie. those that have not had previous contact with the disease and where presumably everyone would be susceptible. The classic example is that of Panum, who reported on the 1846 epidemic on the Faroe Islands (70). He clearly showed an excess mortality in the epidemic year of people less than one year of age and greater than twenty years of age. This rose to an excess mortality of 500% in the 50-60 year olds. The subsequent decline in mortality in people greater than 60 years old was attributed to residual immunity from the last epidemic. Of note was the zero excess mortality during the epidemic in the one to twenty year old age groups. A 1952 measles epidemic was documented in the Canadian Arctic in the Inuit who had no prior experience with measles (68). Again, despite use of antibiotics the case fatality was very high in adults and children less than the age of one (Table 2.4).

TABLE 2.2

FREQUENCY OF ALL COMPLICATIONS OF MEASLES BY AGE (67)

Age	No. Cases	No. with complications	Complications rate per 1,000 cases
0- 5 months	232	20	86.2
6-12 months	1,804	151	83.7
1 year	6,052	435	71.9
2 years	7,559	509	67.3
3- 4 years	14,915	895	60.0
5- 9 years	20,911	1,436	68.7
10-14 years	795	34	42.8
15-19 years	189	13	68.8
20 +	210	17	81.0
Not stated	325	22	67.7
TOTAL	52,992	3,532	66.7

From: Miller DL. Frequency of complication of measles, 1963. Report on a National Inquiry by the Public Health Laboratory Service in collaboration with the Society of Medical Offices of Health. Br Med J 1964;2:75-78.

TABLE 2.3

AGE DISTRIBUTION OF MEASLES CASES ADMITTED TO HOSPITAL (67)

AGE	REASON FOR ADMISSION				RATE PER 1,000 CASES
	COMPLI-CATIONS	SOCIAL	UNKNOWN	TOTAL	
0- 5 months	14	4	0	18	78
6-11 months	51	5	5	61	34
1 year	92	19	7	118	19
2 years	84	12	5	101	13
3- 4 years	101	19	9	129	9
5- 9 years	136	12	9	157	8
10-14 years	5	0	0	5	6
15-19 years	0	1	0	1	5
20 +	7	6	1	14	67
Not stated	6	0	0	6	18
TOTAL	496	78	36	610	12

From: Miller DL. Frequency of complication of measles, 1963. Report on a National Inquiry by the Public Health Laboratory Service in collaboration with the Society of Medical Offices of Health. Br Med J 1964;2:75-78.

TABLE 2.4

MEASLES MORTALITY BY AGE;
INDIANS AND INUIT, UNGAVA BAY 1952 (68)

AGE	% MORTALITY
Under 1	13.4
1 - 9	6.0
10 - 19	9.0
20 - 29	11.9
30 - 39	13.4
40 - 49	16.4
50 - 59	9.0
60 +	19.6
Not known	7.5

Adapted from: Peart AF, Nagler FP. Measles in the Canadian Arctic, 1952. Can J Public Health 1954;44:146-156.

Examination of measles mortality in the vaccine era in the United States supports the contention that measles mortality may be greater in certain age groups (51,52). As can be seen from Table 2.5 (8) the highest mortality appears to be in infants less than one year of age (0.72 deaths per 1,000 cases of measles) and in adults over twenty years of age (2.37 deaths per 1,000 cases of measles). Of note is the lowest death-to-case ratio (0.09 deaths per 1,000 cases) in the 5 to 9 age group - precisely that age group that had the highest incidence of measles in the prevaccine era. The measles encephalitis-to-measles case ratio also appears to increase with increasing age (8,71). Respiratory complications seem to be responsible for the deaths in the younger ages as opposed to neurologic complications in the older ages (52,53,71).

TABLE 2.5

AGE DISTRIBUTION OF MEASLES CASES, DEATHS, AND DEATH-TO-CASE RATIOS*, UNITED STATES, 1976-1978 (8)

AGE GROUP YEARS	ESTIMATED CASES	DEATHS	DEATH-TO-CASE RATIO
< 1	4,170	3	0.72
1 - 4	14,425	6	0.42
5 - 9	33,267	3	0.09
10 - 14	43,785	13	0.30
15 - 19	25,474	3	0.12
20 +	4,222	10	2.37
TOTAL	125,343	38	0.30

* Deaths per 1,000 measles cases.

Adapted from: Centers for Disease Control. Measles Surveillance Report No. 11, 1977-1981.

Waning Immunity

Waning immunity subsequent to live virus vaccine was considered when vaccine failures occurred in measles epidemics in highly immunized populations. It later became apparent that these vaccine failures were mainly primary vaccine failures in appropriately vaccinated children and children immunized before twelve months of age (23-34,37). Thus waning immunity could not be invoked as a cause for most of the measles cases in immunized hosts. A clinical case of measles in a previously seroconverted individual is necessary to demonstrate waning immunity, and to date this has not been shown.

Indirect evidence for the existence of waning immunity has started to appear. Some of the initial serological studies on the duration of protection of the vaccine were done by Krugman in 1965 and 1971 (20,72). By measuring hemagglutination inhibition (HI) titers up to eight years after vaccination he found that institutionalized children had lower measles vaccine titers than non-institutionalized children. Krugman suggested that this was due to a booster effect of natural measles occurring in the community, as opposed to its lack in the institution. He added that

natural measles, as demonstrated by Panum, gave lifelong immunity, and denied ever seeing a case of measles in someone who had seroconverted initially. He thus concluded that the measles vaccines (live) should endow lifelong immunity. In 1973 Linnemann reviewed the issues of immunity, reinfection and revaccination (47). Children with a history of measles vaccine and low HI titers developed a secondary IgG antibody response with revaccination as opposed to the IgM response in those not having had contact with disease or vaccine. This data suggested that despite low vaccine titers in immunized children, the response to the vaccine and disease was anamnestic, and hence protective.

In 1973 Linnemann presented evidence that clinical measles could occur despite a pure IgG response (73) and this was subsequently confirmed by Cherry (26). It was also noted by Cherry that 20% of unvaccinated children with measles did not develop primary IgM responses. Hence there is suggestive indirect evidence that vaccine failure could not only be accounted for by lack of seroconversion, but also by waning immunity.

Recently, Gallagher et al (74) studied cell mediated immunity to measles and found that 100% of patients with naturally occurring measles and only 62% of vaccinees had

evidence of cell mediated immunity. Also, only 40% of umbilical cord specimen showed evidence of cell mediated immunity to measles. Knowing that children with agammaglobulinemia recover normally from measles and are protected subsequently without evidence of any measles antibody (75) demonstrates the importance of cell mediated immunity in this disease, and the complexities of the incompletely understood immune system.

In conclusion, the importance of waning immunity is unknown at this time. However, because of some indirect evidence for its existence and the relatively short (18 years) experience with the attenuated measles vaccine, waning immunity may pose a particular public health problem in the future.

The next chapter reviews the role of mathematical models in the description of measles behavior in populations.

CHAPTER THREE

MATHEMATICAL MODELS AND MEASLES

3.1 - MODELLING AND MEASLES EPIDEMICS

Mathematical models have been used since the early part of this century to describe the mechanics of epidemics. Many of these attempts focussed on measles epidemics and endemicity because of the easily defined parameters of measles infection. As discussed in Chapter One, the disease is universal with a well defined clinical symptomatology, a known incubation period, and a stable antigenic character. As well, it is an infection restricted to humans without a carrier state or third party transmission, and confers solid lifelong immunity subsequent to infection.

The basic theory considers all types of disease transitions within a population at any given time. For example, one could envision in a community of (n) individuals three possibilities - a group of susceptibles (S), a group of infectives (I), and a group who are immune (Z). Model theory describes the kinds of transitions that take place within each group in a given time (t).

The deterministic model, initially proposed by Hamer (76) and further developed by Soper (77) described a fixed equilibrium of susceptibles and infectives given the birth rate, infection rate and recovery rate. In this model infection occurred as a result of adequate contact between an infective and susceptible. The only way to enter the "susceptible" population was through birth and becoming six months of age when maternal immunity wore off; the only way to leave the "infective" population was to recover or die. The reason why this model initially became attractive was that it predicted a cyclicity close to the observed periodicity of measles epidemics. In the prevaccine era this periodicity was approximately two years for all large cities; the model described a periodicity of about seventy-four weeks.

The difficulty with this model was that it did not describe and predict the continuing and perpetual epidemic cycles that were consistent with reality. It only described epidemic waves from assumptions not involving such fluctuations and predicted a progressive damping effect of the cycles leading to a stable endemic situation (78). In other words, the deterministic model could only deal with a disruption of the equilibrium without considering how it came about and always returned to the stable endemic state

of the initial equilibrium, even if factors such as seasonal variation in infection rate, incubation period, and spatial parameters were taken into account.

The stochastic model for recurrent epidemics initially put forward by Bartlett (79) was a reformation of the deterministic model and described the types of transition discerned previously, but in terms of probabilities. In addition, Bartlett added the important parameter of introduction of disease from outside the population in the event of fadeout of infection in a community. This was a much more realistic proposition since communities are generally not totally isolated. This model accounted for properties that corresponded well to actual observation. In the absence of fadeout of infection the fluctuations maintained themselves indefinitely and reproduced the cyclicity seen normally. It also allowed for the observed phenomenon of fadeout of infection and the possibility of reintroduction of epidemic cycles from the exterior. However, some disagree with the primary importance of the stochastic effects in this model and feel that the stochastic influence is only secondary to the primary role of seasonal variation of the transmissibility of the virus (18).

Fadeout is defined as the absence of cases of measles for a period longer than the generation time of the disease. When this happens in any given area it strongly suggests that the transmission has ceased. Various authors have used three weeks or four weeks as the generation time. The four week period is used by the Centers for Disease Control. Mathematical theory aside, it has been observed for a long time that the frequency of fadeout is inversely proportional to community size. With the stochastic model one can predict, depending on community size, the probability of fadeout. This leads to a description of the frequency of oscillations of epidemics based on fadeout and infers that a critical community size would be necessary for fadeout to occur.

In 1957, Bartlett presented data (80) comparing observed data of measles frequency in various towns and cities in England and Wales to computer created epidemics based on his model. He defined the critical community size as one for which the chance of fadeout after a major epidemic was fifty percent, and predicted that size to be about 200,000. The observed size was between 250,000 to 300,000 for towns and cities in England. The theory and the numbers were supported again by Bartlett in 1960 (81) by applying North American data and finding broad agreement

with the English data and his model. Later, Black (82) in studies of island communities showed that frequency of fadeout was also inversely correlated with population density. Thus, the important contribution of the stochastic model was the observation that the frequency of epidemics and probability of subsequent fadeout was dependent on community size and density.

With the introduction of measles virus vaccine a new dimension has been added to measles epidemiology. Now, the transition from susceptible (S) to immune (Z) need not pass through infective (I), and can be bypassed by virtue of the vaccine. An important question, then, is what vaccination level in a community is needed to protect the whole community, break the cyclicity of epidemics, and then possibly eliminate the disease entirely - i.e. how much vaccination can induce herd immunity?

In 1971 Sutherland and Fayers in a descriptive study (83) reported that they could account for the postponement of the expected 1968-69 measles epidemic in England and Wales by the 10% level of vaccination in the population. They also postulated that a 40-50% vaccination rate would be needed to reduce the excess susceptibles by immunization to stay below the critical susceptible mass

needed to incite an epidemic. They emphasized that the effect of vaccination was to prevent the development of natural measles in susceptible unvaccinated children as well as in the vaccinated subject. Thus, an increased number are protected by vaccine directly and indirectly, but this necessarily results in a reduction in the number who attain immunity from natural disease.

In 1973 Griffiths (84), using mathematical model theory demonstrated the consequences of vaccination in communities. He showed that the critical community size for fadeout of 250,000 would grow by a factor of 1/X2 where X equals the proportion of unvaccinated susceptibles. For an immunization program covering fifty percent of the population the critical community size increases four times to approximately one million, and for ninety percent immunization it increases one hundred fold to twenty five million. Thus fadeout becomes a more frequent occurrence after a vaccination program, and its duration depends on vaccination levels.

