

ENDEMIC DISEASE IN HOST POPULATIONS
WITH FULLY SPECIFIED DEMOGRAPHY

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Abstract

This study explores the relationship between the demographic structure of a host population, specified by complete age-specific maternity and mortality schedules, and the epidemiology of an aerogenically transmitted infectious disease following an S.I.R. pattern. A fully age-structured model with interdependent dynamic demographic and epidemiologic systems is developed, and its behaviour is explored with simulation studies. The impact of host population demography upon the effectiveness of immunization programs is also examined.

ENDEMIC DISEASE IN HOST POPULATIONS WITH FULLY SPECIFIED DEMOGRAPHY

1. INTRODUCTION

Directly transmitted childhood infectious diseases such as measles, rubella and diphtheria have received a great deal of attention from mathematicians and population biologists (see, for example, Kermack and McKendrick 1927; Anderson and May 1983; Hethcote 1976; Dietz 1981). Most of the deterministic models of infectious disease transmission dynamics which have been proposed during the past six decades have consisted of systems of three to five nonlinear, ordinary or partial differential equations, although some researchers have used systems of integral equations. Common to virtually all of these models, however, is a set of simplifying assumptions which, in essence, remove all demographic structure from the host population. With rare exception, it is generally assumed that the host population is not growing, that there is no age variation in the risk of death, either from the disease in question or from any other cause, and that the number of births (and so of deaths) is determined by an exogeneously set crude birth rate rather than by a demographically more informative age-specific fertility schedule. While these assumptions may be justified when one considers an epidemic which occurs over a time period much shorter than that in which demographic processes operate, the validity of these assumptions is questionable when attention turns to the behaviour of endemic diseases, which, by definition, are present in the host population for an extended period. Thus there remains unaddressed the question of how the demographic structure of a host

population affects the epidemiology of an endemic infectious disease such as measles or rubella.

Recently, some researchers have explored the effect on disease transmission dynamics of relaxing the restrictive assumptions which underlie standard models of epidemic behaviour, either by allowing the population growth rate to be positive (May and Anderson 1985; McLean 1986), or by introducing age-variation in the force of infection (Hoppenstedt 1974; Anderson and May 1985). Yet the imposition of an arbitrary population growth rate or of an age-dependent force of infection still begs the question of how the demography of the human host population affects disease transmission dynamics, since the maternity and mortality schedules and the population growth rate consistent with those schedules remain unspecified.

The role played by the demographic structure of the host population in determining the equilibrium endemic disease incidence and the age pattern of infection is especially important when considering the design of immunization programs for childhood infectious diseases in developing countries. The standard simplifying assumptions of no population growth and of no mortality until a very old age or of a force of mortality which is invariant by age, are structurally important to the model and its predictions since these assumptions dictate the age distribution of the host population (Coale 1957; Coale 1972); yet these assumptions, and the demographic structure they imply, are clearly unrealistic for most developing nations. Furthermore, many diseases such as measles exhibit extremely high case-fatality among young children in developing countries, a point which is often ignored in extant models of epidemic behaviour. The control or elimination of such a disease would have an impact upon the demography of the host population as mortality patterns, and hence population age structure, change. In turn, the change in the demographic structure of the host population may alter the incidence both of the disease in question and of other diseases.

period. Finally, it is assumed that the host population is demographically stable, and once perturbed, returns to another demographically stable age distribution.

In the long run, the model can be described by two equilibria: the demographic equilibrium, embodied in the population's stable growth rate, r , and the proportion of individuals at each age a , $c(a)$, and the epidemiologic equilibrium, characterized by the *proportion* of the population at each age a who are susceptible, $x(a)$, infected, $y(a)$, and immune, $z(a)$. If the disease becomes established endemically in the population at demographic and epidemiologic equilibrium, then $0 < y(a) < 1$ for some a .

