Epidemiologic Reviews

Vol. 15, No. 2
Printed in U.S.A.

Herd Immunity: History, Theory, Practice

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INTRODUCTION

Herd immunity has to do with the protection of populations from infection which is brought about by the presence of immune individuals. The concept has a special aura, in its implication of an extension of the protection imparted by an immunization program beyond vaccinated to unvaccinated individuals and in its apparent provision of a means to eliminate totally some infectious diseases. It is a recurrent theme in the medical literature and has been discussed frequently during the past decade. This new popularity comes as a consequence of several recent major achievements of vaccination programs, i.e.: the historic success of the global smallpox eradication program; dramatic increases in vaccination coverage stimulated by national programs and by the Expanded Programme on Immunization; the commitment of several countries to eradicate measles; and international dedication to eliminate neonatal tetanus and to eradicate poliomyelitis from the world by the year 2000.[1]

Received for publication January 27, 1993, and in final form July 29, 1993.

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[1]Though the words "eradicate" and "eliminate" have been used interchangeably by some authors in the past, current usage of *eradication* implies reduction of both infection and disease to zero whereas *elimination* implies either regional eradication, or reduction of disease incidence to some tolerably low level, or else reduction of disease to zero without total removal of the infectious agent (1). Thus the 42nd World Health Assembly recommended "elimination of neonatal tetanus by 1995 and global eradication of poliomyelitis by the year 2000" (2).

Along with the growth of interest in herd immunity, there has been a proliferation of views of what it means or even of whether it exists at all. Several authors have written of data on measles which "challenge" the principle of herd immunity (3–5) and others cite widely divergent estimates (from 70 to 95 percent) of the magnitude of the herd immunity threshold required for measles eradication (6–8). Still other authors have commented on the failure or "absence" of herd immunity against rubella (9, 10) and diphtheria (11). Authorities continue to argue over the extent to which different types of polio vaccine *can*, let alone do, induce herd immunity (12–14). Given such differences of opinion, there is need for clarification.

Many authors have based their discussions of herd immunity on an influential paper published in 1971 by Fox et al. titled "Herd immunity: basic concept and relevance to public health immunization practices" (15). This paper took as its starting point a medical dictionary's definition of herd immunity as "the resistance of a group to attack by a disease to which a large proportion of the members are immune, thus lessening the likelihood of a patient with a disease coming into contact with a susceptible individual" (16). While useful, even this definition lends itself to different interpretations; these may be either quantitative (herd immunity as partial resistance, reflected in reductions in frequency of disease due to reductions in numbers of source cases and of susceptibles) or qualitative (herd immunity as total resistance, implying a threshold number or percentage of immunes above which an infection cannot persist). Each of these interpretations has its place, but they are sometimes confused in debates

on the subject. A given population may exhibit one (partial, quantitative) without the other (total, qualitative) form of herd immunity. It will be found that such definitions do not easily fit situations in which vaccine-derived immunity is transferred either directly (as in the case of maternal antibodies against tetanus) or indirectly (as in the case of secondary spread of oral polio vaccines) between members of a population, or in which vaccines impart different levels of protection against infection, disease, or transmission (as in diphtheria, pertussis, and perhaps malaria).

The paper of Fox et al. (15) is also of importance because of its method and the nature of the conclusions which were dictated by that approach. Sufficient years have now elapsed for both the method and the conclusions to be reviewed in perspective.

Interest in applying the "magic" of herd immunity in disease control has encouraged mathematical research exploring the theoretical implications of the subject (6–8, 17–37). Though much of this work has been published in journals and in language unfamiliar to the medical and public health communities, its isolation has been reduced in recent years largely through the publications of Anderson and May and their colleagues (8, 17, 20, 21, 23, 24, 28, 29, 31, 33, 36).

It is the intent of this review to bring together the literature on the history, theory, and practical experience of herd immunity, to consider the variety of issues raised by the application of the concept to different diseases, and to consider how well current theory and practice correspond with each another.