Griffiths then made a computer simulation of epidemics in two communities - one of 450,000 population, the other of 60,000 population in a prevaccine and post-vaccine state. For the larger town, prior to vaccination there was no fadeout, and the epidemic interval was 90 weeks. After

vaccination of fifty percent of the population, fadeout was induced after thirty percent of the epidemics, and the epidemic interval was lengthened to 147 weeks. With the smaller population, whereas fadeout was present after eighty percent of the epidemics prior to vaccination with an epidemic interval of about 150 weeks, after vaccination of fifty percent of the population fadeout occurred after every epidemic with the epidemic interval length increased to 280 weeks.

It still isn't certain what level of vaccination is necessary to achieve elimination in a given population, but it is clear that if eradication was achieved locally and not globally, reintroduction could lead to sporadic disease if the number of susceptibles accumulated during the fadeout period were few, or to endemicity if enough susceptibles had accumulated to permit the perpetuation of the virus. The number of people susceptible to measles needed to sustain endemicity, given favorable seasonality has been estimated to be about six percent of the population (18,85,86).

3.2 - MODELLING AND THE AGE DISTRIBUTION OF MEASLES INFECTION

Modelling can also be used to describe the changing

age-specific attack rates of the virus in a population. Measles, as all infectious diseases, is reported in a cross-sectional way as cases per age group at a given point in time. With measles, cases are grouped into five year age groupings. Thus, the disease experience of a given cohort longitudinally from birth to adulthood is difficult to quantify.

In 1974 Griffiths, using modelling theory, defined a function describing the behaviour of wild measles in populations (15). He showed that the proportion of susceptibles that develop measles in a year can be represented by a linear equation for the first ten years of life:

$$\Psi(t) = a(t+c), \quad + > T$$

where Ψ is the attack rate on susceptibles, a is a constant, t is age, and c is an age conversion factor, also constant. T represents the period when people become susceptible; six months of age, or $T = 0.5$. The function Ψ, or "force of infection" as named by Anderson and May (85), is a modified form of the attack rate, where

the denominator represents susceptibles rather than the entire population.

Griffiths compared his function to two data sets, one from a practicing physician who reported all measles between 1947-1959 seen in his practice, and the other from the Registrar General's returns for England and Wales from 1956-1969, and found that it compared favorably to the existing data. Some interesting points about the comparison were that the values of T and c remained constant, but that of a increased with the degree of urbanization. Thus, in large densely populated communities, the value of a increased, and in small rural ones a decreased. There was also a secular trend where a increased over time. He found that in the period of 1956-1961 a = 0.0412, and in the period 1962-1969 a = 0.0543. This increase was reflected in the decreased mean age of attack prior to the vaccination era. He performed a regression analysis of this function and found a linear decrease of mean age of attack of 0.12 per year; the mean age of attack was six years old in 1956 and dropped to 4-5 in 1968. Griffiths postulated that in the vaccine era the value of a should start to increase, but was uncertain by how much.

This function can be validated by comparing it with other data besides those used by the author. Taking the average $\underline{a}$ = 0.048 over the entire period 1956-1969 with $\underline{c}$ = 0.75, one can simulate the behavior of 100 newborn infants by a cohort analysis described in Table 3.1. Because Ψ is a continuous function, its point value for any interval was taken as the average of its point function at the beginning and at the end of the interval. Based on Table 3.1 one would then expect a peak incidence of measles in the fourth year of life, and by completion of the tenth year of life for the cohort to be 96.6% immune.

TABLE 3.1

Simulated Measles Behavior In A Cohort Of 100 Infants

Age	ψ	Number Susceptible At The End Of The Interval	Number Diseased During Interval	Total Number Immune At The End Of The Interval
0-.49	0	0	0	50.0
.5-.99	.072	96.4	3.6	3.6
1-1.99	.108	86.0	10.4	14.0
2-2.99	.156	72.6	13.4	27.4
3-3.99	.204	57.8	14.8	42.2
4-4.99	.252	43.2	14.6	56.8
5-5.99	.300	30.2	13.0	69.8
6-6.99	.348	19.7	10.5	80.3
7-7.99	.396	11.9	7.8	88.1
8-8.99	.444	6.6	5.3	93.4
9-9.99	.492	3.4	3.2	96.6

$\psi(t) = a(t+c),\ t > \tau^*$
$a = 0.048$
t = age in years
$c = 0.75$
$\tau = 0.5$

If this data is compared to the results of the survey conducted by the Epidemic Intelligence Service in Atlanta in 1961 and other American surveys, some close similarities are evident (12,13,14). The ages of peak incidence in the prevaccine era was about 3 to 4, with at least 90% having had the disease by age ten.

Griffiths' catalytic function of measles infection is then taken to be a reasonable estimate of true measles behavior in prevaccine cohorts, independent of reporting. In the next chapter this relationship will be used with United States demographic data to determine the immunity and susceptibility of the United States population to measles in the prevaccine and vaccine eras.

CHAPTER FOUR

THE FUTURE OF MEASLES IN HIGHLY IMMUNIZED POPULATIONS - A MODELLING APPROACH

4.1 - INTRODUCTION

Indigenous measles is currently facing elimination from American society. This has been due to a safe and efficacious vaccine as well as a highly effective elimination program. However, little is known about how the measles vaccine initiative in the United States has altered the natural equilibrium of those susceptible and those immune to the disease. What has been observed is a large reduction in the number of cases accompanied by changing age-specific attack rates. Some authors have warned that despite short term success with measles elimination, the passage of time will once again see the accumulation of susceptibles and the potential for renewed disease (4,87).

The objective of this chapter is to examine how a highly effective vaccination program modifies the balance between the number of people susceptible and the number of people immune to measles. This is done by quantifying the proportion susceptible to measles in the prevaccine era, during the measles elimination program, and after total measles fadeout. A computer model is described and performs the necessary tasks.

4.2 - METHODS

4.2.1 - Theoretical Basis for the Computer Model

Measles reporting provides a cross-sectional picture of disease at a given point in time, and represents a combination of the longitudinal experience of a number of cohorts. This can be represented by a cohort map as seen in Figure 4.1a. Here, each diagonal line represents a different cohort, and the cross-sectional experience of disease for all children from birth to age 3, 365 days would be the result of the experience of the 1950, 1951, 1952 and 1953 cohorts from 1950 until the end of 1953.

Measles immunity and susceptibility in a given person represent two sides of the same coin. An individual is either susceptible or immune at any moment in his life with the transition or disease phase representing a relatively small period of time. If the rate of transition from susceptibility to immunity can be established then this change can be quantified. For example, one can use four identical cohorts of 100 infants as described in Table 3.1 (Chapter 3) based on Griffiths' linear infection function. Figure 4.1b shows the immunity or disease experience, Figure 4.1c the susceptibility experience. Of a population of four hundred infants at the end of 1953, 87.2 are immune (sum of

the boxes at 1954 in Figure 4.1b) and 312.8 are susceptible (sum of the boxes at 1954 in Figure 4.1c). In other words 22% (87.2/400) of the population is immune to measles, and 78% (312.8/400) susceptible. The total number of cases in 1953 represents the sum of the transitions from susceptibility to immunity by way of disease, or d1+d2+d3+d4, for a total of 42 cases during 1953. In summary, at the end of 1953, out of a population of 400 children ages 0-3, 78% are still be susceptible to measles, 22% are immune, and the number of measles cases in 1953 is 42.

The real life situation is more complicated. Each cohort starts out with a different number of infants because of changing birth rates. In addition, within a given year the cohort can grow from immigration or shrink from death or emigration. These issues can be dealt with if one ignores deaths due to measles in a given cohort because of its rarity (.01% mortality), assumes that people immune and susceptible to measles have similar death rates, and that immigrants have the same disease experience as natives given the global endemicity of measles. For example, if a cohort grows in size by .05% by immigration, the immunes and susceptibles can be corrected proportionately for the increase. Likewise, as the population in a given cohort decreases with age, the deaths can be distributed proportionately to those immune and those still susceptible. These principles and assumptions form the theoretical basis for the computer model.

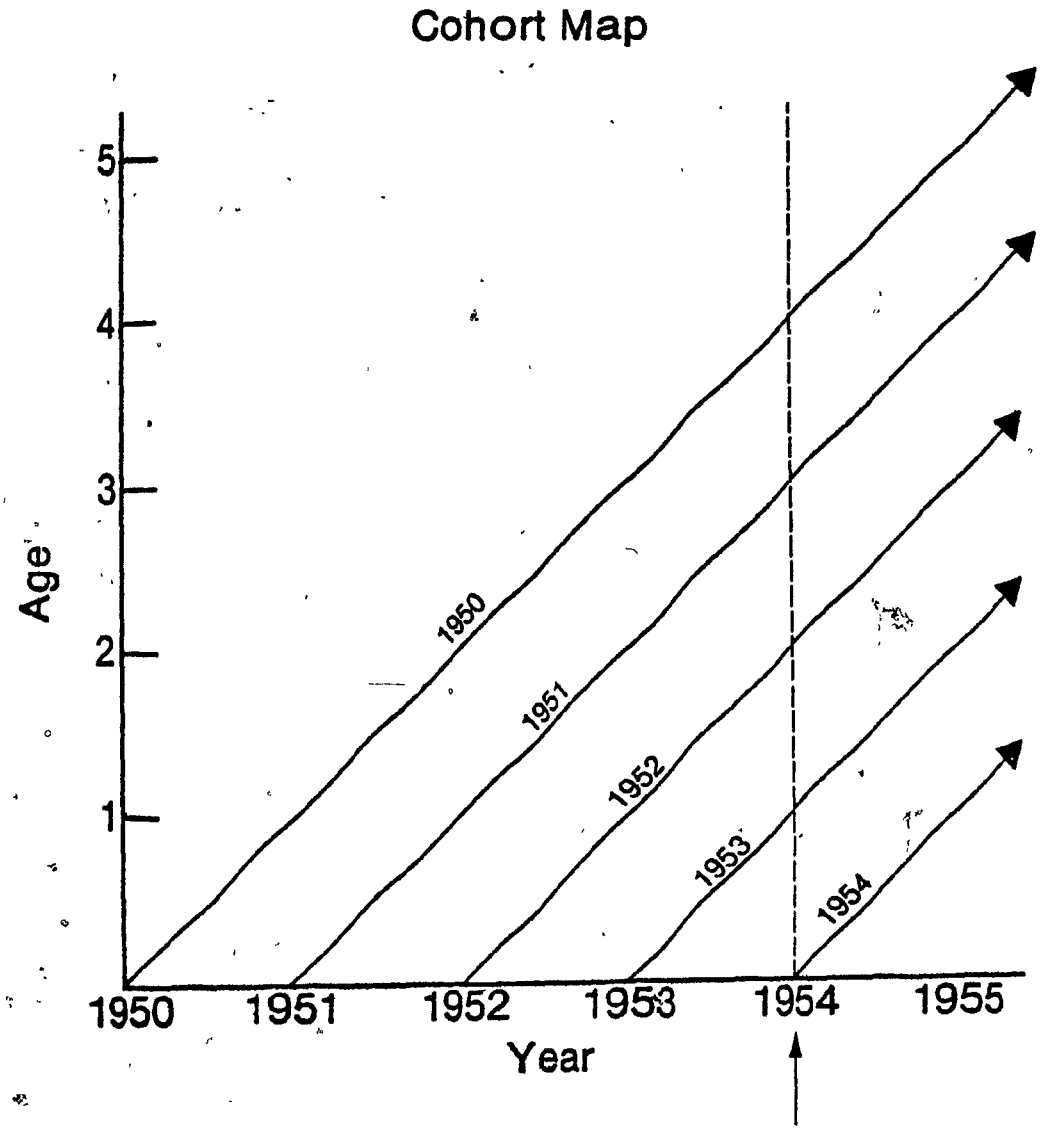


Figure 4.1a) Cohort map. Measles reporting at the end of 1953 (vertical arrow) is a cross-sectional view of the 1950, 1951, 1952, and 1953 birth cohorts.