In classical dynamic models of stable populations, the age distribution of the population is completely determined by the demographic parameters of the population: the maternity schedule, $m(a)$, and the mortality schedule, $\mu(a)$, which together determine the equilibrium population growth rate (Lotka 1931; Coale 1957; Coale 1972). If there is case-fatality associated with the disease, then $\mu(a) = \mu'(a) + y(a) \alpha(a)$, where $\mu'(a)$ is the risk of death from all causes other than the disease in question, and $\alpha(a)$ is the age-specific case fatality rate. The dependence of the number of births at time t , $B(t)$, upon the past history of births and deaths in the population is given by

$$B(t) = \int_0^{\omega} B(t-a) e^{-\int_0^a \mu(a-\tau) d\tau} m(a) da, \quad [1]$$

where ω is the oldest age reached in the population. The number of people age a in the population at time t follows a trajectory which depends on the pattern of births in the population and upon the mortality schedule,

$$N(a, t) = B(t) e^{-ra} e^{-\int_0^a \mu(a-\tau) d\tau}, \quad [2]$$

and the total population size is $N(t) = \int_0^{\omega} N(a,t) da$. The birth rate, b , is given by

$$b = \frac{B(t)}{N(t)} = \frac{1}{\int_0^{\omega} e^{-ra} e^{-\int_0^a \mu(a-\tau) d\tau} da}, \quad [3]$$

and the stable age distribution of the population is given by

$$c(a) = b e^{-ra} e^{-\int_0^a \mu(a-\tau) d\tau}. \quad [4]$$

Finally, consistent with the population's maternity and mortality schedules is the stable growth rate, r , which satisfies the transcendental equation

$$1 = \int_0^{\omega} e^{-ra} e^{-\int_0^a \mu(a-\tau) d\tau} m(a) da. \quad [5]$$

The dynamic of population growth described by equations [1]-[4] is well known, and applies to any population with time invariant maternity and mortality schedules; the system describes the allocation of individuals among ages, expressed in terms either of the proportion of the population at age a , $c(a)$, or the number of people age a at time t , $N(a,t)$. In contrast, the epidemiologic system determines the allocation of individuals at each age a , $N(a,t)$, among the susceptible, infectious and immune subpopulations.

The number of susceptible individuals age a at time t , $X(a,t)$, depends upon $\lambda(a',t)$, which is the risk that an individual is infected at age a' , $a' < a$, given that he was susceptible (the age-specific force of infection), and upon $\theta(a',t)$, which is the risk that an individual is

immunized at age a' , $a' < a$, given that he was susceptible (the age-specific force of immunization):

$$X(a,t) = N(a,t) e^{-\int_0^a \lambda(a-\tau,t-\tau) d\tau} e^{-\int_0^a \theta(a-\tau,t-\tau) d\tau} \quad [6]$$

Equation [6] thus gives the number of people age a at time t who have not yet been infected and who have not yet been immunized.

The people age a who are infectious at time t are those people who were infected at some age $a-\tau$, at time $t-\tau$ (where $0 < \tau < d$, and d is the maximum duration of infection), of whom there are $\lambda(a-\tau, t-\tau)X(a-\tau, t-\tau)$, and who, while infectious, did not die from the disease or from some other cause, and who had not yet recovered by age a :

$$Y(a,t) = \int_0^d \lambda(a-\tau,t-\tau) X(a-\tau,t-\tau) e^{-\int_0^\tau \mu'(a-\sigma,t-\sigma) d\sigma} e^{-\int_0^\tau \alpha(a-\sigma,t-\sigma) d\sigma} e^{-\int_0^\tau \chi(\tau-\sigma) d\sigma} dt. \quad [7]$$

Thus, in equation [7], the first exponentiated term gives the probability that the individual does not die from some other cause while infectious before age a , the second exponentiated term gives the probability that he does not die from the disease in question before age a (in the absence of case-fatality, this term reduces to unity), and the third exponentiated term gives the probability that he does not recover from the disease before age a .