HISTORY

The first published use of the term "herd immunity" appears to have been in a paper published in 1923 by Topley and Wilson titled "The spread of bacterial infection: the problem of herd immunity" (38). This was one of a classic series of studies by these authors on epidemics of various infections in closely monitored populations of laboratory mice (39). Topley and Wilson introduced the term in the following manner: "Consideration of the results obtained during the past five years . . . led us to believe that the question of immunity as an attribute of a herd should be studied as a separate problem, closely related to, but in many ways distinct from, the problem of the immunity of an individual host" (38, p. 243). After describing experiments showing that immunized mice had lower mortality rates from, and were less likely to transmit, *Bacillus enteritidis*, the authors concluded by posing an ". . . obvious problem to be solved. . . . Assuming a given total quantity of resistance against a specific bacterial parasite to be available among a considerable population, in what way should that resistance be distributed among the individuals at risk, so as best to ensure against the spread of the disease, of which the parasite is the causal agent?" (38, pp. 248–9). Wilson later recalled that he had first heard the phrase "herd immunity" in the course of a conversation with Major Greenwood (G. S. Wilson, London School of Hygiene and Tropical Medicine, personal communication, 1981); and Greenwood employed it in his 1936 textbook *Epidemics and Crowd Diseases* (40). Although these authors did not distinguish clearly between direct and indirect protection stemming from vaccine-derived immunity, later authors picked up the phrase and applied it in particular to the indirect protection afforded to nonimmune individuals by the presence and proximity of others who are immune.

That the presence of immune individuals could provide indirect protection to others was itself recognized at least as far back as the 19th century. Farr had noted in 1840 that "The smallpox would be disturbed, and sometimes arrested, by vaccination, which protected a part of the population . . ." (41). Such observations, that epidemics often came to an end prior to the involvement of all susceptibles, led in turn to a major epidemiologic controversy in the early years of this century. This controversy was between those who believed that epidemics termi-

nated because of changes in the properties of the infectious agent (e.g., loss of "virulence" resulting from serial passage) (42) and those who argued that it reflected the dynamics of the interaction between susceptible, infected, and immune segments of the population (43). Each argument was supported by observations and by mathematical reasoning (44). It was the latter explanation that won the day; and its simple mathematical formulation, the "mass action principle," which has become a cornerstone of epidemiologic theory, provides one of the simplest logical arguments for indirect protection by herd immunity.

The concept of herd immunity is often invoked in the context of discussions of disease eradication programs based on vaccination. It is significant that both Jenner (45) and Pasteur (46), key figures in the early development of vaccines, recognized the potential of vaccines to eradicate specific diseases, but neither appears to have considered the practical issues closely enough to have touched on herd effects. Furthermore, the major focus of eradication thinking in the first half of this century did not involve vaccines or vaccine-preventable diseases at all, but concerned vector-borne diseases, malaria in particular. This stemmed from the writings of Ross (47) who, in work on the dynamics of malaria, had deduced that it was not necessary to eliminate mosquitoes totally in order to eradicate the disease. Ross's so-called "mosquito theorem" was the first recognition of a quantitative threshold which could serve as a target for a disease elimination program. So powerful was the argument, and so influential was the tradition of quantitative thinking which it engendered, that the World Health Organization attempted global eradication of malaria before that of any other disease (48).[2] This tradition of mathematical epidemiology relating to vector-borne diseases has been repeatedly a source of important insights for the field of vaccination and herd immunity.

[2]The 1955 World Health Assembly recommended that the World Health Organization take the initiative in "a programme having as its ultimate objective the worldwide eradication of malaria." It was not until 1965 that the Assembly first declared "the worldwide eradication of smallpox to be one of the major objectives of the organization" (49).

THEORY

Three separate theoretical perspectives have been used to derive measures of herd immunity. Over recent years, these perspectives have converged into a general theory.

