Directly Transmitted Infectious Diseases: Control by Vaccination

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light energy in the photosynthetically active range was about 1500 microeinsteins per square meter per second on the surface and about 1 percent of this was transmitted through the rock crust in the zone of the cryptoendolithic lichens.
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Roy M. Anderson and Robert M. May

Observed patterns of human mortality have changed in Europe over the past three centuries, with life expectancy increasing from about 25 to 30 years in 1700 to about 70 to 75 years in 1970 (*1*, *2*). This improvement comes mainly from a decline in deaths from infectious disease; although the phenomenon is still not fully understood, it appears that higher standards of hygiene and nutrition, possibly combined with changes in the genetic structure of human and parasite populations, have acted concomitantly to decrease the pathogenicity of many common disease agents (*1*).

In contrast with this decrease in mortality, the frequency and magnitude of epidemics of disease increased during the 18th and 19th centuries, principally as a result of changing social patterns and the growth of large centers of population in increasingly industrialized societies. The reversal of this trend during the present century is largely due to the development and widespread use of vaccines to immunize susceptible populations against various directly transmitted viral and bacterial diseases (*3*, *4*). Some notable achievements have occurred in the last 50 years. Smallpox has been eradicated worldwide (*5*), and the incidences of diphtheria and paralytic poliomyelitis have declined to very low levels in Europe and North America (*3*).

Many airborne infectious diseases, however, remain endemic throughout most of the developed world, despite the widespread use of vaccines. For example, Fig. 1 shows the history of measles and whooping cough in England and Wales from 1940 to 1979. These two infections remain a hazard to some children in Europe, and in underdeveloped regions of Africa and Asia, where malnutrition is rife, they are a significant threat to life (*6*).

A first step toward the successful control or eradication of a communicable disease is the development of a safe, effective, and cheap vaccine that provides lasting (ideally lifelong) protection. Once this has been done [as it has, for example, for measles (*3*, *6*)], important epidemiological questions remain to be answered. What proportion of the population must be immunized in order to eradicate the disease? What reduction in disease incidence is to be expected from a given age-specific vaccination schedule? What is the effect of vaccination on the average age at which individuals acquire infection, and on the time between epidemics (the "interepidemic period")? This article draws together theory and the extensive data that are available, particularly for measles and whooping cough in Britain, to suggest some answers to these and other, related questions; the answers involve knowledge both of the typical course of infection within an individual [such as the length of the latent period, and the duration of infectiousness (*7*)] and of the overall population biology of the disease agent and its host (*8*–*10*).

The mathematical literature dealing with the design of optimal vaccination programs has expanded rapidly (*11*–*13*). With some notable exceptions (*14*), these insights have had relatively little impact on public health policy. This may be due, in part, to the abstractly mathematical nature of much of this research, to its lack of contact with epidemiological data (*15*), and to the focus on short-term strategies to control isolated epidemics as opposed to long-term national or regional policies to control endemic diseases (*11*). One aim of our article is to

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show how relatively simple models can provide a broad biological understanding of the factors controlling disease persistence and recurrent epidemic behavior (including the changes wrought by specific vaccination programs), and on how they can make detailed contact with data.

Basic Dynamics

There exists a voluminous mathematical literature dealing with epidemics of directly transmitted diseases (*11, 16*). Relatively less attention has been devoted to endemic and recurrent epidemic phenomena, but major advances have been made by Bartlett (*17*) and more recently by Dietz (*18, 19*) and Yorke and co-workers (*8, 20*). In this section, we briefly summarize the main themes of this work; in subsequent sections, we incorporate age-dependent rates of infection and vaccination, and analyze existing data in the light of the theory.

To begin, we assume that the size (or density) of the host population, N, remains roughly constant, or at least changes on a time scale long compared to all other time scales of interest in our epidemiological context. This assumption is reasonable for most populations in western societies. The assumption corresponds to the net input of susceptibles into the population (by births) being roughly equal to the net mortality μN (here μ is the death rate; life expectancy is $1/\mu$). The total population may be divided into susceptibles, infecteds who are not yet infectious (latent), infectious individuals, and those who are recovered and immune; these classes are denoted by X, H, Y, and Z, respectively. Clearly the total population is $N = X + H + Y + Z$. Following conventional lines, we further assume (for this preliminary discussion) that the net rate at which infections are acquired is proportional to the number of encounters between susceptible and infectious individuals, βXY, where β is a transmission coefficient (*21*). Individuals pass from the latent state to the infectious state at a per capita rate σ (such that the average latent period is $1/\sigma$) and recover to join the immune class at a per capita rate γ (where $1/\gamma$ represents the average infectious period). Immunity is taken to be lifelong, as it appears to be for most of the human infections considered below. The assumption that all the rate parameters, β, σ, γ, and μ, are simple constants is clearly artificial, but the resulting model provides a useful basis for subsequent accretion of complexity and realism.

Under the above assumptions, a set of four first-order differential equations describes the dynamics of the infection within its host population (*18, 19*):

$$dX/dt = \mu N - \mu X - \beta XY \quad (1)$$

$$dH/dt = \beta XY - (\mu + \sigma)H \quad (2)$$

$$dY/dt = \sigma H - (\mu + \gamma)Y \quad (3)$$

$$dZ/dt = \gamma Y - \mu Z \quad (4)$$

Adding all four equations gives $dN/dt = 0$, corresponding to the original assumption that N is constant.

may be accurately approximated as $R = \beta X/\gamma$ and $N_T = \gamma/\beta$.