Finally, since every individual in the population must be susceptible, infectious or immune, the immune population age a at time t , $Z(a,t)$, is given by

$$Z(a,t) = N(a,t) - X(a,t) - Y(a,t); \quad [8]$$

the immune individuals, $Z(a,t)$ are those who were rendered immune by immunization before age a , or by recovery from the disease before age a , and who have not subsequently died from some other cause.

The distribution of individuals age a among the three epidemiologic classes is thus dictated by the epidemiologic parameters of the disease: $\gamma(d)$, the duration-dependent recovery rate; $\theta(a,t)$, the age-specific risk of immunization; and $\lambda(a,t)$, the age-specific force of infection. $\gamma(d)$ is a characteristic of the disease itself, and therefore is assumed invariant among host populations. $\theta(a,t)$ is exogeneously determined and thus need not depend upon the structure of the host populations. Therefore the link between the demographic and epidemiologic systems must be embodied in the force of infection function, $\lambda(a,t)$.

Let $\varphi(t)$ be the rate of contacts made by each member of the population with other population members at time t ; a share $y(t)=Y(t)/N(t)$ of these contacts will be with infected individuals. Let β be the fraction of encounters which result in a new infection if the encounter occurs between a susceptible individual and an infectious individual. Then, for $\Delta t > 0$ and small,

$$\lambda(t) \Delta t = 1 - [1 - \beta y(t)]^{\varphi(t) \Delta t} \quad [9]$$

gives the probability of becoming infected during the interval Δt . Expanding this and letting Δt approach zero yields an approximate expression for the instantaneous force of infection:

$$\lambda(t) \cong -\varphi(t) \ln [1 - \beta y(t)] \quad [10]$$

Since $y(t) = \int_0^{\omega} y(a,t) c(a,t) da$, the dependence of $\lambda(t)$ on the age structure of the host population, $c(a,t)$, is clear, even in the simplest case in which $\lambda(t)$ is age-invariant. If the force of infection is written as a function of both age and time, then

$$\lambda(a,t) \cong - \int_0^{\infty} \varphi(a,b,t) \ln \left[1 - \beta(a,b)c(b,t) \frac{Y(b,t)}{N(b,t)} \right] db, \quad [10']$$

where $\varphi(a,b,t)$ is the number of encounters between a person age a and a person age b at time t , $\beta(a,b)$ is the transmissibility of infection from an infectious person age b to a susceptible person age a (given an encounter between two such people), and $Y(b,t)/N(b,t)$ is the proportion of individuals age b who are infectious at time t .

In this model, the force of infection, $\lambda(t)$ or $\lambda(a,t)$, depends upon the age structure, $c(a,t)$, of the host population. Thus changes in the age structure of the host population, stemming from changes in maternity, mortality or migration patterns, may induce corresponding changes in the pattern of disease transmission. If the disease is endemic in the population at equilibrium, then each infectious individual creates, on average, e^{rd} new infections while infectious.

3. BEHAVIOUR OF THE BASIC MODEL

Because of the complex, nonlinear relationships among the expressions for $N(a,t)$, $X(a,t)$, $Y(a,t)$ and $\lambda(a,t)$, analytic solution of the system for the equilibrium distribution of individuals among epidemiologic class by age, and for the equilibrium value of the force of infection and incidence disease is difficult. Closed-form expressions for the effect of an arbitrary change in the maternity, mortality or immunization schedules on the demographic and epidemiologic equilibria are equally intractable. Thus the behaviour of the system is examined through a series of simulation studies which yield *qualitative* insights into the dynamical behaviour of the system. Central to the simulation studies are two questions: does the demography of a host population affect the transmission patterns of childhood infectious disease in that population, and are disease control efforts such as immunization programs equally effective in populations with different demographic structures. The

former question is addressed in this section, while the latter is addressed in the next section.