Cohort Map of Disease (Immune) Experience of Four Simulated Cohorts, Each Containing 100 Infants

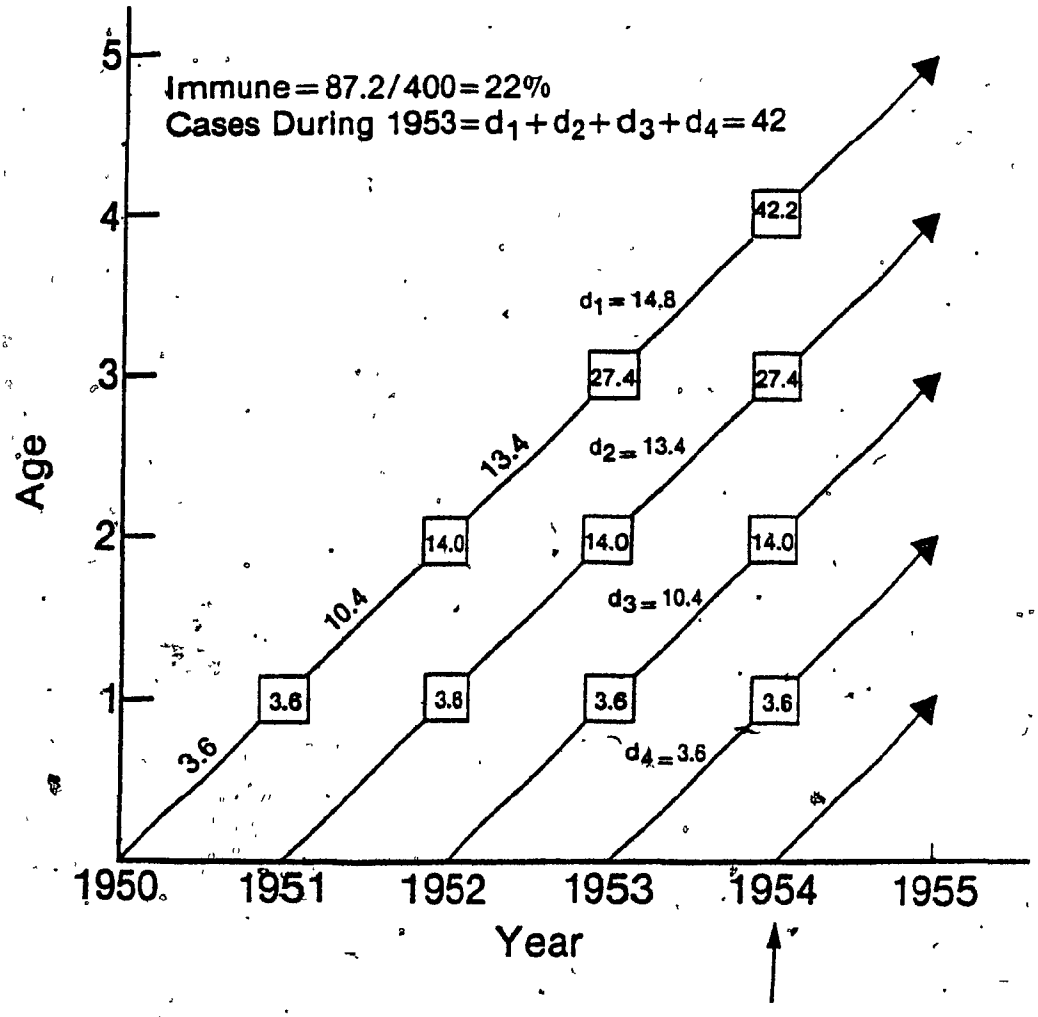


Figure 4.1b) Cohort map of disease (immune) experience of four simulated birth cohorts, each containing 100 infants. The values in the boxes along each cohort line represent cumulated disease within the cohort. Measles cases occur in the intervals between boxes on each cohort line. At the end of 1953 (vertical arrow), the sum of the boxes represents the total immunity of the four cohorts: 42.2 + 27.4 + 14.0 + 3.6 = 87.2/400 = 22%. The number of cases in 1953 is the sum of the transitions in the four cohorts in that year: $d_1 + d_2 + d_3 + d_4 = 42$.

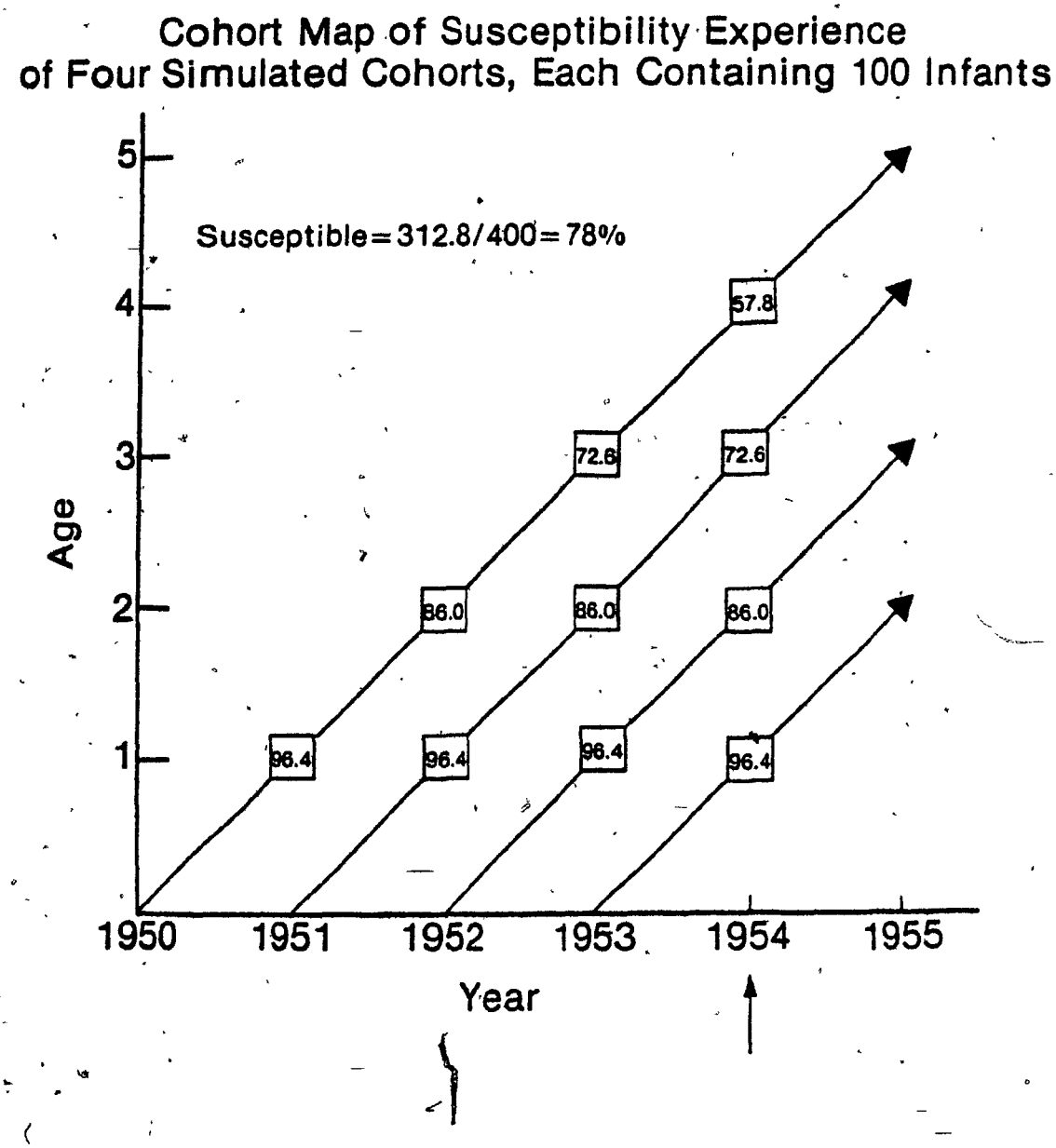


Figure 4.1c) Cohort map of susceptibility experience of four simulated cohorts, each containing 100 infants. As above, the values in the boxes along each cohort line represent cumulated susceptibility within the cohort. The total population susceptibility at the end of 1953 is 96.4 + 86.0 + 72.6 + 57.8 = 312.8/400 = 78%.

4.2.2 - Construction of the Computer Model

The aim of the model is to establish the percentage of the United States population susceptible to measles in the prevaccine era and to follow this through many years after total fadeout.

Although measles occurs in cycles locally, in a macro-epidemiologic setting it is a constant phenomenon. Given the endemicity of the disease, the total percentage of the population susceptible or immune was approximately the same from year to year in the prevaccine era. Accordingly, the calculation of the percentage of the population susceptible in the last prevaccine year is taken to be representative of the level of susceptibility in the years preceeding the vaccination program.

The year 1965 was chosen as the first year of the vaccination program and consequently 1964 is the prevaccine year. Knowing that all adults over the age of 20 were 99% immune by disease (10) in the prevaccine era (1964), it remains only to fill in the disease experience of the 19 youngest birth cohorts to get a full cross-sectional picture of the population at the end of 1964. This is shown by the cohort map of Figure 4.2a.

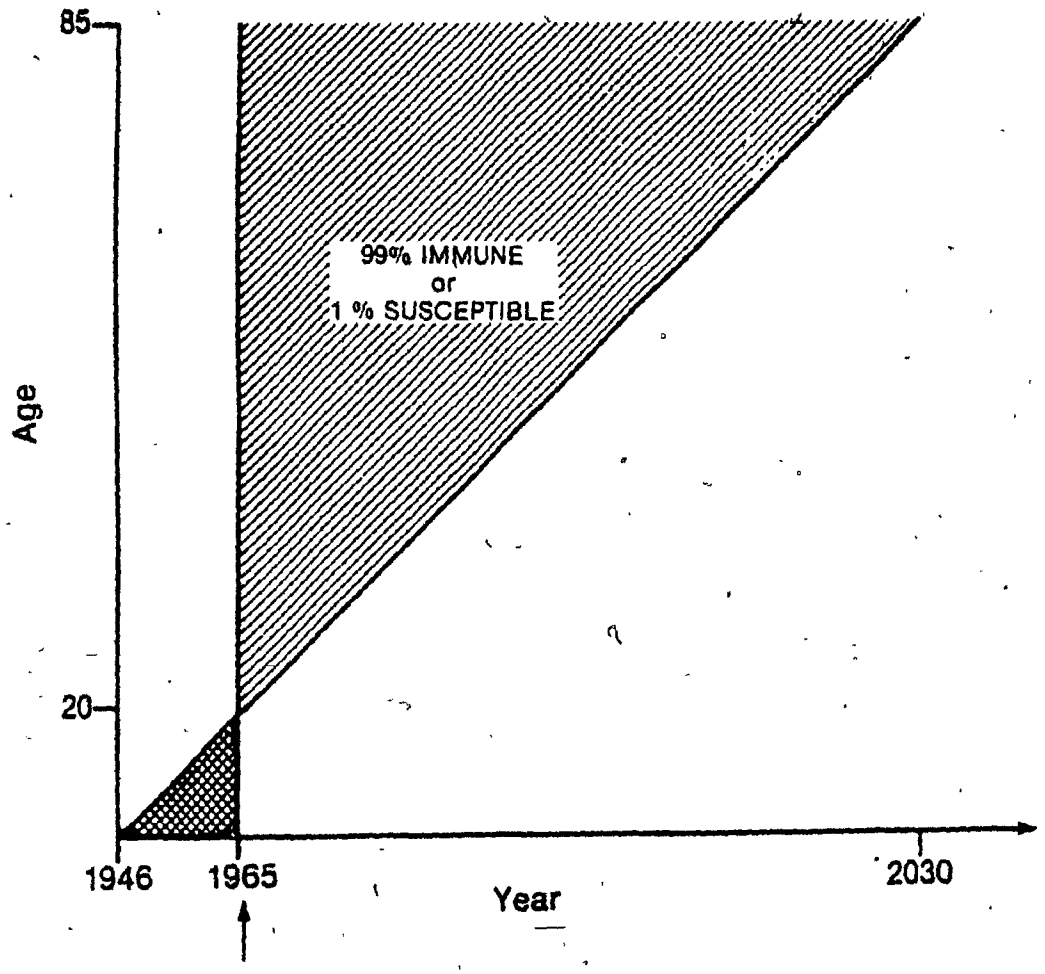


Figure 4.2a) Cohort map. The cross-sectional measles experience at the end of 1964 (vertical arrow) is derived from the collective experience of those aged 0-19, calculated by $\Psi(t) = a(t+c)$, and of those 20 and over, 99% of whom are immune.