The "intrinsic reproductive rate" of the disease, R_0, may be defined as the value of R in a disease-free population. In the case where all individuals are susceptible (assuming no vaccination), $X = N$; and (*23*)

$$R_0 = N/N_T \quad (7)$$

If the disease can establish itself, then at equilibrium $R = 1$; the equilibrium density of susceptibles, X^*, is equal to the threshold density, N_T (*18, 24*)

Summary. Mathematical models for the dynamics of directly transmitted viral and bacterial infections are guides to the understanding of observed patterns in the age-specific incidence of some common childhood diseases of humans, before and after the advent of vaccination programs. For those infections that show recurrent epidemic behavior, the interepidemic period can be related to parameters characterizing the infection (such as latent and infectious periods and the average age of first infection); this relation agrees with the data for a variety of childhood diseases. Criteria for the eradication of a disease are given, in terms of the proportion of the population to be vaccinated and the age-specific vaccination schedule. These criteria are compared with a detailed analysis of the vaccination programs against measles and whooping cough in Britain, and estimates are made of the levels of protection that would be needed to eradicate these diseases.

The disease will maintain itself within the population provided the "reproductive rate," R, of the infection is greater than, or equal to, unity; R is the expected number of secondary cases produced by an infectious individual in a population of X susceptibles (*18, 19, 22*). For the system defined by Eqs. 1 to 4,

$$R = \frac{\sigma\beta X}{(\sigma + \mu)(\gamma + \mu)} \quad (5)$$

The formal expression, Eq. 5, can be related to the biological definition of R by observing that secondary infections are produced at a rate βX throughout the expected lifetime, $1/(\gamma + \mu)$, of the infectious individual; of these, a fraction $\sigma/(\sigma + \mu)$ will survive the latent period to become the second generation of infectious individuals. The criterion $R > 1$ for the establishment of the disease can equivalently be expressed as the requirement that the population of susceptibles exceed a "threshold density" (*16*), $X > N_T$, with the definition

$$N_T = (\gamma + \mu)(\sigma + \mu)\beta\sigma \quad (6)$$

Thus, in general, Eq. 5 can be reexpressed as $R = X/N_T$. For most of the common diseases in developed countries, the duration of the latent and infectious periods, $1/\sigma$ and $1/\gamma$, is of the order of a few days to a few weeks (Table 1), while $1/\mu$ is of the order of 70 years. Under these circumstances ($\sigma >> \mu$ and $\gamma >> \mu$), Eqs. 5 and 6

Of the parameters determining R, some are specific to the disease agent; examples are the parameters σ and γ, and the component of β that reflects the transmissibility of the disease (often related to the expected life-span of the infective particle or spore in the external environment). Other components of R, such as the density of susceptibles, X, and the component of β that reflects the average frequency of contacts between individuals, vary greatly from one locality to the next depending on the prevailing environmental and social conditions. Even the value of $1/\gamma$ may be influenced by such conditions, since the isolation of infected children can substantially reduce the effective infectious period.

The density of susceptibles depends mainly on the net birth rate in the community, which itself depends on the total population density, N; hence we have the observed correlation between endemic maintenance of disease without periodic "fade-out" and community size (*11, 17*). For measles in Britain and North America, the critical community size appears to be from 200,000 to 300,000 people (*8, 17*). As emphasized by Yorke *et al.*, seasonality in disease transmission may, however, lead to fade-out even in much larger communities, as a result of stochastic effects during those months when transmission is low [notably August to December for measles (*10, 12, 20*)]. On a more local scale, in

Table 1. Epidemiological parameters and the average interepidemic period, T, for various diseases [condensed from (25), where a more extensive compilation of data is given; see also (36)].

Infectious disease	Latent period $1/\sigma$ (days)	Infectious period $1/\gamma$ (days)	Incubation period* (days)	Interepidemic period (years) Average	Range	Geographical location	Time period
Measles	6 to 9	6 to 7	11 to 14	2.2	2 to 4	England and Wales	1855 to 1979
				2.2	2 to 3	New York City	1928 to 1968
Whooping cough	6 to 7	21 to 23	7 to 10	3.0	2 to 5	England and Wales	1855 to 1979
				3.2	2 to 4	Baltimore, Maryland	1928 to 1954
Poliomyelitis	1 to 3	14 to 20	7 to 12	4.0	3 to 5	England and Wales	1950 to 1966
				4.2	2 to 5	Finland	1940 to 1972
Chicken pox	8 to 12	10 to 11	13 to 17	2.5	2 to 4	New York City	1928 to 1972
				3.0	2 to 4	Glasgow, Scotland	1929 to 1972
Rubella	7 to 14	11 to 12	16 to 20	3.3	2 to 5	Glasgow, Scotland	1928 to 1964
				3.4	2 to 7	Baltimore, Maryland	1928 to 1974
Mumps	12 to 18	4 to 8	12 to 26	3.0	2 to 4	Baltimore, Maryland	1928 to 1973
				3.0	2 to 6	New York City	1928 to 1967
Diphtheria	2 to 5	14 to 21	2 to 5	5.1	4 to 6	England and Wales	1897 to 1979
Scarlet fever	1 to 2	14 to 21	2 to 3	4.4	3 to 6	England and Wales	1897 to 1978

*Time to the appearance of the symptoms.

low-density rural communities (where $X < N_T$), epidemics will be unable to develop, and the disease will not persist in the absence of a continual inflow of infecteds.