Three host populations were created with identical mortality schedules, $\mu'(a)$, drawn from the Coale-Demeny West model life table with an expectation of life at birth of 55 years (Coale and Demeny 1984). The fertility schedules, $m(a)$, of the three populations were scalar multiples of each other, and produced populations with different age structures and growth rates: $r=0.037$ (Population 1), typical of many developing countries; $r=0.013$ (Population 2); and $r=0.001$ (Population 3). Individuals age 10 years and older were classified by single year of age, while children less than 10 years old were indexed by two-week age groups. No one survived past age 80. The simulation proceeded in two-week time intervals. In the absence of infectious disease, the simulation model reduces to a standard population projection model based on a Leslie matrix for biweekly projection.

The epidemiologic parameters of the system describe the spread of the infectious organism through the host population. For simplicity, the age-invariant formulation of $\lambda(t)$ is employed. ϕ_t is set at 14 contacts per two-week interval (qualitatively similar results arise from setting ϕ_t at 7 or 21), and β is set at 0.95, corresponding to a highly infectious disease such as measles. It is assumed that all individuals are infected for exactly two weeks, and that there is no case fatality associated with the disease, so $\mu(a)=\mu'(a)$.

Starting with an arbitrary initial populations and an infection seed of one percent of the population less than 10 years old, each simulation model was run for 50 years (1300 biweekly projection periods), so that the system could settle to its equilibrium demographic and epidemiologic configuration. Epidemiologic equilibrium was defined as disease incidence and age patterns of infection that displayed regular patterns (constant or periodic) for at least 10 years. Demographic equilibrium was defined by a stable age distribution.

In the absence of immunization programs, the three host populations exhibit very different disease transmission patterns (Table 1). The slower the growth of the host population, the lower the equilibrium incidence of the disease. For example, the most

rapidly growing population (Population 1) has an equilibrium incidence of 15.2 cases per 10,000 population, whereas Population 3 exhibits an equilibrium incidence averaging 6.4 cases per 10,000 population. This difference stems from the different rates at which susceptible individuals enter the populations: a slowly growing population corresponds to a slow infusion of susceptibles into the population.

There are also pronounced differences in the age pattern of infection and in the cohort mean age at infection in the populations (Figure 1). It is important to distinguish between the cohort mean age at infection and the period mean age, since the period mean age will always be lower than the cohort mean age in a growing population. Thus the period mean age at infection will understate the age at which a true birth cohort of children is infected. The cohort mean age at infection in Population 3 is nearly 1.5 years greater than in Population 1: the lower the incidence of the disease in the population, the lower will be λ_t and so the greater will be the cohort mean age at infection.

Host populations with different demographic structure also vary in the stability of the epidemiologic equilibrium configurations. The population which is growing rapidly (Population 1) settles to a constant equilibrium level of disease incidence, while the population which is growing very slowly (Population 3) displays, at equilibrium, the regular cycles characteristic of a mild, recurrent epidemic, oscillating with a period of 2.6 years between 5.5 cases per 10,000 population and 7.6 cases per 10,000 population per year.

4. THE BASIC MODEL WITH IMMUNIZATION

It is clear that the behaviour of an infectious disease, as modeled here, is affected by the demography of the host population. In order to explore whether the effectiveness of immunization programs also varies with host population demographic structure, each

population was subjected to three immunization programs after reaching an initial demographic-epidemiologic equilibrium. Each population was followed for 45 years after the introduction of an immunization scheme in year 5, thereby allowing it to settle to its post-immunization equilibrium. The effectiveness of each immunization program was expressed in terms of its impact on equilibrium disease incidence, cohort mean age at infection, and whether the equilibrium configuration displayed constant or cyclical values.