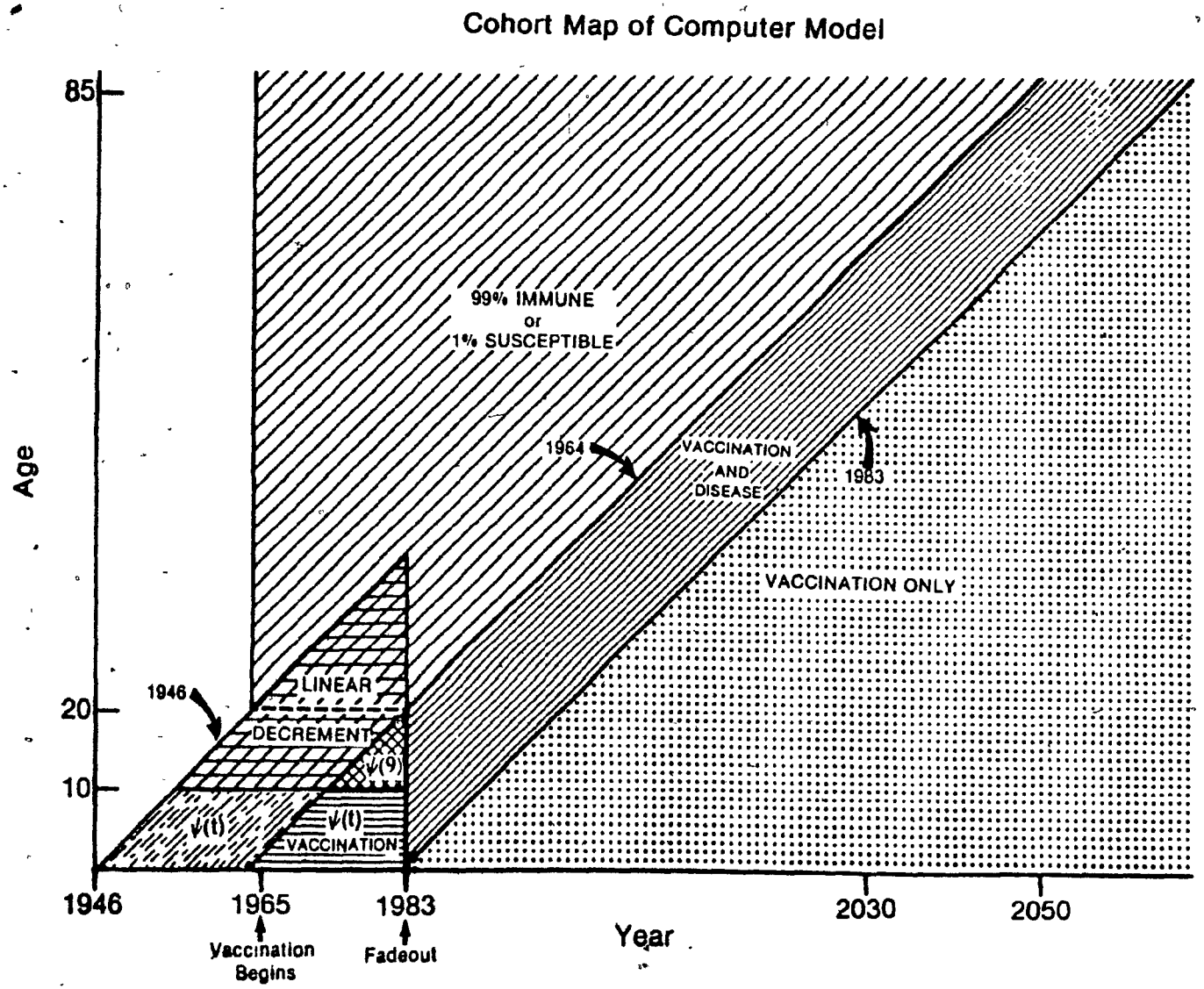


Figure 4.2b) Cohort map of computer model. The 1946-1963 cohorts are exposed to disease, calculated by $\Psi(t)$ to the age of ten, and linearly decremented thereafter. Beginning in 1965, the 1964 cohort (immunized at age one in 1965) to 1982 cohorts are exposed to natural measles $\Psi(t)$ and vaccination of all one year olds. All subsequents cohorts receive vaccination only.

Birth cohorts beginning in 1946 are exposed to three possible types of measles immunity - disease, a combination of disease and vaccination, and vaccination only. In the 1946-1963 birth cohorts, Griffiths' linear infection function is used up to and including the age of nine. For the 1946 cohort, the percentage of the population susceptible at the age of ten is then linearly decremented to reach 1% by the age of twenty. In the remaining cohorts 90% of this decline in susceptibles older than 10 years is set to occur by 20 years of age, with the last 10% distributed evenly until fadeout.

The 1964 cohort is the first to be immunized at the start of the program in 1965. Thus, the 1964 to 1982 cohorts are exposed to natural measles and vaccination. Their disease induced immunity is calculated by the linear measles function from birth to the end of age nine, at which point Ψ retains the value of $\Psi(9)$ for ages ten and over. The value of the constant a is 0.041 from 1946 to the end of 1961 as desribed by Griffiths, and adjusted to account for the changing age distribution of measles in the vaccine era as follows: 1962-1964, a = 0,050; 1965-1969, a = 0.045; 1970-1974, a = 0.035; 1975-1976, a = 0.030; 1977-1979, a = 0.020; 1980, a = 0.012; 1981, a = 0.010. Age in years is represented by t, and c equals 0.75. Immunity by

vaccination begins in 1965 for the 1964-born one year old children, and all subsequent cohorts are immunized at the age of twelve months. The total immunity of these cohorts is the sum of the immunity induced by vaccine and the immunity induced by natural disease.

Total measles fadeout was declared Jan. 1, 1983. The 1983 cohort and subsequent cohorts are exposed only to measles vaccination at age one year, and derive their immunity from that source only.

In summary, the 1946-1963 cohorts experience disease induced immunity, the 1964-1982 cohorts become immune by both disease and vaccination, and all subsequent cohorts are immunized artificially by vaccination. The model may be summarized by the cohort map in Figure 4.2b.

4.2.3 - Utilization of the Computer Model

A population matrix was constructed using United States population data from 1946 to 1981 (88-90). These data included all 50 states as well as the population of the armed forces overseas. The populations of Hawaii and Alaska were excluded from 1946-1949. This population matrix was then extended to the year 2050 using the latest life table

data, that of the year 1978 (91) with the 1978 birth rate of 15.8 per thousand (92). The matrix was truncated so that age 85 was the endpoint, as all ages greater than 85 are reported in one category making a probability function of life in that age group impossible. The first age group was split in two so that the first age interval was 0-5.99 months, the second 6-11.99 months, the third 1-1.99 years, the fourth 2-2.99 years, and so on until the eighty-sixth interval which represented the age 84-84.99 years.

All birth cohorts beginning in 1946 were then moved through time calculating their year to year measles experience based on the computer model described above. By the end of the year 1964 a cross-sectional measles experience for all persons less than age 85 became available. This continuing experience was then advanced to the year 2050, when the 1966 birth cohort turns 85 years old. In the cohort analysis matrices that represented disease, vaccination, total immunity, corrected immunity, and susceptibility were progressively filled with numbers derived from the calculations of every year's experience in every cohort. The end results were cohort maps representing 105 cohorts over a total of 105 years. The following assumptions were made in the analysis:

i) the immunization program begins in 1965 with a 50% vaccine coverage of one year olds that augments 10% per year for four years until 1969 when the vaccine coverage is 90%. This is based on a vaccine efficacy of 95% and a vaccination rate of 95% (.95 x .95 = .90);

ii) all children receive vaccine at the age of twelve months. This age was chosen for three reasons - most of the immunization program in the United States was conducted with this age recommendation, this is the continuing age recommendation for most of the rest of the world, and simplicity;

iii) January 1, 1983 is the fadeout time for indigenous measles in the United States;

iv) 20 years after fadeout, ie. in the year 2003, because 10% of childbearing women would be susceptible to disease, 10% of newborns have no benefit of maternal immunity and are susceptible for the first six months of life;

v) waning immunity (secondary vaccine failure) in immunized individuals does not occur.

The computer program was written in Fortran IV and processed via an Amdahl V7A central processing unit. The

graphs were drawn with the aid of a Statistical Analysis Institute graph package (SAS Institute Inc., Cary, North Carolina). It is presented in its entirety in the Appendix.

4.3 - RESULTS

4.3.1 - Incidence of Disease (Figure 4.3 and Table 4.1). The number of cases of measles in the prevaccine year of 1964 is estimated to be 4,371,824. This declines 94.4% to 243,813 cases prior to total fadeout. Since the reported cases in the prevaccine era accounted for about 10% of all cases (11), and in 1964 458,083 cases were actually reported, the model appears to be realistic.

4.3.2 - Age Distribution. In 1964 (Figure 4.4) the model predicts 40.6% of the cases to occur at less than five years of age, 52.4% between the ages of 5 and 9, 3.8% between the age of 10 and 14, and 3.2% at greater than 15 years of age. This is compared to the 1960-1964 (11) reported data of 37.2%, 52.8%, 6.5%, and 3.4% respectively. Also compared are the years 1973, 1975, and 1980 (93,94). For the years 1964 and 1975 the age distribution of disease is given for the first twenty years of life (Figure 4.5) as described by the model.

The average age of infection is also calculated. Figure 4.6 is a regression line of age versus year based on the model. As can be seen, it rises from 5.6 to 13.7 from the prevaccine year of 1964 to the year prior to fadeout, 1982.

4.3.3 - Susceptibility. The cross-sectional susceptibility to measles measured as a percentage of the population in each age group is shown in Figure 4.7. The effect of the immunization program is to distribute the susceptibles through the age groups with time. Table 4.2 and Figure 4.8 show the change in percentage of the population susceptible to measles from the prevaccine era to the year 2050. As can be seen, 10.6% of the population is susceptible to measles in 1964, and these susceptibles consist mainly of children under the age of ten. With the onset of the immunization program the percentage of the population susceptible falls quickly to 'bottom out' in the years 1979 to 1981 at 3.1%. Despite absence of disease, the proportion of the population susceptible to measles starts to rise in 1982 by about 0.1% per year or by between 220,000 and 300,000 new susceptible persons each year to reach the prevaccine level of 10.6% in the year 2045, and 10.9% by the year 2050.