The concept of the intrinsic reproductive rate, R_0, is central to an understanding both of the epidemiology of infectious diseases and of the impact of control policies. To eradicate an infection, it is necessary to reduce R_0 below unity. This may be achieved by immunizing a proportion, p, of the population by vaccination soon after birth, provided (4, 18, 19, 25)

$$p > 1 - (1/R_0) \tag{8}$$

This relation is an important one. It follows from the observation that, in such a population, the number of susceptibles is at most $N' = N(1 - p)$, whence the intrinsic reproductive rate, R'_0, is $R'_0 = R_0(1 - p)$ with R_0 defined by Eq. 7; the condition $R'_0 < 1$ then gives Eq. 8. If R_0 is large, the proportion that must be vaccinated approaches unity; other things being equal, diseases with high R_0 values will be much more difficult to control than those with low values. Table 2 gives estimates of the intrinsic reproductive rates of some common infectious diseases in various regions of the world.

A direct estimate of the intrinsic reproductive rate, R_0, from Eq. 5 (or, equivalently, of N_T from Eq. 6) is usually impossible, because of the difficulties inherent in any direct estimate of the transmission factor β. However, Dietz (18, 19) has shown that R_0 can be estimated from the relation

$$R_0 = 1 + L/A \tag{9}$$

Here L is the human life expectancy ($L = 1/\mu$) and A is the average age at which individuals acquire the infection [$A = 1/\lambda$, where λ is the "force of infection" of catalytic models (26); in the specific case of Eqs. 1 to 4, $\lambda = \beta Y$]. Dietz's derivation of Eq. 9 assumes all the rate parameters (such as σ, γ, and μ) are constants, independent of the age of the host. A more general expression for R_0 is derived and discussed below, where it is seen that Eq. 9 usually remains a useful approximation even when the rate processes are age dependent.

The average age at infection, A, can be found from data showing the proportion in each age class who have experienced the infection (the proportion serologically positive) (25). Some such estimates of A for various diseases in various places and times are presented in Table 2.

The Interepidemic Period

Long-term records reveal that many common childhood diseases exhibit marked variations in incidence from year to year. These fluctuations are often of a regular nature, tending to arise as a

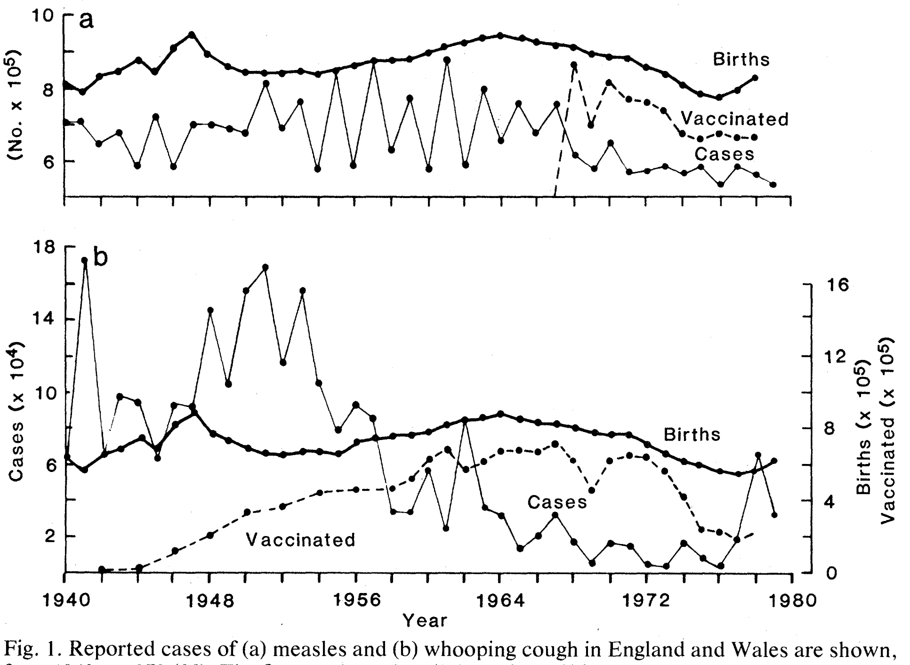


Fig. 1. Reported cases of (a) measles and (b) whooping cough in England and Wales are shown, from 1940 to 1979 (28). The figures show the total number of births (thick line), the total number of reported cases (thin line), and the total number of people vaccinated (dashed line) each year (vaccination records were supplied by the Department of Health and Social Security, United Kingdom).

broad consequence of the depletion and renewal of the supply of susceptibles. The 2- to 3-year cycles of measles, a typical example of which is shown in Fig. 1a, are remarkable (*8, 9, 20*). In general, the interval between major epidemics is termed the interepidemic period; the results of several representative studies of various childhood diseases are shown in Table 1 (*25*).

The deterministic model of Eqs. 1 to 4 exhibits damped oscillation, thus settling toward a stable equilibrium (*11, 18, 19*). For diseases that are of short duration relative to the host life-span ($\sigma >> \mu$, $\gamma >> \mu$), the period, T, of the oscillation is approximately (*25*)

$$T = 2\pi[LD/(R_0 - 1)]^{1/2} = 2\pi(AD)^{1/2} \quad (10)$$

Here D is the sum of the lengths of the latent and infectious periods ($D = 1/\sigma + 1/\gamma$), and R_0, L, and A are as defined above. The tendency for these oscillations to damp out is clearly at odds with the patterns of persistent oscillation shown in Fig. 1 and documented in the studies listed in Table 1.

Analytic (*17*) and numerical (*25*) studies show, however, that stochastic effects can indefinitely perpetuate the oscillation of the system. Alternatively, as emphasized by Dietz (*18, 19*), Yorke (*8, 20*), and others, seasonality in transmission rates (a common feature of infections such as measles, mumps, and chicken pox) can pump the otherwise-damped oscillations, locking the system into sustained cycles whose periods are an integral number of years; the resulting interepidemic period is approximately determined by the period T in Eq. 10. In short, various mechanisms can pump the system's propensity to oscillate, resulting in cycles whose periods T depend on the biological parameters D (that is, σ and γ) and A or L and R_0 (which are related to the rate of entry of new susceptibles), roughly according to Eq. 10.

