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THE FUTURE OF MEASLES IN HIGHLY IMMUNIZED POPULATIONS

A MODELING APPROACH[1]

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Levy, D. L. (Dept. of Social Medicine, Montefiore Medical Center, The Bronx, NY 10467). The future of measles in highly immunized populations: a modeling approach. *Am J Epidemiol* 1984;120:39-48.

Little is known about how an intensive measles elimination program changes the overall immune status of the population. 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 reveals that in the prevaccine era, approximately 10.6% of the population was susceptible to measles, most of whom were children less than 10 years of age. With the institution of the measles immunization program, the proportion of susceptibles in the population fell to 3.1% from 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. The model did not consider the potential effect of waning immunity. The results of this study suggest that measles elimination in the United States has been achieved by an effective immunization program aimed at young susceptibles combined with a highly, naturally immunized adult population. However, despite short-term success in eliminating the disease, long-range projections demonstrate that the proportion of susceptibles in the year 2050 may be greater than in the prevaccine era. Present vaccine technology and public health policy must be altered to deal with this eventuality.

forecasting; immunization; measles

Indigenous measles is currently facing elimination from US society. This is because of 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 (1, 2) 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.

The objective of this paper is to examine how a highly effective immunization program modifies the balance be-

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tween 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.

Methods

Theoretic 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. 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 infection phase representing a relatively small period of time. If the rate of transition from susceptibility to immunity can be established, this change can be quantified.

In 1974, Griffiths (3), using modeling theory, defined a function describing the behavior of wild measles in populations. He showed that the proportion of susceptibles that develops measles in a year can be represented by a linear equation for the first 10 years of life:

$$\psi(t) = a(t + c), t > \tau,$$

where ψ is the attack rate on susceptibles, t is age in years, a and c are constants, and τ is 0.5 years (six months of age), the age at which most infants become susceptible to disease. Thus, the transition from susceptibility to immunity by contact with measles can be quantified until 10 years of age. For example, the susceptibility experience of four imaginary cohorts, each with 100 infants, is portrayed by the cohort map in figure 1 using Griffiths' average values of a = 0.048 and c = 0.75. At the end of 1953, of a population of 400 children aged 0–3 years, 78 per cent are still susceptible to measles, and 22 per cent are immune.

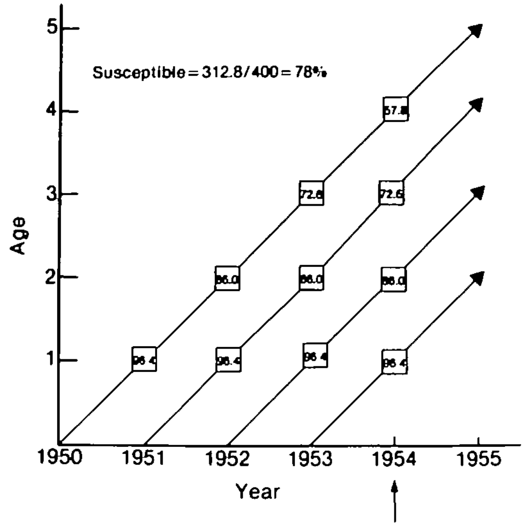

FIGURE 1. Cohort map of susceptibility experience of four simulated cohorts, each containing 100 infants. The values in the boxes along each diagonal line represent cumulated susceptibility within the cohort. The total population susceptibility at the end of 1953 is 96.4 + 86.0 + 72.6 + 57.8 = 312.8/400 = 78 per cent.

In reality, the 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 the deaths due to measles in a given cohort because of their rarity (0.01 per cent mortality), assumes that people immune and susceptible to measles have similar death rates, and assumes that immigrants have the same infection experience as natives given the global endemicity of measles. For example, if a cohort grows in size by 0.05 per cent by immigration, the immunes and susceptibles can be corrected proportionately for the increase. Likewise, as the population of 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 theoretic basis for the computer model.