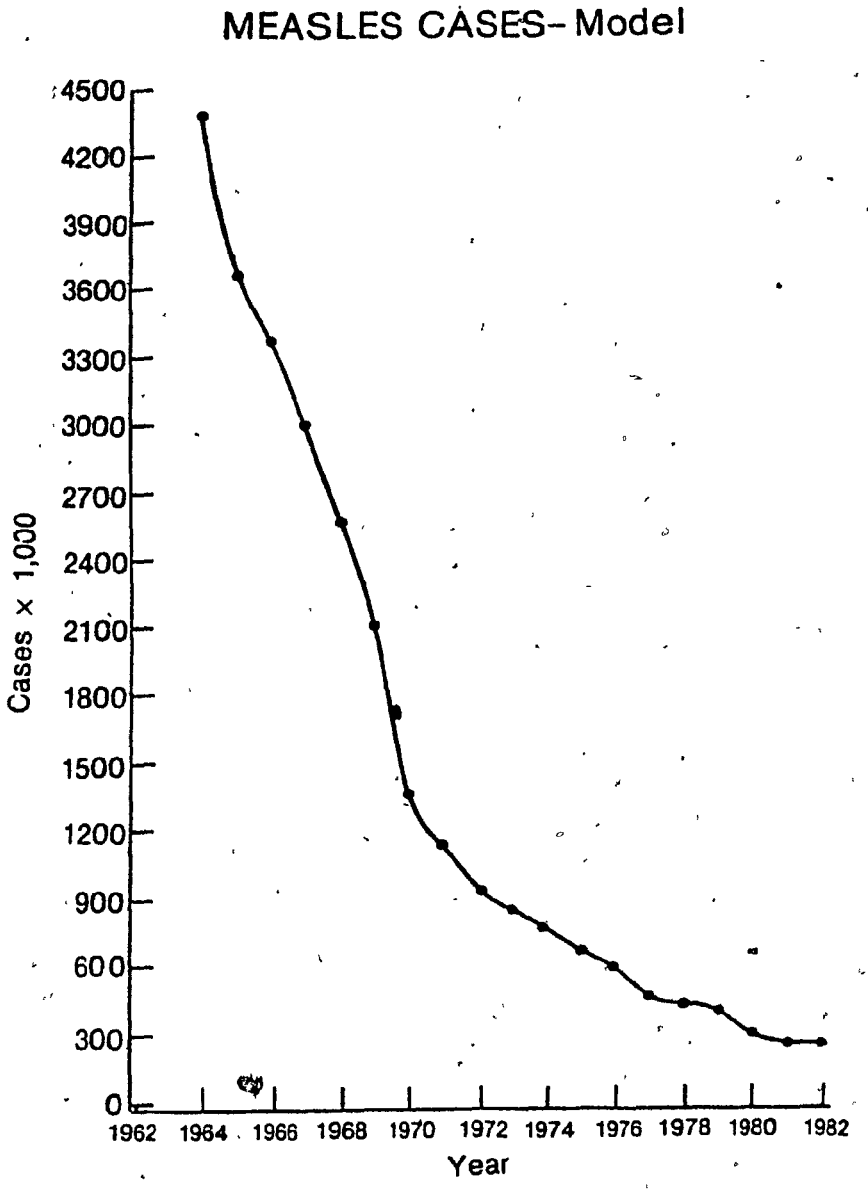


Figure 4.3 Measles cases as predicted by the computer model. The prevaccine year of 1964 has 4,371,824 measles cases. The model describes a 94.4% reduction of cases to 243,913 cases in 1982.

TABLE 4.1

ANNUAL MEASLES CASES PREDICTED BY MODEL

1964	4,371,824
1965	3,650,779
1966	3,357,756
1967	2,987,819
1968	2,556,242
1969	2,094,565
1970	1,353,438
1971	1,131,730
1972	915,719
1973	842,154
1974	766,905
1975	648,782
1976	594,322
1977	455,655
1978	421,970
1979	394,495
1980	287,458
1981	250,374
1982	243,913

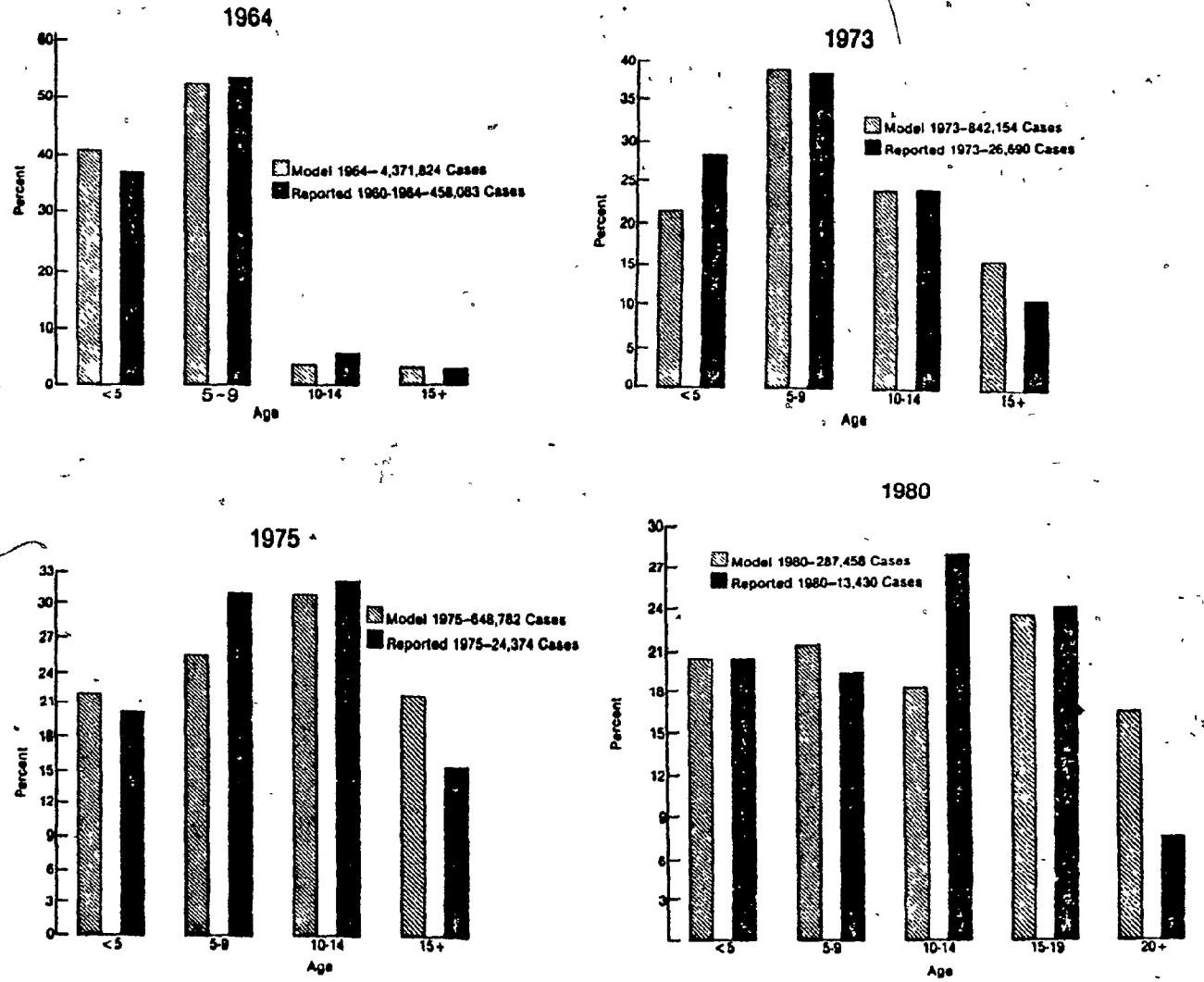


Figure 4.4 Age distribution of measles - computer model compared to reported data. 458,083 cases were reported in 1964, with the age distribution representing that of the years 1960-1964 (10). The model predicts approximately ten times the reported number of cases, realistically accounting for underreporting (10).

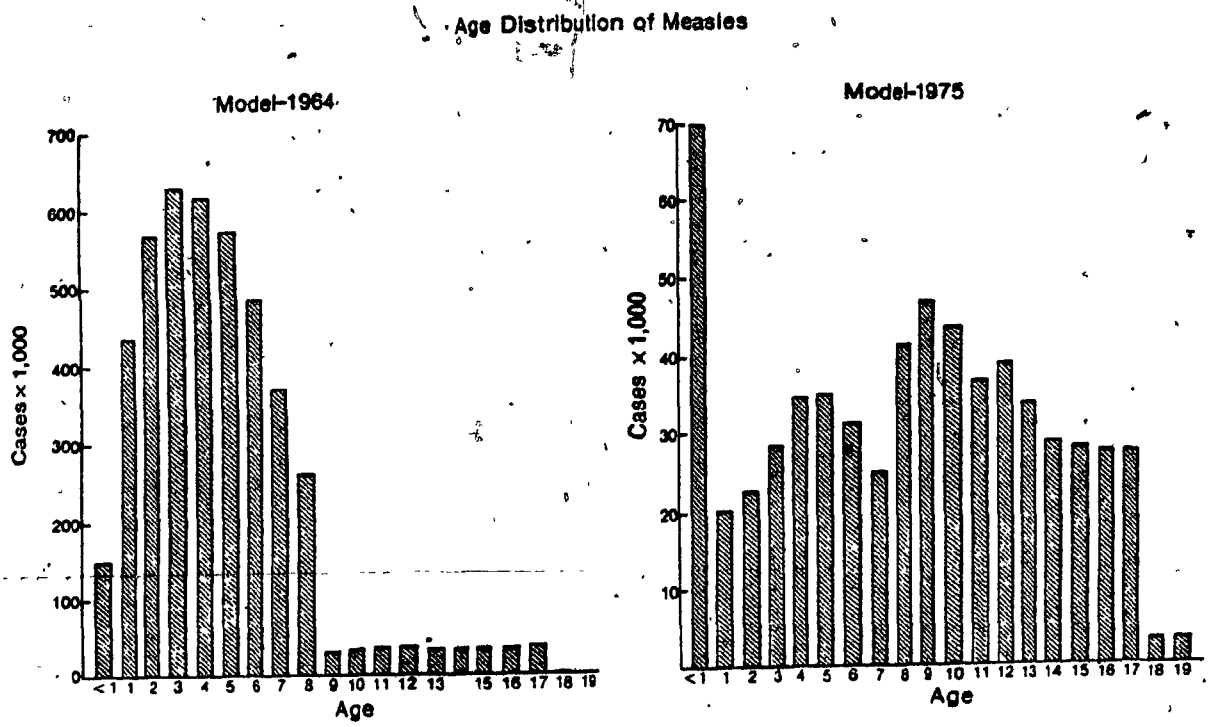


Figure 4.5 Age distribution of measles in the first 20 years of life - computer model. From 1964 to 1975 the vaccination program reduces the incidence of measles and distributes the remaining cases to older age groups.

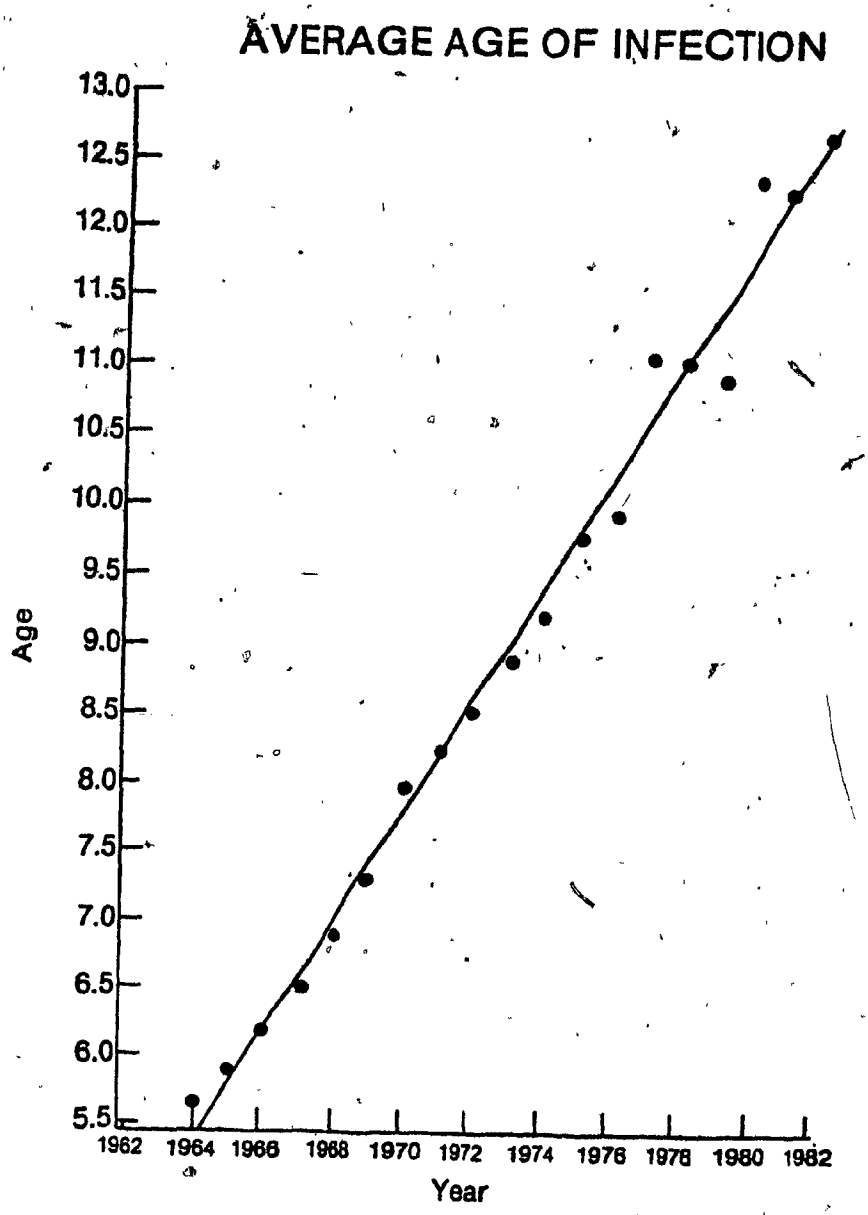


Figure 4.6 Average age of infection of measles. In the vaccine era the average age of infection rises to over twelve in 1980.