We find striking agreement between these simple theoretical insights and the observed values of the epidemiological variables T, D, and A or R_0 (as cataloged in Tables 1 and 2). Equation 10 gives a successful account both of the relation among T, D, A, and R_0 for a particular disease, and of the systematic trends in the interepidemic period T after widespread vaccination (*25*).

For measles in Britain, substitution into Eq. 10 of the average values of D, R_0, and L given in Tables 1 and 2 predicts a value of T between 2 and 3 years; this accords with the observed interepidemic period. Similar estimates lead to the prediction that T is about 3 to 4 years for whooping cough, and about 5 years for diphtheria, again in agreement with the observations summarized in Table 1. For chicken pox, polio, rubella, mumps, and scarlet fever, the agreement is somewhat less good (with Eq. 10 giving T about 4 to 5 years, whereas the observed interepidemic periods are shorter, typically averaging around 3 to 4 years).

The foregoing analysis pertains to macroepidemiological patterns in large communities, and variations from the predictions are to be expected in small subpopulations. Another caveat has to do with those developing countries where birth rates are high and life expectancy short; here, Eq. 10 suggests a pronounced reduction in the interepidemic period compared with the corresponding period in a developed country.

The effect of vaccination programs is to reduce the intrinsic reproductive rate, R_0, of the disease (and thus, as discussed below, to increase the average age at first infection, A). It follows from Eq. 10 that such programs therefore tend to lengthen the interepidemic period T (*27*). This prediction accords with observations on measles, whooping cough, and polio in Europe and North America (*3, 12, 28*). For example, in England and Wales, as a consequence of immunization programs, the average interepidemic period for measles has increased from 2.2 to 2.6 years, and for whooping cough has increased from 2.8 to 3.5 years [see Fig. 1 and the more detailed analysis in (*25*)].

Among other public health measures, the practice of isolating infected individuals once symptoms appear has the effect of reducing R_0 (by decreasing the infectious period, $1/\gamma$). This practice, however, also reduces the value of D, and hence (see Eq. 10) has a less marked impact than vaccination on the value of T.

Age-Dependent Parameters and Vaccination Schedules

Although Eqs. 1 to 4 are useful in illuminating certain basic principles, their assumption that all rate parameters are age-independent constants is a gross oversimplification (Fig. 2). We now generalize these equations to include the effects of age dependence, particularly in the transmission rates and in vaccination schedules; this permits a more rigorous discussion of R_0 and of vaccination policies.

Under such a generalization, there are two independent variables (time, t, and age, a) instead of the single independent

Table 2. The intrinsic reproductive rate, R_0, and average age of acquisition, A, for various infections [condensed from (*25*); see also (*36*)]. Abbreviations: r, rural; u, conurbation.

Disease	Average age at infection, A (years)	Geographical location	Type of community	Time period	Assumed life expectancy (years)	R_0
Measles	4.4 to 5.6	England and Wales	r and u	1944 to 1979	70	13.7 to 18.0
	5.3	Various localities in North America	r and u	1912 to 1928	60	12.5
Whooping cough	4.1 to 4.9	England and Wales	r and u	1944 to 1978	70	14.3 to 17.1
	4.9	Maryland	u	1908 to 1917	60	12.2
Chicken pox	6.7	Maryland	u	1913 to 1917	60	9.0
	7.1	Massachusetts	r and u	1918 to 1921	60	8.5
Diphtheria	9.1	Pennsylvania	u	1910 to 1916	60	6.6
	11.0	Virginia and New York	r and u	1934 to 1947	70	6.4
Scarlet fever	8.0	Maryland	u	1908 to 1917	60	7.5
	10.8	Kansas	r	1918 to 1921	60	5.5
Mumps	9.9	Baltimore, Maryland	u	1943	70	7.1
	13.9	Various localities in North America	r and u	1912 to 1916	60	4.3
Rubella	10.5	West Germany	r and u	1972	70	6.7
	11.6	England and Wales	r and u	1979	70	6.0
Poliomyelitis	11.2	Netherlands	r and u	1960	70	6.2
	11.9	United States	r and u	1955	70	5.9

variable (t) of Eqs. 1 to 4; we have a set of partial differential equations describing the change in, for example, the number of susceptibles as a function of time and age, $X(a, t)$ (*18, 29*). The analysis may be simplified by following the dynamics of a cohort of $\tilde{N}$ newly born susceptibles, within a community where the population has a constant size and a stable age distribution, and where the disease is at its endemic equilibrium (with the total number of infectious individuals having a constant value, Y^*). A given immunization schedule may be represented by assuming that susceptible individuals are vaccinated at an age-dependent rate $c(a)$, and that vaccinated individuals join the immune class and remain protected for life. The numbers of susceptible, latent, infectious, and immune individuals as functions of age, a [denoted by $X(a)$, $H(a)$, $Y(a)$, and $Z(a)$, respectively] in this cohort now obey the differential equations:

$$dX/da = -[\lambda(a) + \mu(a) + c(a)]X(a) \tag{11}$$

$$dH/da = \lambda(a)X(a) - [\sigma + \mu(a)]H(a) \tag{12}$$

$$dY/da = \sigma H(a) - [\gamma + \mu(a)]Y(a) \tag{13}$$

$$dZ/da = \gamma Y(a) + c(a)X(a) - \mu(a)Z(a) \tag{14}$$

Susceptibles are lost by natural mortality, by vaccination (passing directly to the immune class), and by infection (passing into the latent class, and thence to the infectious and finally the immune class, unless mortality intervenes along the way). The latent and infectious periods ($1/\sigma$ and $1/\gamma$) are taken to be age independent as is usually roughly true (although age dependence could easily be incorporated if the data warranted it). The mortality rate, $\mu(a)$, will typically have the kind of age dependence shown in Fig. 2c. The age-specific vaccination rates, $c(a)$, can be determined from the data for a particular program (Fig. 2, d and e).