Construction of the computer model

The aim of the model is to establish the percentage of the US 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 macroepidemiologic 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 preceding the immunization program.

The year 1965 was chosen as the first year of the immunization program, and consequently 1964 is the prevaccine year. Knowing that of all adults over the age of 20 years, 99 per cent were immune by infection with wild virus (4) in the prevaccine era (1964), it remains only to fill in the infection experience of the 19 youngest birth cohorts to get a full cross-sectional picture of the population at the end of 1964.

Birth cohorts beginning in 1946 are exposed to three possible types of measles immunity—infection, a combination of infection 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 years. For the 1946 cohort, the percentage of the population susceptible at the age of 10 is then linearly decremented to reach 1 per cent by age 20. In the remaining cohorts (1947–1963), 90 per cent of this decline in susceptibles older than 10 years is set to occur by age 20, with the last 10 per cent distributed evenly until fadeout.

The 1964 cohort is the first to be immunized at the start of the program in 1965. Thus, the 1964–1982 cohorts are exposed to both natural measles and vaccination. Their immunity induced by wild virus is calculated by the linear measles function from birth to the end of age nine, at which point it retains the value of $\psi(9)$ for ages 10 and over. The value of the constant a is 0.041 from 1946 to the end of 1961, as described by Griffiths, and was 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, $a = 0.011$; 1982, $a = 0.010$. Age in years is represented by t, and c equals 0.75. Immunity by vaccination begins in 1965 for the one-year-old children born in 1964, and all subsequent cohorts are immunized at the age of 12 months. The total immunity of these cohorts is the sum of the immunity induced by vaccine and the immunity induced by natural infection.

Total measles fadeout was declared January 1, 1983. The 1983 and later cohorts are exposed to measles vaccination at age one year; because endemic measles ceases to exist and the infection function equals zero, these cohorts derive their immunity only from vaccination.

In summary, the 1946–1963 cohorts experience infection-induced immunity, the 1964–1982 cohorts become immune by both infection and vaccination, and all subsequent cohorts are immunized artificially by vaccination. The model may be summarized by the cohort map in figure 2.

Utilization of the computer model

A population matrix was constructed using US population data from 1946 to 1981 (5–7). 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 to 1949. This population matrix was

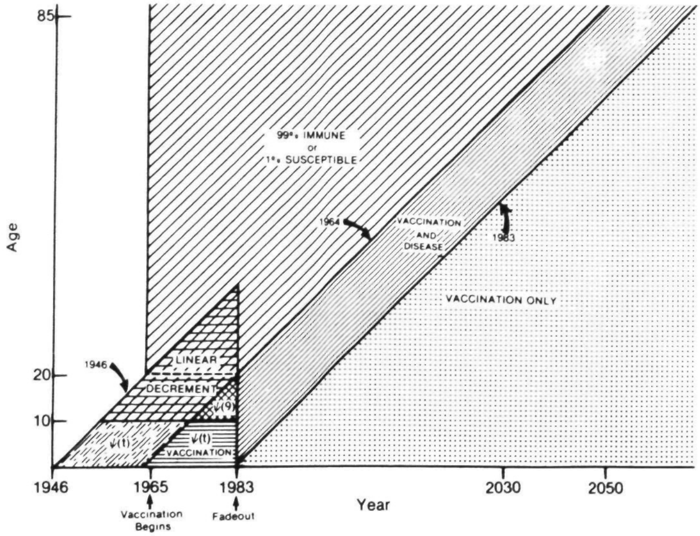

FIGURE 2. Cohort map of computer model. The 1946–1963 cohorts are exposed to disease calculated by $\psi(t)$ to the age of 10, and linearly decremented thereafter. Beginning in 1965, the cohorts from 1964 (vaccinated at age one in 1965) to 1982 are exposed to vaccination of all one-year-olds and to natural measles $\psi(t)$. All subsequent cohorts receive vaccination only.

then extended to the year 2050 using the latest life table data, that of the year 1978 (8) with the 1978 birth rate of 15.8 per 1,000 (9). The matrix was truncated so that age 85 was the end point, since 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 those aged 84–84.99 years.