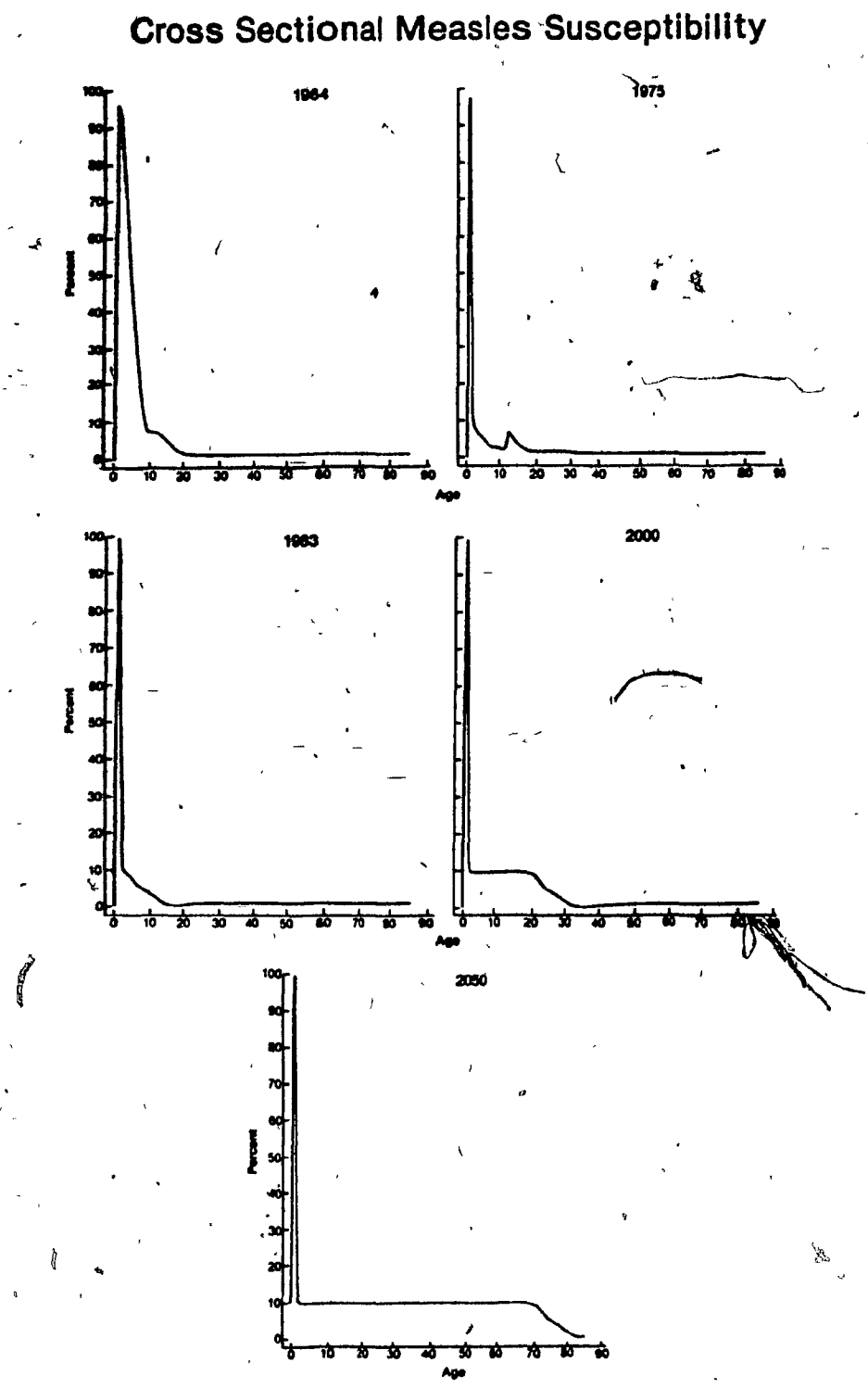


Figure 4.7 Cross-sectional measles susceptibility. The model demonstrates that in the prevaccine year of 1964 most susceptibles were children younger than ten years of age. The total population susceptibility, or the area under each curve, decreases in 1975 and 1983, but increases in the years 2000 and 2050, with susceptibility re-distributed to all age groups.

TABLE 4.2

TOTAL POPULATION SUSCEPTIBILITY TO MEASLES

Year	Percent Susceptible	Year	Percent Susceptible
1964	10.6	2008	6.5
1965	9.5	2009	6.6
1966	8.3	2010	6.7
1967	7.3	2011	6.9
1968	6.3	2012	7.0
1969	5.4	2013	7.1
1970	4.9	2014	7.2
1971	4.6	2015	7.3
1972	4.1	2016	7.4
1973	3.8	2017	7.5
1974	3.5	2018	7.7
1975	3.2	2019	7.8
1976	3.2	2020	7.9
1977	3.2	2021	8.0
1978	3.1	2022	8.1
1979	3.1	2023	8.2
1980	3.1	2024	8.3
1981	3.1	2025	8.4
1982	3.2	2026	8.5
1983	3.3	2027	8.7
1984	3.4	2028	8.8
1985	3.5	2029	8.9
1986	3.7	2030	9.0
1987	3.8	2031	9.1
1988	3.9	2032	9.2
1989	4.1	2033	9.3
1990	4.2	2034	9.4
1991	4.3	2035	9.5
1992	4.5	2036	9.7
1993	4.6	2037	9.8
1994	4.7	2038	9.9
1995	4.9	2039	10.0
1996	5.0	2040	10.1
1997	5.1	2041	10.2
1998	5.2	2042	10.3
1999	5.3	2043	10.4
2000	5.5	2044	10.5
2001	5.6	2045	10.5
2002	5.7	2046	10.6
2003	5.9	2047	10.7
2004	6.0	2048	10.8
2005	6.2	2049	10.9
2006	6.3	2050	10.9
2007	6.4		

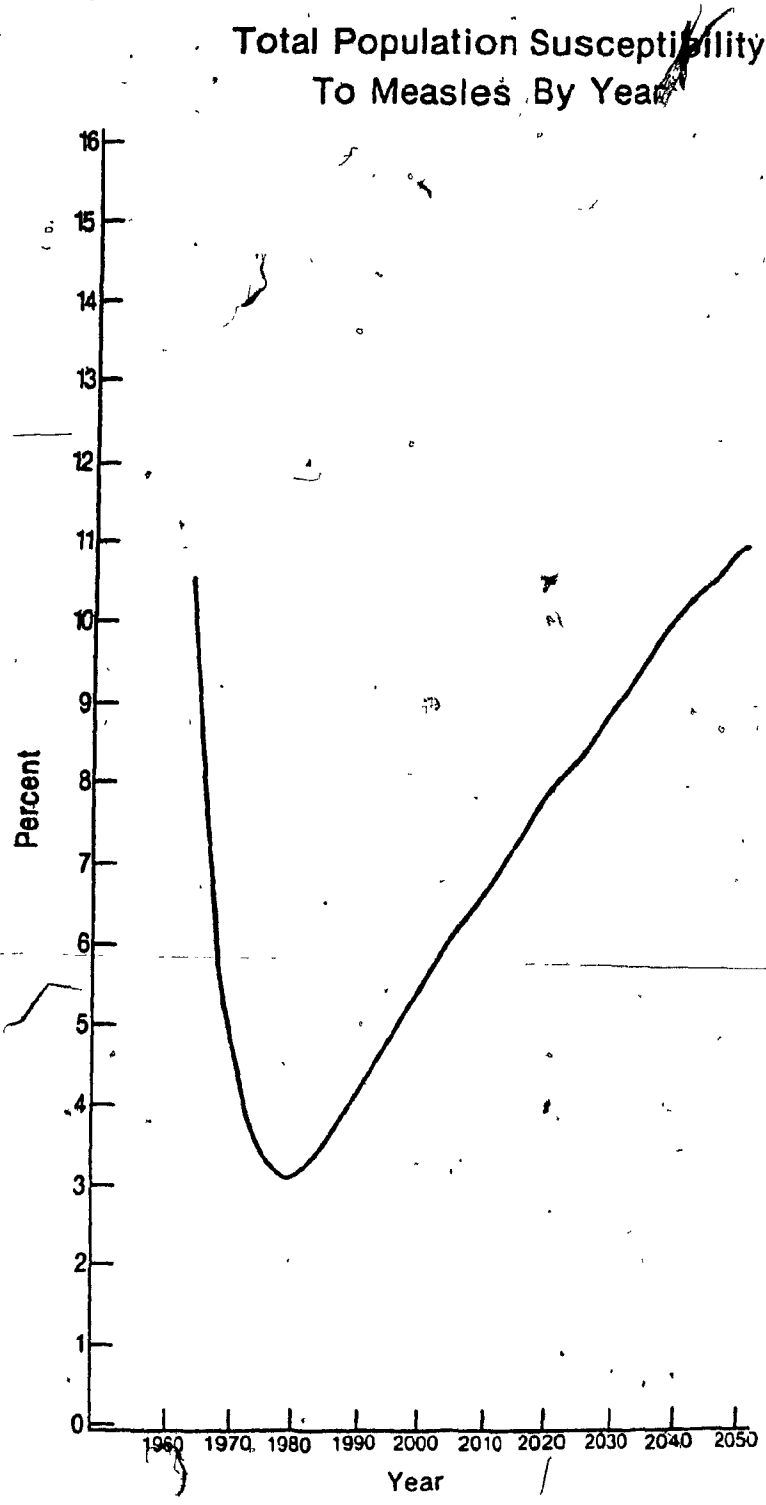


Figure 4.8 Total population susceptibility to measles by year. Each of the points of this curve represents the area under cross-sectional curves similar to those in Figure 4.7. In the prevaccine year of 1964, 10.6% of the population is susceptible to measles; this falls to 3.1% in 1978-1981, but rises thereafter to eventually reach prevaccine levels.

4.4 - VALIDITY

In assessing the validity of the results two issues must be considered - the application and subsequent adjustment of Griffiths' linear infection function, and the utilization of the computer model.

Griffiths' linear function for measles infection describes the natural longitudinal measles experience of cohorts in the prevaccine era. As reviewed in Chapter Three, it does seem to represent measles behaviour in England and the United States (12,14). Using the exact values of all the constants described by Griffiths except for *a* in 1962, 1963 and 1964, the computer model accounts for both the theoretical number of cases expected in 1964 (prevaccine year) as well as the age distribution of the cases (11). The precise values of *a*, the only adjusted constant, were derived by matching the changing age distribution in the model to reported data in the vaccine era. If the value of *a* had been left to its original value, the number of cases predicted by the computer model would have been closer to reality but at the expense of an inappropriately young age distribution. Rather than 0.54 from 1962-1969 as described by Griffiths, *a* was given a value of 0.050 from the period 1962-1964. From 1964

onwards, a was decreased to account for immunization. This effect was foreseen by Griffiths, and reflects the overall reduced density of susceptibles because of the added artificial immunity in the population.

The computer model developed in this project uses a large population matrix based on actual demographic data from 1946 to 1981 which was projected to the year 2050 using 1978 life table values. The population grid after 1981 is not intended to be a population forecast. Susceptibility figures are calculated as proportions of the population value in each cell of the grid, so that projected proportions susceptible to measles are independent of the actual numbers used.