The mass-action principle

The theoretical basis of herd immunity was introduced by Hamer (43) in 1906 in the context of a discussion of the dynamics of measles. Hamer argued that the number of transmissions (he called it the "ability to infect") per measles case was a function of the number of susceptibles in the population. We can paraphrase his argument as:

$$C_{t+1}/C_t \text{ varies with } S_t, \qquad (1)$$

where S_t and C_t are numbers of susceptibles and cases, respectively, in some time period t, C_{t+1} is the number of cases in the succeeding time period, and C_{t+1}/C_t is, thus, the number of successful transmissions per current case (see figure 1). The time period used in this formulation is the average interval between successive cases in a chain of transmission, sometimes called the "serial interval" (50), which is approximately 2 weeks for infections such as measles and pertussis (see table 1). This relation can be expressed:

$$C_{t+1} = C_t S_t r, \qquad (2)$$

where r is a transmission parameter, or "contact rate," in effect the proportion of all possible contacts between susceptible and infectious individuals which lead to new infections. In order to simulate successive changes over time, the number of susceptibles is recalculated for each new time period as

$$S_{t+1} = S_t - C_{t+1} + B_t, \qquad (3)$$

where S_{t+1} is the number of susceptibles in

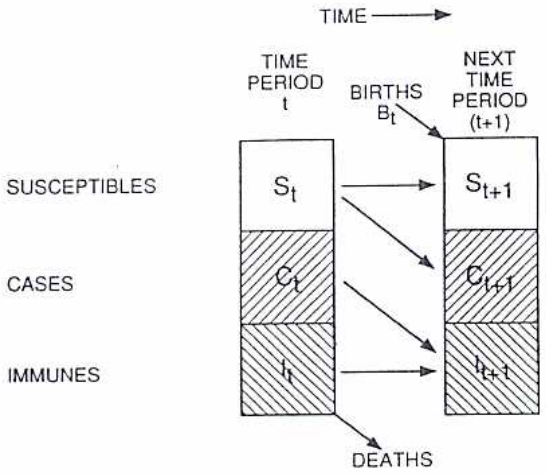


FIGURE 1. Relation between susceptibles (S), infectious cases (C), and immunes (I) in successive time intervals (t, $t+1$) in the simple discrete time mass action or Reed-Frost models. In each time period some (C_{t+1}) susceptibles become cases and the others remain susceptible. Each case is assumed to remain infectious for no more than a single time period (= serial interval). B_t individuals may enter as susceptible births during each time period (e.g., equation 3). Note that neither the simple mass action (equations 2 and 3) nor Reed-Frost (equation 9) equations include an explicit term for immunes. By implication, deaths prior to infection are not considered in these simplest models and the total population is assumed constant (i.e., in each period the same number of immunes die as susceptibles are born into the population).

the next time period and B_t is the number of new susceptibles added (e.g., born into) to the population per time period.

The relation in equation 2, that future incidence is a function of the product of current prevalence times current number susceptible, has become known as the epidemiologic "law of mass action" by analogy with the physical chemical principle that the rate or velocity of a chemical reaction is a function of the product of the initial concentrations of the reagents.[3] Often expressed as a differential (continuous time) rather than a difference (discrete time) equation, as here, this relation underlies most

[3]This analogy was apparently first made by Soper (51). The inspiration from physical chemistry is of more than passing interest in that it reflects a tradition among biomedical theorists to strive for the simplicity and elegance of the physical sciences. Not only mass action, but also the concepts of catalysis and of critical mass have close analogies in the behavior of infections, as mentioned below.

TABLE 1. Approximate serial intervals, basic reproduction rates (in developed countries) and implied crude herd immunity thresholds (H, calculated as $1 - 1/R_0$) for common potentially-vaccine-preventable diseases. Data from Anderson and May (8), Mcdonald (54), and Benenson (135). It must be emphasized that the values given in this table are approximate, and do not properly reflect the tremendous range and diversity between populations. They nonetheless give an appreciation of order-of-magnitude comparability

Infection	Serial interval (range)	R_0*	H* (%)
Diphtheria†	2–≥30 days	6–7	85
Influenza‡	1–10 days	?	?
Malaria§	≥20 days	5–100	80–99
Measles‖	7–16 days	12–18	83–94
Mumps	8–32 days	4–7	75–86
Pertussis¶	5–35 days	12–17	92–94
Polio#	2–45 days	5–7	80–86
Rubella	7–28 days	6–7	83–85
Smallpox	9–45 days	5–7	80–85
Tetanus	NA*	NA	NA
Tuberculosis**	Months–years	?	?