All birth cohorts beginning in 1946 were then moved through time by 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 each 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:

1. The immunization program begins in 1965 with a 50 per cent vaccine coverage of one-year-olds that augments 10 per cent per year for four years until 1969 when the vaccine coverage is 90 per cent. This is based on a vaccine efficacy of 95 per cent and a vaccination rate of 95 per cent ($0.95 \times 0.95 = 0.90$).

2. Children receive vaccine at the age of 12 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 for simplicity.

3. January 1, 1983, is the fadeout time for indigenous measles in the United States.

4. Twenty years after fadeout, i.e., in

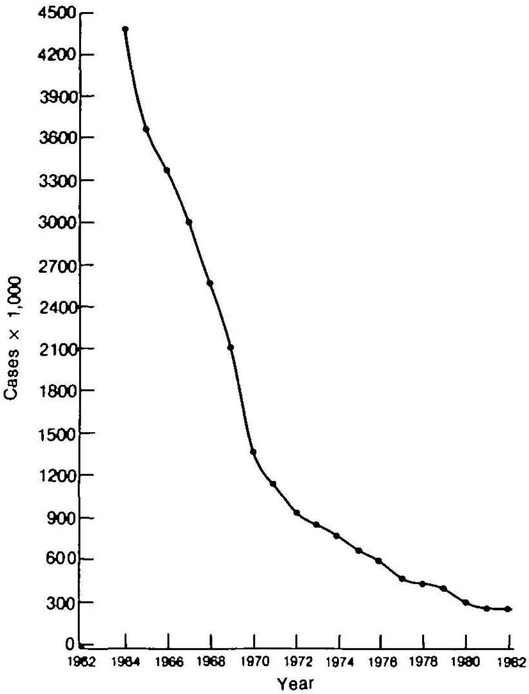

FIGURE 3. Measles cases as predicted by the computer model. The prevaccine year of 1964 has 4,371,824 measles cases. The model describes a 94.4 per cent reduction of cases to 243,913 cases in 1982.

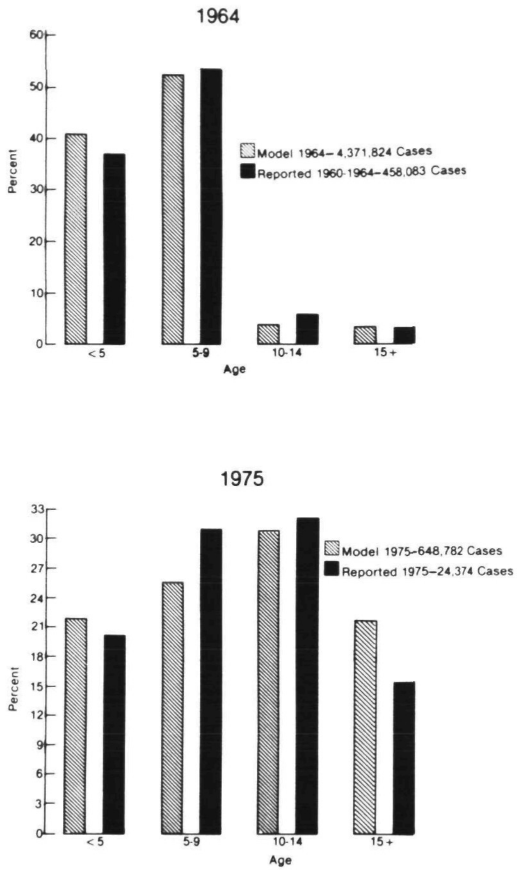

FIGURE 4. Age distribution of measles—computer model compared with reported data, 1964 and 1975; 458,083 cases were reported in 1964, with the age distribution representing that of the years 1960–1964 (10).

the year 2003, because 10 per cent of childbearing women would be susceptible to disease, 10 per cent of newborns have no benefit of maternal immunity and are susceptible for the first six months of life.