The parameter $\lambda(a)$ represents the age-dependent "force of infection," the per capita rate at which susceptible individuals acquire infection. This quantity can be inferred directly from available data (as indicated in Fig. 2, a and b) for measles and whooping cough in England and Wales. Some catalytic models (*26*) take λ to be a constant, but $\lambda(a)$ for the data in Fig. 2, a and b, is seen to increase approximately linearly with age (at least for children under 8 years old) (*30*).

If Eqs. 11 to 14 are taken to be a direct generalization of Eqs. 1 to 4 (in which the transmission term is βXY), $\lambda(a)$ can be written as $\lambda(a) = \beta(a)y^*N$, where $\beta(a)$ is the age-specific transmission parameter and y^* is the equilibrium proportion of the population N who are infectious (that is, y^* is the "prevalence" of the infection). Although the force of infection will generally depend linearly on the prevalence of infection, it will not always depend linearly on the total population size. For example, as discussed by Bailey (*11*) and in more detail by Yorke *et al.* (*8, 14*), for most sexually transmitted diseases it is likely that λ depends only on y^*, independent of N. For the childhood diseases listed in Table 2, λ does depend on N, although the dependence is often less strong than the conventionally assumed linear dependence of Eqs. 1 to 4; this is set out more fully in (*25*). Evidence bearing on this point is summarized in Tables 3 and 4, which show the mean age at first infection, A, as a function of community size and of the degree to which the population is an urban rather than a rural one, for several diseases. The data in Tables 3 and 4 are for unvaccinated communities, and A is therefore inversely proportional to λ; as expected, A tends to increase with decreasing N or decreasing urbanization,

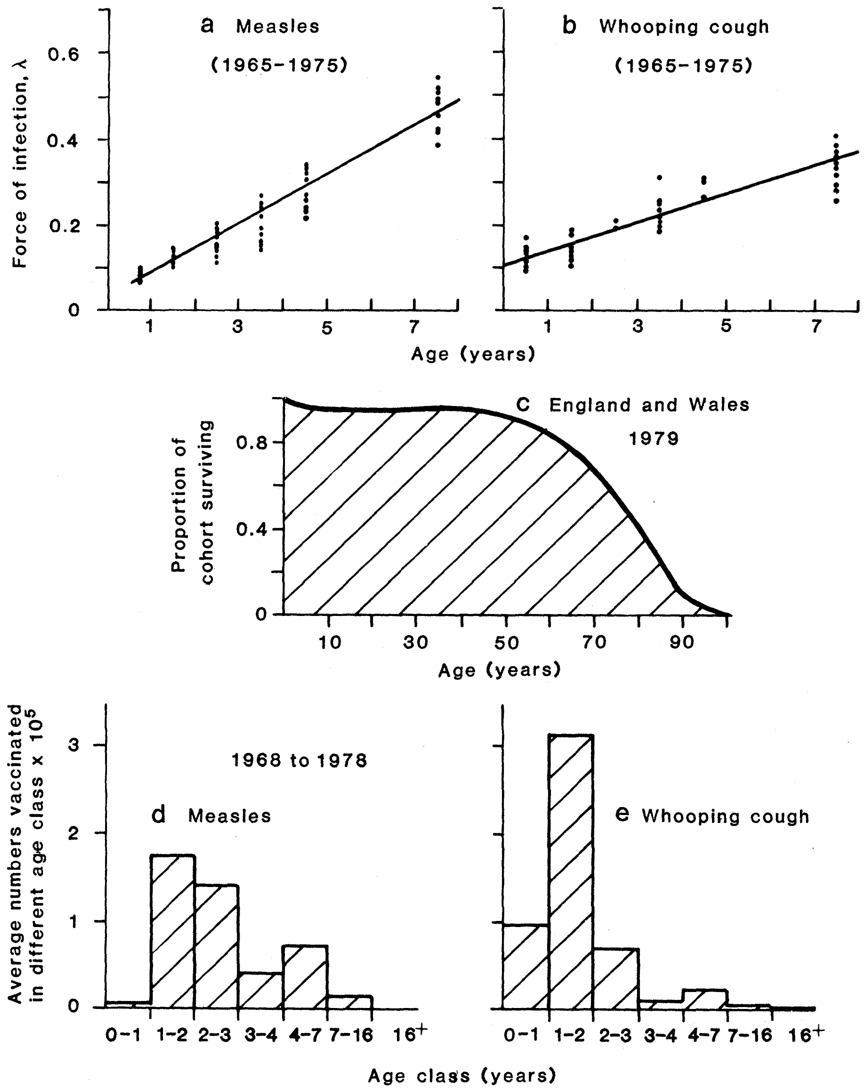


Fig. 2. (a) The "force," or instantaneous rate, of infection, λ, is shown as a function of age for measles in England and Wales between 1965 and 1975. This rate λ is estimated from data presented in the *Registrar General's Statistical Reviews* (*28*), by methods described by Griffiths (*30*); λ is defined per annum per susceptible. The dots represent yearly estimates of the age-dependent rates, while the solid line is the best linear fit. The relation between λ and age, a, up to the age of 10 years, is indeed described well by the linear expression $\lambda(a) = \alpha + ba$, where α and b are constants: $\alpha = 0.030$ and $b = 0.057$ (and $r^2 = 0.99$). (b) The conditions are as for (a), except that the data are for whooping cough. The linear relation between λ and a here has coefficients $\alpha = 0.109$ and $b = 0.033$ (and $r^2 = 0.95$). (c) The age-dependent survival curve for the population of England and Wales in 1977 (*28*). The age-specific mortality rate, $\mu(a)$, is the logarithmic derivative of this curve with respect to a. (d) The average number of individuals, in various age classes, who are vaccinated against measles is shown. These average values are for the span 1968 to 1978, and are calculated from data supplied by the Department of Health and Social Security, United Kingdom. (e) As for (d), except that the data are for whooping cough from 1965 to 1978.