The assumptions made on the measles elimination program appear to be reasonable. Because of variable vaccination practices in 1963 and 1964, 1965 was the first full year under the vaccination program. The initial vaccine coverage of 50% that augments 10% per year to 90% in 1969 represents a vaccine efficacy of 95% and a vaccination rate of 53%, 63%, 74%, 84%, and 95% of the population. If anything, this overestimates the vaccine coverage of the population. After fadeout in the United States the percentage of the population susceptible to measles as predicted by the model should be adjusted to account for the

difference in the small number of children between twelve and fifteen months who in reality are immunized at fifteen months of age. The January 1st, 1983 fadeout for indigenous measles in the United States is for practical purposes a reflection of the situation at this writing. Although 10% of the newborns after 2003 were assigned as susceptible though only theoretically at risk, the group itself represents a very small percentage (about 0.15%) of the United States population. Finally, waning immunity although possibly important, was not considered because of the present lack of knowledge with respect to its magnitude and epidemiologic importance.

The computer model describes the number of cases and their age distribution in the prevaccine era very well. However, it does not in itself predict the fadeout of measles. In fact, just before fadeout in 1982, 243,913 cases of measles are listed. This does not pose a serious threat to the validity of the model. Griffiths' linear infection function describes the "wild" behaviour of measles in a population and thus cannot account for the artificial interruption of transmission by school exclusions, case surrounding, vaccination of susceptible contacts, etc... that is characteristic of the measles elimination program. If all 243,913 cases predicted in 1982 are in fact not

susceptible but immune, the percentage of the population susceptible would be reduced from 3.2% to 3.1%. Thus, the effect of these residual cases with respect to total susceptibility is not large.

An advantage to this modelling approach in studying measles susceptibility is its independence of measles reporting. In 1982, Fine and Clarkson (87) studied the same problem of the effect of a measles vaccination program on immunity to measles in England. Their observations were similar, but necessitated a number of assumptions that had to correct for underreporting and age grouping of the notifications. The model used in this project avoids these issues by assuming a priori that the childhood population contacts measles in a prescribed way.

4.5 - DISCUSSION

The most important observation of the computer simulation is the effect the measles elimination program has on the percentage of the United States population susceptible to measles. It is clear that the success of the current program in the United States is not only due to a relatively high vaccine coverage of 90% but to the almost

complete natural immunity of at least 99% in the adult population, which together reduce the numbers susceptible to measles enough to induce fadeout. As the natural immunity is slowly replaced by an artificial one of lesser coverage the proportion susceptible reflects this change. The future susceptible population is not only children but people of all ages whose morbidity and mortality from measles is increased (8,67,68,70). In theory, if an epidemic were to occur in the year 2050, and only half of those susceptible are infected, based on a 2.37/1,000 death-to-case ratio in those over twenty years of age (8), over 25,000 measles deaths would occur.

Can the susceptibility levels rise to the predicted figure of close to 11%? If measles vaccine technology is unchanged and measles remains endemic in the rest of the world with no protection from importation offered to United States residents, then disease and perhaps epidemics would reduce the numbers susceptible. Some authors have suggested that the proportion of susceptibles needed in a closed population to sustain endemicity is 6% (17,85,86). Although difficult to extrapolate this figure to a macro-epidemiologic setting, and knowing that the mechanics of disease propagation may differ in an adult susceptible population, this level could be reached in about the year

2000. Subsequent to disease, the number of susceptibles would decrease and measles would recur only when the necessary susceptibles have re-accumulated. However, if measles were eliminated globally, or the United States population protected completely from reintroduction, the number of susceptible people would accumulate to about 11%, but be irrelevant due to the absence of virus to incite disease.

Although the first measles battle, that of eliminating indigenous measles in the United States has been virtually won, the war is not over. Computer simulation indicates that with every new year the United States population will contain over 220,000 more persons susceptible to measles. Despite the great benefits that have been achieved, the challenge of the future is to preserve that gain for today's younger generation and the generations of tomorrow.

Chapter Five examines these public health issues and makes recommendations for the future.

CHAPTER FIVE

PUBLIC HEALTH STRATEGIES FOR MEASLES CONTROL IN THE FUTURE

Based on the observations of the model developed in Chapter Four, it is apparent that to ensure continuing fadeout of measles in the United States certain public health strategies must be considered.

In a fadeout situation two essential elements are necessary for the reappearance of disease and epidemics - persons susceptible to measles, and introduction of the virus from outside of the population. Once the disease is reintroduced, the difference between a situation of sporadic outbreaks of disease and epidemics depends upon the number of susceptible people in that target population. If either of these two elements were to be eliminated independently, leaving a 100% immune population, or no chance of importation, fadeout would persist indefinitely. Looked at another way, if no measles importations could come about despite a largely susceptible population, fadeout would continue, and if importations were abundant but the population completely immune, disease would not occur. These two issues will now be examined more closely; strategy options will be discussed with the goals of reducing the

number of people susceptible to measles, and minimizing the chance of measles reintroduction to the United States.

5.1 - REDUCTION OF SUSCEPTIBLES

With the current measles elimination program it is clear that susceptibility to measles could never be entirely eliminated. Even if all children were vaccinated with a 100% efficacious vaccine, all those between the ages of six months and fifteen months would become and remain susceptible until their measles injection. The realistic goal is to reduce susceptibles below threshold levels as much as possible so that any reintroduction of disease would lead at most to sporadic rather than epidemic disease.

In a highly vaccinated population like the United States, susceptibles accumulate by the herd immunity effect. Vaccine coverage is a function of the vaccine efficacy multiplied by the percentage of the population vaccinated. Unfortunately, the current vaccine coverage of 90% is not sufficient to keep the percentage susceptible below the estimated measles perpetuation threshold level of 6%. Thus, two important strategies must be:

1) Increase the percentage of the population initially vaccinated. Although 95% of the population is already routinely vaccinated, efforts must be made to improve this figure. The subgroup of unvaccinated school children must be identified and vaccinated at the school age level.

2) Improve the quality and utilization of the vaccine. The aim would be to achieve a vaccine efficacy as close to 100% as possible by improved field trial seroconversion and better vaccine delivery to achieve the maximum possible seroconversion in a community setting. If vaccine efficacy were 99%, the vaccine coverage would reduce the number of susceptibles accumulating through time by almost four percent.

With the growing concern about susceptible subgroups and waning immunity potentially becoming a problem, "repeat vaccination" measles programs might be considered. The goal would be to increase the vaccine coverage of the population by a second dose of vaccine in adulthood. A subset of this strategy could include serologic surveys to determine those susceptible, and then selective immunization.

Because of the blocking effect of maternal antibodies

on seroconversion (24,36,95) revaccination has been recommended for children initially immunized at less than one year of age. However, Wilkin and Wehrle (36), Linnemann (96), and Deseda-Tous et al (97) have shown that ten months after revaccination of children who had their first measles injection at ten months of age or less, between 40% and 49% were still without measurable antibody by the HI technique, despite an initial antibody response in the majority. This led to the recommendation by these authors that in the situation of measles epidemics, the appropriate preventive measure for those less than twelve months of age should be immune serum globulin rather than vaccine, as the latter may prevent successful future immunization. Are these children susceptible to measles? Unfortunately this cannot be answered at the present time. The neutralizing antibody response may be more sensitive in defining measles immunity than the HI titers, and in one study (36) all revaccinated children demonstrated an anamnestic neutralizing antibody titer even in those who failed to develop an HI response. Nevertheless, the possibility exists that booster vaccination with measles vaccine may not have a lasting effect on attenuated titers and thus may not help to resolve the potential problem of waning immunity.

Secondary vaccine failure, if truly an entity, is difficult to distinguish from a serologically low titer that reacts anamnestically and provides protection (98). HI titers appear to be specific but insensitive in describing immunity. This was demonstrated by Cherry (4) in a Los Angeles County where twenty-six of sixty-seven children who had an HI titer of less than five showed a pure IgG rather than IgM response to measles vaccine.

A history of disease or vaccination is also an unreliable indicator of immunity. The measles epidemic in young adults (48) on the U.C.L.A. campus in California in 1977 demonstrated this well. Of thirty-four documented cases of measles, ten students gave a history of vaccination, six had a history of measles, eight had a history of neither, one had a history of both, and eight were uncertain. Of 40 students who thought they were non-immune (by disease or vaccine), thirty-five had HI titers greater than five. Of 19 students with HI titers less than five who were vaccinated, 15 responded with a secondary IgG, antibody rise. Thus, there was a very poor correlation between histories of immunization and susceptibility or immunity to measles. Similar situations have been experienced elsewhere (96,97). The fact that so many revaccinated subjects developed an IgG response may

mean that the ability to respond anamnestically to vaccine does not necessarily indicate protection against measles (97).

There are still many unanswered questions with respect to measles revaccination. Some authors suggest serologic surveys to better define susceptibles (99,100), but poor negative predictive properties of serology make this difficult. Revaccination to boost waning immunity has questionable value - boosted titers attenuate rapidly. A search for susceptibles at an adult age might seroconvert some, but would have doubtful effect on the whole group, and the benefit of a mass second-dose program would serve only those who had no disease or vaccine experience at the price of large numbers of needless vaccinations. In summary, the strategy to increase vaccine coverage at a later date that could also correct waning immunity by either selective or mass second dose programs has little proven value. More appropriate current strategies are increasing the proportion of children vaccinated in childhood and the improvement of vaccine efficacy.

5.2 - MINIMIZE THE PROBABILITY OF REINTRODUCTION OF MEASLES VIRUS

As fadeout is approached and maintained, any new case of measles, by definition, must be imported. This is true for the United States where the proportion of cases of measles accounted for by importation is increasing. In 1980, the total importation of measles by United States citizens and foreigners (95 cases) accounted for 0.7% of all cases of reported measles in the United States in that year (101). By the first half of 1982 importations accounted for 64/895 or 7.2% cases of measles, which if projected to an annual basis, is more than the absolute number of cases in 1980. 13 of these 64 cases led to an additional 164 cases within the United States for a total of 228 importation related cases, or 25.5% of all measles cases in the first half of 1982. A single imported case of measles to Florida in the autumn of 1982 led to an epidemic of over 200 measles cases in 57 schools, 4 day care centers, one community college and one military school (102). With the projected annual increase of over 220,00 new susceptible people to measles in the United States, methods must be implemented to reduce the chance of reintroduction of the virus.

Reintroduction of measles virus can occur two ways. A

United States susceptible can acquire the disease abroad and then import it, usually in its prodromal phase, and an infected foreigner can enter the population from outside its borders. Control measures at this level clearly imply vaccination certificates for all United States citizens born after 1953-1957 leaving the country (or alternately re-entering) and all foreigners entering the United States who may be susceptible and hence infective. The population at risk to be infective would depend on the degree of endemicity in the country of origin, so that in areas of high endemicity only those less than age ten would need a vaccination certificate or proof of disease, and in areas of low endemicity older ages would need to show proof of disease or vaccine. This strategy, similar to the one used for smallpox, should limit reintroduction. Remaining potential infectives would be children less than 15 months of age and illegal immigrants. If measles elimination were to continue as policy of the WHO, vaccination requirements for travellers between these fadeout countries would gradually become unnecessary. With the ultimate result of global fadeout, vaccine requirements would be eliminated for everyone.

Recently, the goal of worldwide elimination of measles has been questioned. Despite the great benefit versus cost

of immunization programs in developed countries (56,103,104), the advantages are less clear in undeveloped countries (105,106). This issue was recently reviewed in a Lancet editorial (107) where it was concluded that if measles were demonstrated to be a disease that can be eliminated, only then would the world decide to "rationalize measles vaccine into redundancy".

A continuing strategy in measles elimination should include progressive worldwide elimination. As the benefits/cost ratio becomes infinite, the pressure for public funds will also rise. Thus, the faster the elimination programs move ahead, the greater the chance for success. Resources must be allocated to international health agencies to ensure continuity of the global measles elimination program.

The final chapter of this thesis will summarize the findings herein and make recommendations for public health strategies for the future.

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

Based on a review of the literature and the findings of the computer model described in this thesis, the following conclusions are reached:

1) Measles elimination in the United States has come about by the combination of an effective vaccination program and a highly naturally immunized population.

2) Despite indigenous measles elimination, between 220,000 and 300,000 susceptible persons will accumulate every year as long as fadeout persists so that their numbers will rise to, and perhaps above prevaccine levels. These susceptibles will be distributed among the entire spectrum of age groups.