5. Waning immunity (secondary vaccine failure) in immunized individuals does not occur.

The computer program was written in Fortran IV and processed on an Amdahl V7A central processing unit. The graphs were drawn with the aid of a Statistical Analysis System Institute graph package (SAS Institute, Inc., Cary, NC).

RESULTS

Incidence of disease

The number of cases of measles in the prevaccine year of 1964 is estimated to be 4,371,824. This declines 94.4 per cent to 243,913 cases prior to total fadeout in 1982 (figure 3).

Age distribution

In 1964, the model predicts 40.6 per cent of the cases to occur at less than five years of age, 52.4 per cent between the ages of five and nine, 3.8 per cent between the ages of 10 and 14, and 3.2 per cent at greater than 15 years of age (figure 4). This is compared with the 1960–1964 (10) reported data of 37.2, 52.8, 6.5, and 3.4 per cent, respectively. Also shown in figure 4 is the comparison between the model and reported data for 1975 (11, 12).

Susceptibility

The cross-sectional susceptibility to

measles measured as a percentage of the population in each age group is shown in figure 5. The effect of the immunization program is to distribute the susceptibles through the age groups with time. Figure 6 shows the change in the percentage of the population susceptible to measles from the prevaccine era to the year 2050. As can be seen, 10.6 per cent of the population is susceptible to measles in 1964, and these susceptibles consist mainly of children under 10 years of age. With the onset of the immunization program, the percentage of the population susceptible falls very quickly to "bottom out" in the years 1978–1981 at 3.1 per cent. Despite absence of disease, the proportion of the population susceptible to measles starts to climb in 1982 by about 0.1 per cent per year or by between 220,000 and 300,000 new susceptible persons each year to reach the prevaccine level of 10.6 per cent by the year 2045 and 10.9 per cent by the year 2050.

Discussion

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. It shows that measles had its peak incidence at ages three to four and that over 90 per cent of children were immune by 10 years of age. This is very similar to the results of the survey conducted by the Epidemic Intelligence Service in Atlanta, Georgia, in 1961 and to other US data which demonstrate that in the prevaccine era, measles incidence peaked in children three to four years old with at least 90 per cent naturally immune by 10 years of age (13). With 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 theoretic number of cases expected in 1964 (prevaccine year) as well as the age distribution of the cases (10). 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 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 0.054 from 1962 to 1969 as described by Griffiths, a was given a value of 0.050 from the period 1962 to 1964. From 1964 onward, 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 1964 to 1981 which was projected to the year 2050 by means of 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 immunization program. The initial vaccine coverage of 50 per cent that augments 10 per cent per year to 90 per cent in 1969 represents a vaccine efficacy of 95 per cent and a vaccination rate of 53, 63, 74, 84, and 95 per cent of the population, respectively. 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