Table 3. Average age at first infection, A, as a function of community size, for various childhood diseases [data for New York state in the years 1918–1919 (46)].

Community size	Mean age, A (years)			
	Measles	Whooping cough	Scarlet fever	Diphtheria
200,000 to 50,000	9.0	6.3	10.5	10.6
50,000 to 10,000	9.0	5.7	10.2	11.5
10,000 to 2,500	10.7	6.9	11.2	12.5
< 2,500	12.9	8.2	12.3	14.2

but the effects are weaker than linear. These underlying details of the transmission process, however, are avoided if we use Eqs. 11 to 14 and simply determine $\lambda(a)$ from the empirical data (31).

For a system described by Eqs. 11 to 14, we can generalize a result obtained by Dietz (18) to show that the intrinsic reproductive rate R_0 is now

$$R_0 = \frac{\int_0^\infty \exp\{-\int_0^a [\mu(v) + c(v)]dv\}da}{\int_0^\infty \exp\{-\int_0^a [\lambda(v) + \mu(v) + c(v)]dv\}da} \qquad (15)$$

Of interest, as a point of departure, is the simple limiting case when all the rate parameters (λ, c, μ) are constants (18). In the absence of vaccination ($c = 0$), Eq. 15 then reduces to $R_0 = 1 + (\lambda/\mu)$, and the average age at first infection is $A = 1/\lambda$. In conjunction with the definition $L = 1/\mu$, this gives Eq. 9 for R_0; this expression was discussed above. More generally, if a proportion p of the population is vaccinated at the constant rate c (while the remaining fraction $1 - p$ is not embraced by the vaccination program), we can show that the intrinsic reproductive rate R'_0 is (25)

$$R'_0 = R_0 [1 - cp/(c + \mu)] \qquad (16)$$

Here R_0 (given by Eqs. 7 or 9) is the intrinsic reproductive rate of the disease before the implementation of a vaccination program.

As was outlined earlier, the criterion for a vaccination program to eradicate the disease is $R'_0 < 1$. From Eqs. 16 and 9, this requires that the fraction of the population to be protected must exceed

$$p > \frac{1 + V/L}{1 + A/L} \qquad (17)$$

Here V is the average age at which individuals are vaccinated ($V = 1/c$), and A remains the average age at first infection in the prevaccinated population. Since p cannot exceed unity, it is clear that eradication is possible only if $V < A$.

We emphasize that the values of R_0 and like quantities given in Fig. 4 below and in Table 2 are the result of numerical computations based on the exact Eq. 15, with the use of empirical data of the kind shown in Fig. 2 for $\lambda(a)$, $\mu(a)$, and $c(a)$. But for childhood diseases in developed countries, where the mortality rate is very small throughout the first 10 to 20 years of life, Eq. 17 remains a useful approximation [with A, V, and L being the reciprocals of appropriately averaged values of $\lambda(a)$, $c(a)$, and $\mu(a)$].

The conclusion that eradication is impossible if $V > A$ is of practical importance. For example, available evidence for rubella in Britain suggests that the value of A lies between 10 and 12 years (Table 2), and the adopted policy is to vaccinate girls (and only girls) between 11 and 15 years of age (32). Such a policy, combined with selective postpartum vaccination in women found not to have antibodies during antenatal care, protects the individuals most at risk; but Eq. 17 suggests it will have little impact on the overall incidence of rubella in Britain. This prediction is in accord with available epidemiological evidence, and with experience in the United States where a greater reduction in the prevalence of rubella has been achieved by vaccinating boys and girls at a preschool age (33). Any judgment about which is the "better" policy—that of Britain or of the United States—depends, of course, on complicated cost-benefit calculations (34).

In general, if the goal is eradication, the optimum vaccination policy will maintain the value of V as low as possible [taking into account, however, the duration of protection provided by maternal antibodies (6, 35)]. Moreover, infections with relatively high A values prior to control will be easier to eradicate. Experience with smallpox, polio, and diphtheria (with their relatively high values of A and relatively low values of R_0), as opposed to that with measles and whooping cough, may support this conclusion.

Measles and Whooping Cough

We now proceed to use these ideas to analyze the epidemiology of measles and whooping cough, before and after the advent of vaccination programs. Attention is concentrated on England and Wales, where long-term records for both incidence and numbers vaccinated are available; other countries are also referred to.

Measles. The epidemiological trends for measles in Britain since 1940 are displayed in Fig. 1a. The disease is highly infectious, with the average age of acquisition, A, being between 4 and 6 years of age in both Europe and North America; in certain underdeveloped countries with high birth rates the value of A is much lower. As discussed above, significant differences also exist in the values of A between rural and urban communities (30), with the average age being higher in smaller and less densely populated areas.