Three immunization programs were considered. Children eligible for immunization were defined as *susceptible* children more than 36 weeks (nine months) but less than five years old; children less than 36 weeks old were deemed protected by maternal antibodies and were neither at risk for infection nor for immunization. The immunization schedule, $\theta_{a,t}$, specifies the annual risk of immunization for a susceptible individual age a at time t ; its value was set at 0.1 for ages 36 weeks to 5 years in the first program, 0.2 in the second program, and 0.3 in the third.¹

In Population 1, the immunization programs reduce the equilibrium incidence of infection (Figure 2): immunizing 30 percent of susceptible children between the ages of 36 weeks and 5 years each year, cuts the incidence of the disease in the population in half. Corresponding to this fall is a rise in the *cohort* mean age at infection for the cohort born 25 years after the introduction of the immunization program, to 3.21 years. In essence, then, an immunization program works in much the same way as does a reduction in fertility, reducing the growth rate of the supply of susceptibles to the population.

The result of reducing the effective rate of growth of the susceptible population is further illustrated by the trajectory followed by the disease incidence. The introduction of an immunization program produces damped oscillations in disease incidence following an

¹ $\theta_{a,t}$ is *not* the same as the coverage rate of immunization. In the absence of disease, for example, an annual risk of immunization of 0.2 between ages 36 weeks and 5 years would imply that, by age 5, 62 percent of each birth cohort would be immunized; setting $\theta_{a,t}$ at 0.3 would imply, in the absence of disease that by age 5, 78 percent of each birth cohort would be immunized. In the presence of disease, the relationship between $\theta_{a,t}$ and would differ since $\theta_{a,t}$ refers only to susceptible children.

initial drop immediately after program implementation. The more extensive the immunization program, the greater is the initial reduction in disease incidence, the greater is the amplitude of the subsequent oscillations, and the longer is the period of the oscillations.

In Population 2, the effect of immunizing 10 percent or 20 percent of eligible children each year is similar to that observed in Population 1: a sharp initial drop in disease incidence, followed by damped oscillation for 25 years, until a new equilibrium is reached (Figure 3). In contrast, the immunization of 30 percent of eligible children produces an unanticipated trajectory for disease incidence. Less than three years after the implementation of the immunization program, disease incidence falls from 9.0 cases to less than 1 case per 10,000 population, suggesting that the immunization program is indeed effective and might have the potential for eliminating the disease from the population. Yet, only 5 years after the introduction of the immunization program, disease incidence rises to 13.3 cases per 10,000 population, nearly 50 percent higher than the pre-immunization level of disease incidence. In contrast, the immunization of 40 percent of eligible children each year induces an initial drop which is sufficiently large to eradicate the disease from the population shortly after the introduction of the immunization program.

In Population 3, which is growing at 0.001 per annum, the introduction of a program in which 20 percent of eligible children are immunized each year produces epidemic cycles which are not damped, but to the contrary, exhibit increased amplitude at each cycle until, 20 years after the introduction of the immunization program, the disease is finally eradicated from the population (Figure 4). A more ambitious program, involving the immunization of 30 percent of eligible children each year, is sufficient to eliminate the disease from Population 3, but not from Populations 1 and 2.

Thus, in this stylized model of three host populations which differ only in their maternity patterns, the behaviour of a childhood infectious disease and the effectiveness of immunization programs depends upon the demography of the host population. The demographic structure of the host population determines not only the pace at which

susceptible individuals enter the population, but also affects the force of infection, thereby influencing both the age pattern of infection and disease incidence in the population.

5. CONCLUSION

It appears from this study that the demography of host populations may be an important factor underlying the endemic and epidemic behaviour of childhood infectious diseases, especially in developing countries in which population growth, infant and child mortality, and fertility are high, and the mean age at infection is low. The demographic structure of the host population can also have a strong influence on the effectiveness of immunization programs. Thus studies of childhood infectious disease transmission dynamics and immunization policy which assume away the demography of the host population are in danger of ignoring an important element of the problem. While the inclusion of fully specified demographic structure in models of infectious disease transmission renders them analytically intractable, computer simulation can be used instead to gain insights into model behaviour.