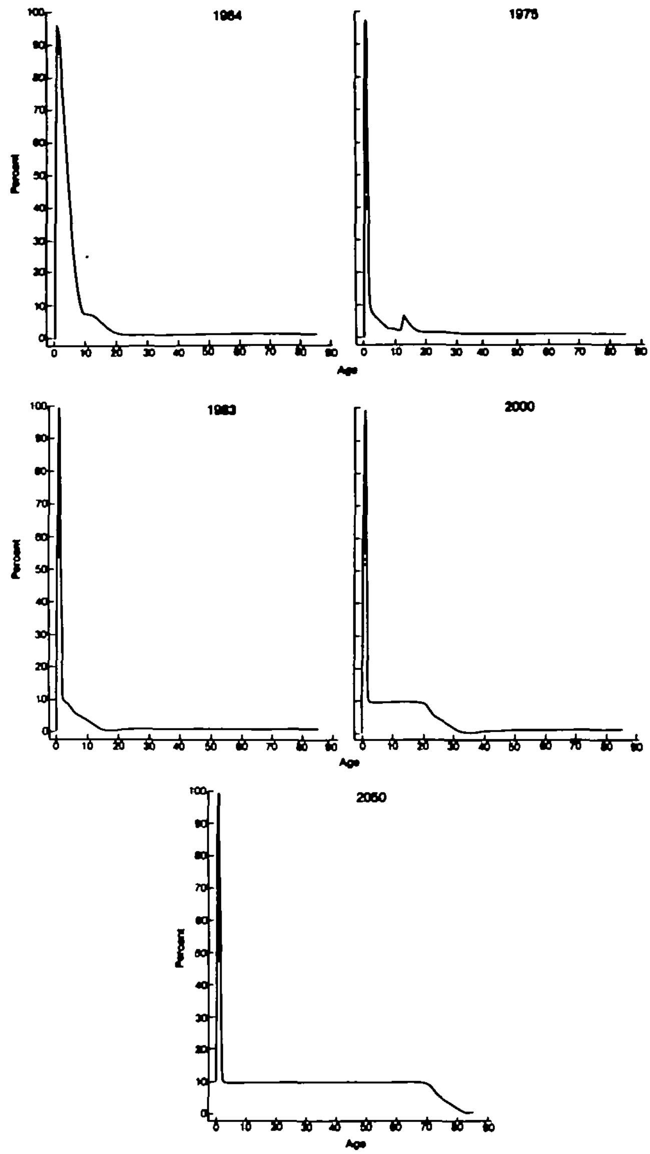

FIGURE 5. Cross-sectional measles susceptibility. The model demonstrates that in the prevaccine year of 1964 most susceptibles were children younger than 10 years of age. The total population susceptibility, or the area under each curve, decreases in 1975 and 1983, but increases in the years 2000 and 2050, with susceptibility redistributed to all age groups.

predicted by the model should be adjusted to account for the difference in the small number of children between 12 and 15 months who in reality are immunized at 15 months. The January 1, 1983, fadeout for indigenous measles in the United States is for practical purposes a reflection of the situation at this writing (14). Although 10 per cent of the newborns after 2003 were assigned as susceptible but only theoretically at risk, the group itself represents a very small percentage (about 0.15 per cent) of the US 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.