There has been a tendency for A to decrease since records were first kept (30). In England and Wales, A decreased from 5.5 to 4.4 years between 1944 and the introduction of widespread immunization in 1968 (25). The trend is thought to be due to greater social mobility and increased population density. Since the introduction of vaccination, the trend has reversed, and both the interepidemic

Table 4. Average age at first infection, A, in relation to the degree of urbanization [data for different states in the United States in the years 1910 to 1922 (46)].

State	Urban population* (%)	Mean age, A (years)				
		Measles	Whooping cough	Chicken pox	Scarlet fever	Diphtheria
Massachusetts	94.8	7.3	5.4	—	9.5	9.7
New Jersey	78.4	6.7	5.4	7.1	9.7	9.0
Connecticut	67.8	7.3	5.6	7.6	10.4	10.5
Pennsylvania	64.3	—	—	—	9.2	9.6
Maryland	60.0	8.4	5.7	7.6	8.9	10.4
New York	57.6	—	—	—	11.1	11.6
Kansas	24.9	10.8	—	—	10.7	12.7

*Percentage of the total population in the given state classified as living in urban (rather than rural) communities.

period, T, and the average age at infection, A, have increased (*25*, *36*). Throughout the span 1944 to 1979, 90 to 98 percent of reported cases have been in children less than 10 years old (*25*, *36*); by following specific cohorts through time to monitor the decline in the proportion that are susceptible, these data may also be used to estimate that the degree of underreporting of cases on a national scale lies between 40 to 45 percent (*37*, *38*). Similar estimates have been made in North America (*8*), with such studies indicating the degree of underreporting varies with age (*39*).

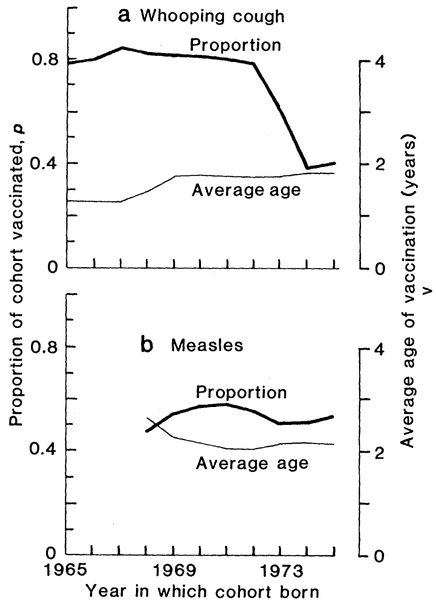
Vaccination coverage in England and Wales since 1968 has been relatively low. As shown in Fig. 3b, the average age at vaccination, V, has been between 2.0 and 2.6 years; of each yearly cohort, 15 to 35 percent have been vaccinated by this age, and between 46 and 57 percent were vaccinated in total. Using Eq. 15, we estimate the value of R_0 for measles in Britain before 1968 to lie in the range 14 to 18. This calculation allows for the fact that maternal antibody provides protection for, on average, the first 6 months of life (*25*). Vaccination has reduced the average value of R_0, but not by much. For example, Fig. 4a shows the decline in the susceptible population over time for the 1956 cohort (before vaccination) and for the 1970 cohort (after vaccination); we estimate the values of R_0 to be 16.0 and 12.8, respectively. Thus the vaccination of an eventual total of 57 percent of the 1970 cohort (of whom only 34 percent were vaccinated by the average age of vaccination at 2.2 years) reduced the value of R_0 by about 20 percent.

Assuming the vaccine to be 100 percent effective, we estimate that with average A and V values of 4.6 and 2.2 years, respectively, approximately 96 percent of each cohort would have to be vaccinated for measles to be eradicated. The optimum policy is clearly to vaccinate at an average age close to, or less than, 1 year, but even under such a regime eradication would require a vaccination coverage of roughly 94 percent. This figure is an average value for England and Wales, with higher levels of coverage being required in densely populated cities (with relatively high values of R_0 and relatively low values of A), and lower levels in rural communities. In North America such local considerations would possibly be of greater significance, as a result of much larger variations in population density and relatively less intermixing of the total population (*8*). Stochastic effects (*17*, *25*), accentuated by seasonality in transmission (*8*, *20*), would probably result in fade-out of disease at marginally lower levels of protection than those predicted by deterministic models (*12*). The reintroduction of measles into Britain, however, would always be a risk if the level of herd immunity fell below 94 percent.

Whooping cough. Similar analyses of the available data for whooping cough in England and Wales between 1940 and 1979 can be carried out, to determine: macroepidemiological patterns (Fig. 1b); the average age at infection, A; the proportion of reported cases represented by individuals over 10 years of age; the proportion of each cohort immunized; and the average age at vaccination. Such analysis (*25*) reveals that whooping cough was somewhat closer to being eradicated than measles (particularly during the mid-1960's) prior to public concern about the dangers of vaccination for whooping cough.

Figure 4b, in analogy to Fig. 4a, shows the decline in the proportion of susceptibles in the 1940 cohort (before vaccination) and in the 1970 cohort (after vaccination); we estimate the values of R_0 to be approximately 16.3 and 6.3, respectively. With A and V values of 4.4 and 1.7 years, respectively, in the 1970 cohort, a vaccination coverage of 81 percent in total (and 42 percent by the average age of vaccination) produced a 61 percent decline in the value of R_0, and a very low overall incidence of the disease during the early 1970's. Since 1977, however, the vaccination rate has declined to low levels (see Fig. 3a), and the incidence has predictably begun to increase (Fig. 1b).