3) This accumulation of susceptible people is a result of herd immunity alone. Waning immunity (secondary vaccine failure) is not taken into account.

4) Measles in these new age groups can be expected to have both higher morbidity and mortality.

5) The potential for renewed disease and perhaps epidemics exists, and this will become more important as the year 2000 is approached.

In this context, the following recommendations are made for public health policy for the United States and for all other countries that achieve high levels of artificial immunity to measles:

1) Efforts must be made to vaccinate more than 95% of children prior to school entry.
2) Vaccine efficacy must be improved by higher seroconversion rates in community settings.
3) The relationship between serological markers and protection from disease must be better understood. At this time neither selective screening nor booster vaccine can be recommended.
4) Vaccination certificates should be required for all potential infectives or susceptibles re-entering, or entering the United States for the first time.
5) Renewed and additional resources must be directed to the rest of the world where measles remains endemic to institute or improve measles elimination programs to achieve global measles eradication.

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APPENDIX

COMPUTER MODEL

SIMULATING MEASLES

IMMUNITY AND SUSCEPTIBILITY

COMPUTER MODEL

SIMULATING MEASLES

IMMUNITY AND SUSCEPTIBILITY

DESCRIPTION OF VARIABLES

N(A.B)	-POPULATION FOR AGE(A) YEAR(B)
ID(A.B)	-IMMUNE BY DISEASE
IV(A.B)	-IMMUNE BY VACCINE
TOTIM(A.B)	-TOTAL IMMUNE
CTOTIM(A.B)	-CORRECTED TOTAL IMMUNE
S(A.B)	-NUMBER OF PEOPLE SUSCEPTIBLE
FI(I)	-FORCE OF INFECTION
TPOP(B)	-POPULATION TOTAL
TSUS(B)	-SUSCEPTIBLE TOTAL
TPS(B)	-TOTAL PERCENT SUSCEPTIBLE
PCAS(A.B)	-PERCENT AGE SUSCEPTIBILITY
FDO	-YEAR OF COMPLETE FADEOUT
COH	-YEAR FIRST COHORT REACHES AGE 20 AFTER VACCINE ERA
ATK	-ATTACK CONSTANT
CON	-AGE CORRECTION
ALLIM	-AGE PRIOR TO VACCINE ERA WHEN 99% IMMUNE
ENDLIN	-AGE AT WHICH MODEL STOPS BEING LINEAR
PCDEC	-PERCENT DECREMENT IN SUSCEPTIBLES AFTER MODEL STOPS BEING LINEAR
PREVI	-% OF ADULTS SUSCEPTIBLE BEFORE VACCINE ERA
BEGIV	-YEAR OF INITIATION OF PROGRAM
VACOV	-% VACCINE COVERAGE

```
      REAL N(86,106)
      REAL ID(86,106),TOTIM(86,106),CTOTIM(86,106),S(86,106),TSUS(106)
      REAL TPS(106),FI(86),TPOP(106),IV(86,106),PCAS(86,106)
      REAL AAI(38),TOTINF(37),SUMID(37),GRID5(37),GRID10(37)
      REAL GRID15(37),GRID20(37,GRID21(37),GRPC5(37),GRID10(37)
      REAL GRIC15(37),GRPC20(37),GRPC21(37)
      REAL ATK,CON,PCDEC
      REAL PREVI,VACOV
      INTEGER  FDO,COH,ALLIM,ENDLIN,BEGIV
      INTEGER  YEAR,AGE,POP,A,B,ISTART,IEND
```

```
      READ POPULATION MATRIX

10        READ(1,*,END=20) YEAR,AGE,POP
          IF (AGE.EQ.86) GO TO 10
             A=AGE+1
             B=YEAR-1946+1
             N(A.B)=POP
             GO TO 10
20        IF (YEAR.EQ.2051.AND.AGE.EQ.86) GO TO 22
          STOP

      READ CONSTANTS

22        READ(5,*) FDO,COH,CON,ALLIM,ENDLIN,PREVI,BEGIV,VACOV
          FDO=38,COH=57,CON=.75,ALLIM=20,ENDLIN=10,PREVI=.01,
          BEGIV=19,VACOV=0.90

      INITIALIZE ARRAYS

          A=0
          B=0
          ISTART=0
          IEND=84
          DO 30 J=1,106
             TSUS(J)=0.0
             TPOP(J)=0.0
             TPS(J)=0.0
             DO 29 I=1,86
                IF (J.GT.1) GO TO 28
                   FI(I)=0.0
28              S(I,J)=0.0
                ID(I,J)=0.0
                IV(I,J)=0.0
                TOTIM(I,J)=0.0
                CTOTIM(I,J)=0.0
                PCAS(I,J)=0.0
29           CONTINUE
30        CONTINUE
          KK=BEGIV-1
          DO 40 J=KK,106
             DO 35 I=ALLIM,86.
                S(I,J)=PREVI*N(I,J)
35           CONTINUE
40        CONTINUE
```

```
START


45          ISTART=ISTART+1
            IF (IEND.EQ.105) IEND=104
            IEND=IEND+1
50          A=A+1
            B=B+1
            IF (B.LE.IEND.AND.A.LT.86) GO TO 51
               IF (A.EQ.3) GO TO 100
                  A=0
                  B=ISTART
                  GO TO 45
51          IF (B.LT.17)  ATK=.041
            IF (B.GE.17.AND.B.LT.20)  ATK=.05
            IF (B.GE.20.AND.B.LT.25)  ATK=.045
            IF (B.GE.25.AND.B.LT.30)  ATK=.035
            IF (B.GE.30.AND.B.LT.32)  ATK=.030
            IF (B.GE.32.AND.B.LT.35)  ATK=.020
            IF (B.EQ.35)  ATK=.012
            IF (B.EQ.36)  ATK=.011
            IF (B.EQ.37)  ATK=.010


A=1


            IF (A.GT.1) GO TO 60
               FI(A)=0.0
               TOTIM(A,B)=N(A,B)
               IF (B.GE.COH)  GO TO 55
                  S(A,B)=0.0
                  GO TO 56
55             S(A,B)=(1-VACOV)*N(A,B)
56             CTOTIM(A,B)=TOTIM(A,B)
               B=B-1
               GO TO 50


A=2


60          IF (A.GT.2) GO TO 65
               IF (B.LT.FDO) GO TO 61
                  FI(A)=0.0
                  GO TO 62
61             FI(A)=ATK*(.75+CON)
62             ID(A,B)=N(A-1,B)*FI(A)
```

```
      TOTIM(A,B)=ID(A,B)
      CTOTIM(A,B)=TOTIM (A,B)+TOTIM(A,B)*(N(A+1,B+1)-(N(A-1,B)+
                 N(A,B)))/(N(A-1,B)+N(A,B))
      S(A,B)=N(A,B)+N(A-1,B)-ID(A,B)
      GO TO 50

A=3

65    IF (A.GT.3.OR.B-A.LT.17) GO TO 70
         IF (B.LT.FDO) GO TO 66
            FI(A)=0.0
            GO TO 67
66       FI(A)=ATK*(1.5+CON)
67       IF(B.GE.BEGIV+4)  IV(A,B)=VACOV*S(A-1,B-1)
         IF(B.GE.BEGIV.AND.B.LT.BEGIV+4)
            IV(A,B)=(((B-BEGIV)/10.0)+.5)*S(A-1,B-1)
         ID(A,B)=(S(A-1,B-1)-IV(A,B))*FI(A)
         TOTIM(A,B)=ID(A,B) IV(A,B)+CTOTIM(A-1,B-1)
         CTOTIM(A,B)=TOTIM(A,B)+TOTIM(A,B)*(N(A+1,B+1)-N(A,B))/N(A,B)
         S(A,B)=N(A,B)-TOTIM(A,B)
         GO TO 50

A>3

70    IF (B-A.GE.17) GO TO 91
         IF (A.GE.ALLIM) GO TO 71
            IF (A.GT.ENDLIN) GO TO 80
               FI(A)=ATK*(A-1.5+CON)
               ID(A,B)=S(A-1,B-1)*FI(A)
               TOTIM(A,B)=ID(A,B)+IV(A,B)+CTOTIM(A-1,B-1)
               CTOTIM(A,B)=TOTIM(A,B) TOTIM(A,B)*(N(A+1,B+1)
                           -N(A,B))/N(A,B)
               S(A,B)=N(A,B)-TOTIM(A,B)
               GO TO 50
80          IF (A.GT.ENDLIN+1) GO TO 81
               PERC=(S(A-1,B-1)/N(A-1,B-1))-0.01
               PCDEC=PERC/10.0
               IF (PCDEC.LT.0.0) PCDEC=0.0
               GO TO 81
71       IF (B.GE.FDO) GO TO 50
            IF (A.GT.ALLIM) GO TO 81
               PERC=(S(A-1,B-1)/N(A-1,B-1))-0.01
               PCDEC=PERC/(FDO-B+1)
               IF (PCDEC,LT,0.0) PCDEC=0.0
```

```
81          S(A,B)=((S(A-1,B-1)/N(A-1,B-1))-PCDEC)*N(A,B)
            ID(A,B)=PCDEC*N(A,B)
            GO TO 50
91      IF (B.GE.FDO) GO TO 93
          IF (A.GT.ENDLIN) GO TO 92
            FI(A)=ATK*(A-1.5+CON)
            GO TO 95
92        FI(A)=FI(ENDLIN)
          GO TO 95
93      FI(A)=0.0
95      ID(A,B)=S(A-1,B-1)*FI(A)
        TOTIM(A,B)=ID(A,B)+IV(A,B)+CTOTIM(A-1,B-1)
        CTOTIM(A,B)=TOTIM(A,B)+TOTIM(A,B)*(N(A+1,B+1)
                    -N(A,B))/N(A,B)
        S(A,B)=N(A,B)-TOTIM(A,B)
        GO TO 50
```

CALCULATE TOTALS

```
100     M=BEGIV-1
        DO 120 J=M,105
          DO 110 I=1,86
            TSUS(J)=TSUS(J)+S(I,J)
            TPOP(J)=TPOP(J)+N(I,J)
110       CONTINUE
120     CONTINUE
        DO 130 J=M,105
          TPS(J)=TSUS(J)/TPOP(J)
130     CONTINUE
        DO 160 J=M,105
          DO 150 I=1,86
            IF (I.NE.2) GO TO 140
              PCAS(I,J)=S(I,J)/(N(I-1,J)+N(I,J)
              GO TO 150
140         PCAS(I,J)=S(I,J)/N(I,J)
150       CONTINUE
160     CONTINUE
        KL=FDO-1
        KK=BEGIV-1
        DO 195 J=KK,KL
          SUMID(J)=0.0
          TOTINF(J)=0.0
          GRID5(J)=0.0
          GRID10(J)=0.0
          GRID15(J)=0.0
```

```
                GRID20(J)=0.0
                GRID21(J)=0.0
                DO 190 I=2,86
                   SUMID(J)=SUMID(J)+ID(I,J)
                   TOTINF(J)=TOTINF(J)+I*ID(I,J)
                   IF (I.GT.5) GO TO 186
                      GRID5(J)=GRID5(J)+ID(I,J)
                      GO TO 190
  186              IF (I.GT.10) GO TO 187
                      GRID10(J)=GRID10(J)+ID(I,J)
                      GO TO 190
  187              IF (I.GT.15) GO TO 188
                      GRID15(J)=GRID15(J)+ID(I,J)
                      GO TO 190
  188              IF (I.GT.20) GO TO 189
                      GRID20(J)=GRID20(J)+ID(I,J)
                      GO TO 190
  189              GRID21(J)=GRID21(J)+ID(I,J)
  190           CONTINUE
                AAI(J)=TOTINF(J)/SUMID(J)
                GRPC5(J)=GRID5(J)/SUMID(J)
                GRPC10(J)=GRID10(J)/SUMID(J)
                GRPC15(J)=GRID15(J)/SUMID(J)
                GRPC20(J)=GRID20(J)/SUMID(J)
                GRPC21(J)=GRID21(J)/SUMID(J)
  195        CONTINUE


             OUTPUT
             END
```