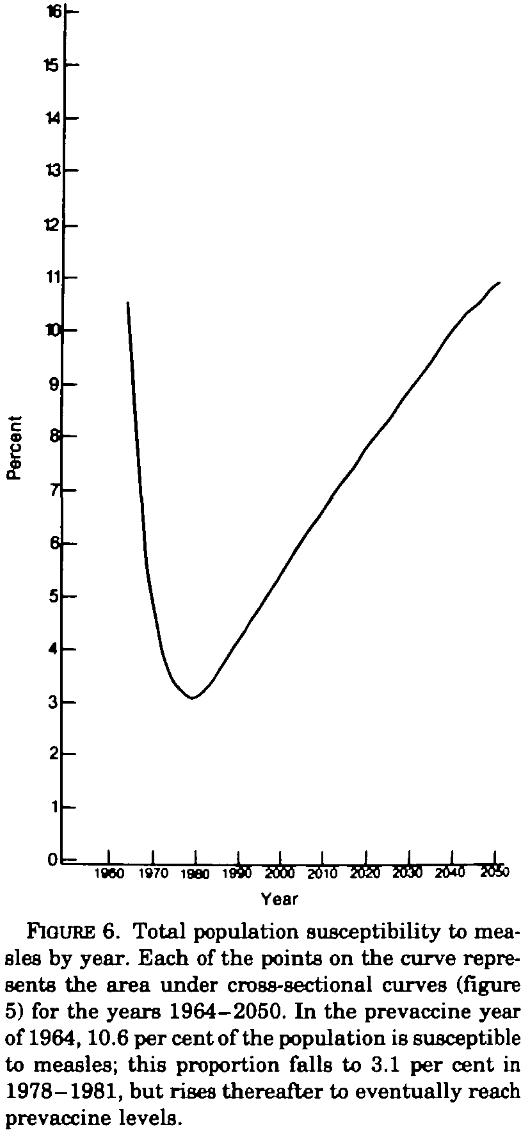

FIGURE 6. Total population susceptibility to measles by year. Each of the points on the curve represents the area under cross-sectional curves (figure 5) for the years 1964–2050. In the prevaccine year of 1964, 10.6 per cent of the population is susceptible to measles; this proportion falls to 3.1 per cent in 1978–1981, but rises thereafter to eventually reach prevaccine levels.

The objective of the model is to examine the change in balance between immunity and susceptibility in the pre- and post-vaccine eras. What has not been previously quantified and, in the author's opinion, what is the most crucial finding, is that 10.6 per cent of the population was susceptible to measles in the prevaccine era. Susceptibility is calculated through its mirror image of infection and must be validated in the same way. By predicting 10 times the reported cases in the prevaccine era when only one tenth of the cases were reported (10), as well as the exact age distribution of these cases, the total population susceptibility of 10.6 per cent appears valid. The long-range outcome of 10.9 per cent susceptibility is implicit in the initial model assumptions, and is for the most part a simple derivation of the 90 per cent vaccine coverage offered by the measles elimination program. Its importance lies only in the context of prevaccine susceptibility—if 30 per cent of the prevaccine population was susceptible, a totally different perspective of the changing balance of immunity and susceptibility would be cast. The model should thus be viewed as descriptive rather than predictive, and shows how the measles elimination program alters the balance of nature.

The fact that prior to fadeout in 1982 the model lists 243,913 cases of measles, as opposed to the actual full reporting of about 1,700 cases (14), does not invalidate the model or the message. Griffiths' linear infection function describes the behavior of the wild measles virus in a population, and cannot expect to account for the artificial interruption of transmission (by school exclusions, case surrounding, etc.) that is characteristic of the elimination program. The 243,913 cases in the year prior to fadeout should only be regarded with respect to the effect on population susceptibility. If all these cases in 1982 were misclassified as susceptible to infection when really immune, the percentage of the population susceptible in that year would be reduced from 3.2 per cent to 3.1 per cent. Thus, the effect of these residual cases on total susceptibility is small.

An advantage to this modeling approach in studying measles susceptibility is its independence of incomplete measles reporting. In 1982, Fine and Clarkson (2) 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 the present study avoids these issues by assuming a priori that the childhood population contracts measles in a prescribed way.

Implications

The computer simulation describes the effect of the measles elimination program on the percentage of the US population susceptible to measles. It is clear that the success of the current program in the United States is due not only to a relatively high vaccine coverage of 90 per cent in young susceptibles but to the almost complete natural immunity of at least 99 per cent in the adult population, which together reduce the numbers susceptible to measles enough to induce fadeout. As natural immunity is slowly replaced by the 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 (15–18). 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 20 years of age (17), over 25,000 measles deaths could occur.

Can the susceptibility levels rise to the predicted figure of close to 11 per cent? If measles vaccine technology does not change and measles remains endemic in the rest of the world with no protection from importation for US residents, sporadic infection 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 per cent (19–21). Although difficult to extrapolate this figure to a macroepidemiologic setting, 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 reaccumulated. However, if measles were eliminated globally, or the US population were protected completely from reintroduction, the number of susceptible people would accumulate to about 11 per cent, but be irrelevant because of the absence of virus to incite disease. Public health strategies for the future clearly imply continuing improvement of the childhood vaccination and seroconversion rates as well as the institution of methods to protect the ever-growing susceptible population from measles contact.

Conclusion

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 population susceptibility may eventually reach the prevaccine level despite the measles elimination program, and that with every new year, the US population will contain over 220,000 more persons susceptible to measles. Although great benefits have been achieved, the challenge of the future is to preserve the gain for today's younger generation and the generations of tomorrow.

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