Our models suggest that, with an aver-



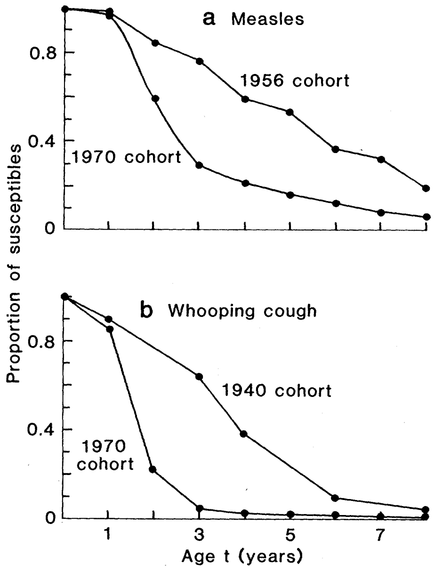


Fig. 3 (left). (a) The thick line (corresponding to the vertical axis to the left) shows the proportions of the cohorts born in England and Wales during the years 1965 to 1975 and vaccinated against whooping cough. The thin line (corresponding to the vertical axis to the right) represents the average age, V, at which vaccination was received by the individuals in these cohorts who were indeed immunized. (b) As for (a), except the data here pertain to vaccination against measles, for cohorts born in the years 1968 to 1975 (data supplied by the Department of Health and Social Security, United Kingdom). Fig. 4 (right). (a) The estimated decline in the proportions of the 1956 and 1970 cohorts that were susceptible to measles is shown as a function of age, in England and Wales. The cohorts were chosen to represent epidemiological patterns before (1956) and after (1970) the introduction of immunization programs for measles. The proportions susceptible are estimated from the reported cases in the *Registrar General's Statistical Review* (*28*), and the annual records of vaccination were provided by the Department of Health and Social Security, United Kingdom; underreporting of cases is taken into account by the assumption that 95 percent of susceptibles will experience an attack of the disease by the age of 10 years (*25*). The intrinsic reproductive rate, R_0, for measles within these cohorts was estimated by numerical integration of Eq. 15: for the 1956 cohort, $R_0 = 16.0$; and for the 1970 cohort, $R_0 = 12.8$. Of the 1970 cohort, a total of 57 percent was vaccinated against measles, at an average age, V, of 2.3 years. The proportion of susceptibles as a function of age in the 1956 cohort shows evidence of the 2-year cycle in measles incidence. (b) As along the lines laid down in (a), the estimated decline in the proportions of the 1940 and 1970 cohorts susceptible to whooping cough, as a function of age, in England and Wales. The cohorts were again chosen to represent epidemiological patterns before (1940) and after (1970) the introduction of immunization programs. Corrections were made to allow for the underreporting of cases, by means of the method described for measles. Values for R_0 were estimated by numerical integration of Eq. 20. $R_0 = 16.3$ and 6.3 for the 1940 and 1970 cohorts, respectively. Of the 1970 cohort, a total of 81 percent was vaccinated against whooping cough, at an average age, V, of 1.7 years.

age age of vaccination around 1.7 years, a coverage of about 96 percent would be necessary to eradicate whooping cough in Britain. A coverage around 95 percent would be adequate if the average age at vaccination were reduced below 1 year of age. In actuality, the coverage would need to be even higher, as current vaccines against pertussis are far from being 100 percent effective (*40*).

Conclusions

Our principal conclusion is that very high levels of artificially induced herd immunity are required to eradicate diseases whose intrinsic reproductive rates are high, as is the case for measles and whooping cough. A rough relation exists between the level of protection required, the average age at vaccination, and the value of R_0 (or the average age at infection in the population before vaccination); see Eqs. 8, 16, and 17. The proportion to be vaccinated may be minimized by vaccinating at as young an age as possible (and eradication is simply impossible if $V > A$). In developing countries with high birth rates, and consequently high rates of introduction of susceptibles, extremely high levels of vaccination coverage may be required (although these may be somewhat counterbalanced by high case mortality rates).

On this basis, we suggest that part of the reason immunization has proved successful in controlling diseases such as polio, diphtheria, and smallpox (*3, 5*) is that they have relatively low intrinsic reproductive rates (as indicated by the average ages at which individuals acquired infection prior to the instigation of control programs). The information recorded in Table 2 suggests that rubella, mumps, and chicken pox may be good candidates for eradication (*25*), although, as noted by Yorke and co-workers (*8*), in the case of mumps and chicken pox it is debatable whether the costs of eradication would be justified by the potential benefits. Other diseases for which vaccines are, or soon will be, available include the hepatitis A and B viruses and cytomegaloviruses (*3, 8*). An assessment of the extent to which these infections may be controlled by vaccination (*4, 41*) requires serological surveys to measure the average age at which such infections are acquired and thence to estimate typical values of R_0.

The design and implementation of immunization programs should ideally be based on quantitative assessments of their overall effectiveness. In Britain, for example, there has been some disagreement over the level of herd immunity required to eradicate measles and whooping cough (*12, 35, 37, 42*). The essential task is to determine the intrinsic reproductive rate of the disease, on either a local, a regional, or a national scale; methods for doing this are outlined above. A necessary further step in the analyses undertaken by public health authorities is consideration of the economic and social costs and benefits of alternative control strategies (*43*). We have avoided all such complications, concentrating purely on the population biology of communicable infections; there is, however, no great difficulty in grafting such cost-benefit considerations onto our model (*34*).

More broadly, the above methods can be applied—with appropriate modifications—to infectious disease agents with more complex life cycles, including indirectly transmitted infections such as malaria. Such an extension seems called for, in light of the current interest in the development of vaccines against the protozoan malarial parasites (*44*); attempts to control malaria by vaccination are likely to be made complicated by the facts that values of R_0 are very high in endemic regions (much higher than those recorded for measles and whooping cough) and that naturally acquired immunity seems to be transient and to depend on the intensity of transmission within the population (*45*).

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