Yet another consideration arises from this study. Typically, calculation of the proportion of a population which must be immunized in order to eliminate a disease from that population is an exercise in comparative statics: pre- and post-immunization program equilibrium levels of disease incidence (or equivalently, disease reproductive rate, or density of susceptibles) are calculated, and, if the post-immunization equilibrium index implies that the disease is still endemic in the population, then it is inferred that the immunization program cannot eliminate the disease. The question of *how* the population moves from pre-immunization to post-immunization immunity--the trajectory that, for example, disease incidence follows--is generally ignored. Yet this may explain why, many cases, herd immunity is achieved at lower levels of immunization than is predicted by theory. For example, in Population 2, the immunization of 40 percent of the population is

sufficient to eradicate the disease. Suppose, however, that the incidence of a disease could indeed be negative, so that immunization of 40 percent of children would simply produce damped cycles in disease incidence, eventually settling to an equilibrium, *positive* level of disease incidence. A simple comparative static analysis--calculation of this positive post-immunization incidence--would lead to the erroneous conclusion that this immunization program could not eliminate the disease from the population. Lost to such an analysis is the fact that there is no trajectory by which the positive post-immunization equilibrium incidence can be attained. Hence evaluation of immunization programs requires not only a consideration of pre- and post-immunization equilibria, but also of the trajectories which the population follows in moving from one equilibrium to the other.

TABLE 1. Demographic and epidemiologic characteristics of three host populations and pre- and post-immunization equilibrium.

	immunization program $\theta(a)$	disease incidence per 10,000	period mean age at infection	cohort mean age at infection
Population 1	0.0	15.2	2.23	2.46
	0.1	12.5	2.58	2.75
	0.2	10.1	2.70	2.93
	0.3	7.7	2.87	3.21
Population 2	0.0	9.0	3.57	3.78
	0.1	7.0	4.22	4.42
	0.2	5.1	4.73	5.02
	0.3	3.6*	5.37*	5.76*
Population 3	0.0	7.5*	3.93*	4.35*
	0.1	5.0*	5.83*	5.92*
	0.2	---	---	---
	0.3	---	---	---

* mean value of cycles

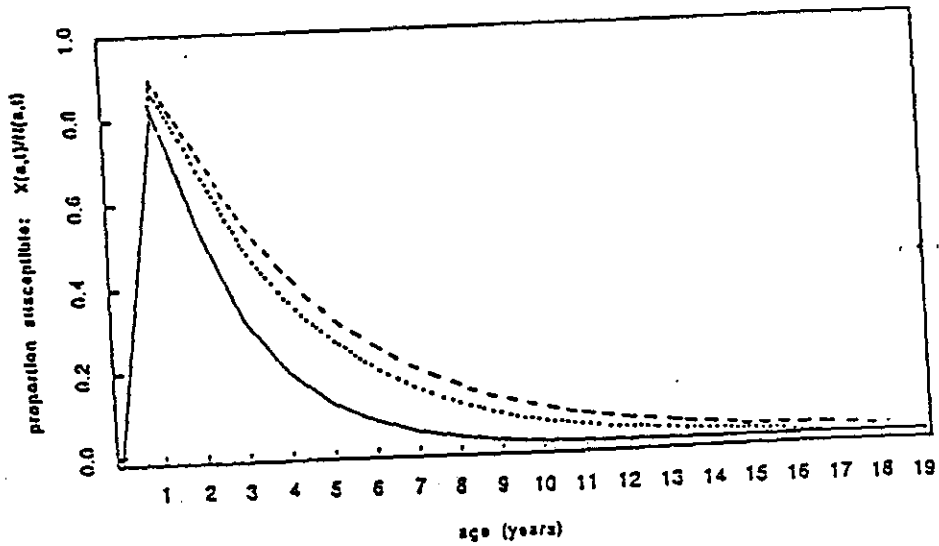


FIGURE 1. Age distribution of susceptible individuals (proportion of individuals susceptible at each age) at epidemiologic equilibrium for three host populations: Population 1 ($r = 3.7$ percent per annum) —; Population 2 ($r = 1.3$ percent per annum) ····; Population 3 ($r = 0.08$ percent per annum) —.

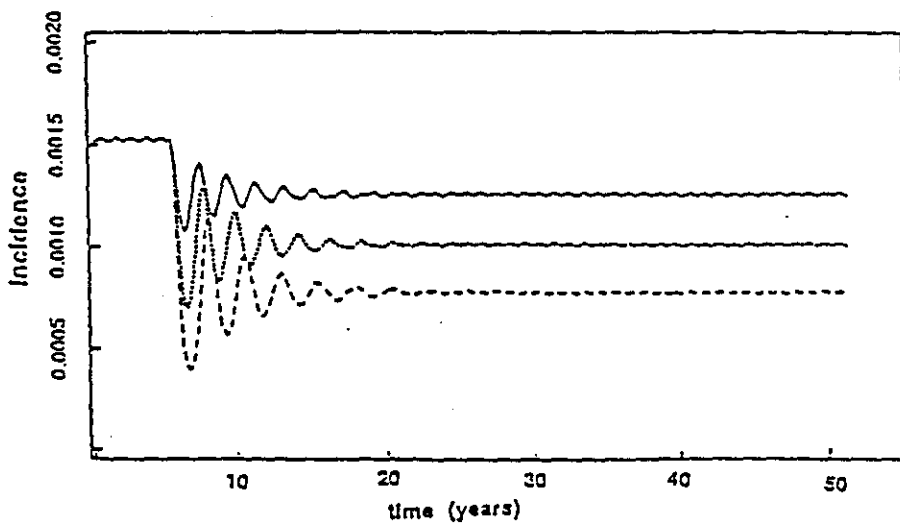


FIGURE 2. Disease incidence for Population 1 ($r = 3.7$ percent per annum) following introduction of an immunization program at year 5. Program level: $\theta = 0.1$ —; $\theta = 0.2$ ····; $\theta = 0.3$ —.

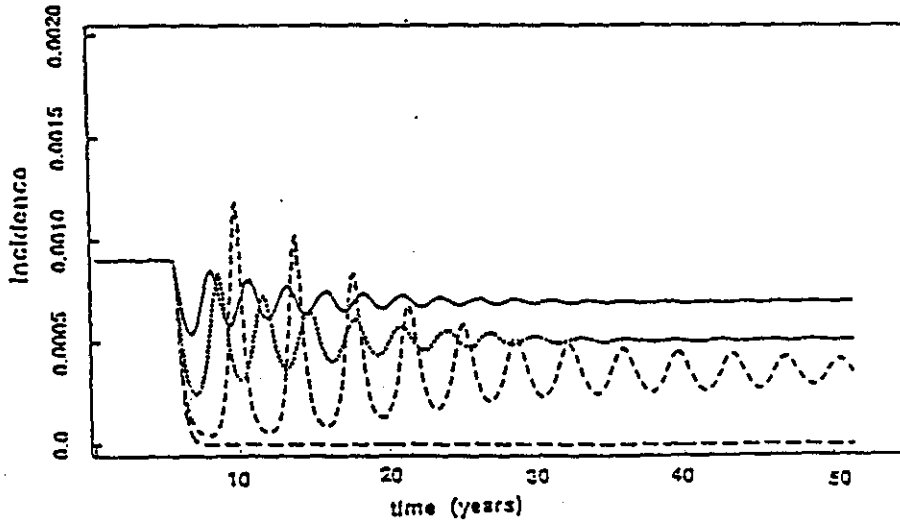


FIGURE 3. Disease incidence for Population 2 ($r = 1.3$ percent per annum) following introduction of an immunization program at year 5. Program level: $\theta = 0.1$ —; $\theta = 0.2$; $\theta = 0.3$ — —; $\theta = 0.4$ — — —.

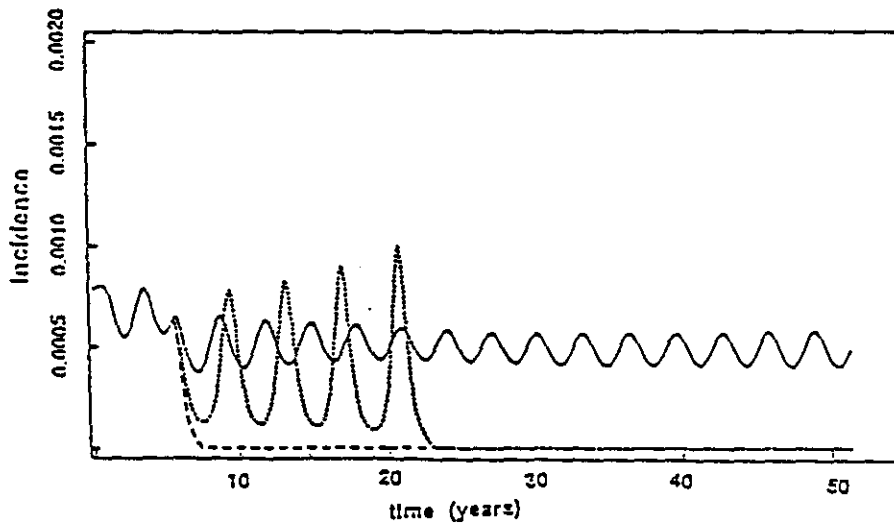


FIGURE 4. Disease incidence for Population 3 ($r = 0.08$ percent per annum) following introduction of an immunization program at year 5. Program level: $\theta = 0.1$ —; $\theta = 0.2$; $\theta = 0.3$ — —.

REFERENCES

1. Anderson, R.M. and May, R.M. 1983. Vaccination against rubella and measles: quantitative investigations of different policies. *Journal of Hygiene, Cambridge*, 90, 259-325.
2. Anderson, R.M. and May, R.M. 1985. Age-related changes in the rate of disease transmission: implications for the design of vaccination programmes, *Journal of Hygiene, Cambridge*, 94, 365-436.
3. Coale, A.J. 1957. How the age distribution of a human population is determined, *Cold Spring Harbor Symposia on Quantitative Biology*, 22, 83-88.
4. Coale, A.J. 1972. *The Growth and Structure of Human Populations*. Princeton: Princeton University Press.
5. Coale, A.J. and Demeny, P. 1984. *Regional Model Life Tables and Stable Populations*, New York: Academic Press.
6. Dietz, K. 1981. The evaluation of rubella vaccination strategies, in *The Mathematical Theory of the Dynamics of Biological Populations, Vol. II*, ed R.W. Hiorns and D. Cooke (New York: Academic Press).
7. Hethcote, H.W. 1976. Qualitative analyses of communicable disease models. *Mathematical Biosciences*, 28, 335-56.
8. Hoppensteds, F. 1974. The General Age-Dependent Epidemic Model, *Journal of the Franklin Institute*, 297, 325-333.
9. Kermack, W.O. and McKendrick, A.G. 1927. A contribution to the mathematical theory of epidemics, *Proceedings of the Royal Society of London, Series A*, 115, 700-721.
10. Lotka, A.J. 1931. The structure of a growing population, *Human Biology* 4, 459-93.
11. May, R.M. and Anderson, R.M. 1985. Endemic infections in growing populations, *Mathematical Biosciences*, 77, 141-56.
12. McLean, A. 1986. Dynamics of childhood infections in high birthrate countries, in *Immunology and Epidemiology*, ed G.W. Hoffmann and T. Hraba, *Lecture Notes in Biomathematics*, 65, 171-97.