* R_0, basic case reproduction rate; H, herd immunity threshold defined as the minimum proportion to be immunized in a population for elimination of infection; NA, not applicable.

† Long-term infectious carriers of *Corynebacterium diphtheriae* occur. See the text for a discussion of the definition of immunity.

‡ R_0 of influenza viruses probably varies greatly between subtypes.

§ All these variables differ also between *Plasmodium* species. The serial interval may extend to several years. See the text for a discussion of implications of genetic subtypes.

‖ See the text for a discussion and variation in estimates of R_0 in table 5.

¶ See the text for a discussion relating to the definition of immunity in pertussis.

Distinct properties of different polio vaccines need to be considered in interpreting the herd immunity thresholds.

** R_0 has been declining in developed countries; protective immunity is not well defined.

theoretical work on the dynamics of infections in populations (23, 52).

Figure 2 illustrates what happens when equations 2 and 3 are iterated and serves to illustrate several fundamental principles of the epidemiology of those acute immunizing infections (such as measles, mumps, rubella, chickenpox, poliomyelitis, pertussis, etc.) which affect a high proportion of individuals in unvaccinated communities.

First, the model predicts cycles of infection incidence, such as are well recognized for many of the ubiquitous childhood infections (figure 3). The incidence of infection cycles above and below the "birth" rate, or rate of influx of new susceptibles.

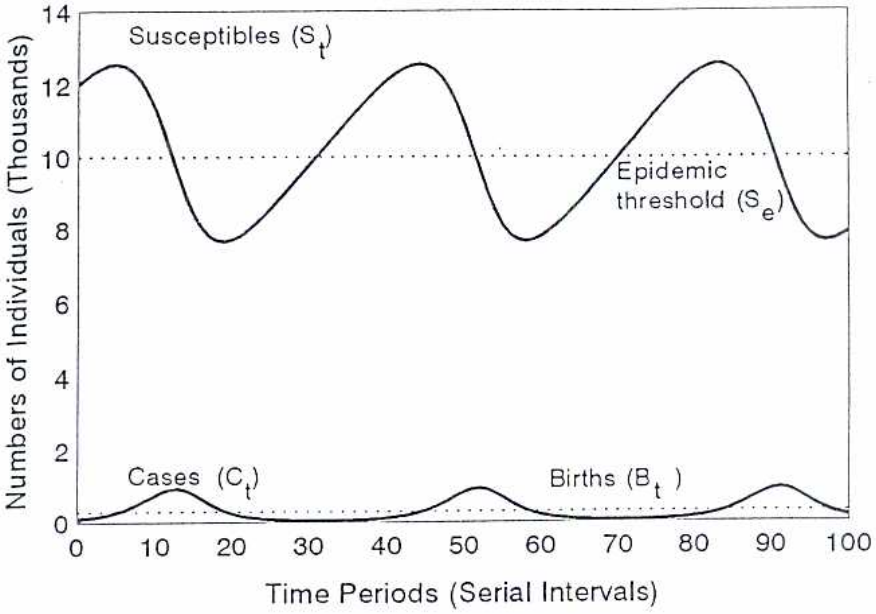


FIGURE 2. Mass action model. Results obtained on reiteration of equations 2 and 3. The illustrated simulation was based on 12,000 susceptibles and 100 cases at the start, $r = 0.0001$ and 300 births per time period. Note that the incidence of cases cycles around the birth rate and that the number of susceptibles cycles around the epidemic threshold: $S_e = 1/r = 10{,}000$.

Second, the number of susceptibles also cycles, but around a number which is sometimes described as the "epidemic threshold," S_e. Simple rearrangement of equation 1 to $C_{t+1}/C_t = S_t r$ reveals that this threshold is numerically equivalent to the reciprocal of the transmission parameter r; as incidence increases (i.e., $C_{t+1} > C_t$) when, and only when, $S_t > 1/r$; and, thus, $S_e = 1/r$. This important relation is implicit in Hamer's original paper (43), and was formalized as a "threshold theorem" in 1927 by Kermack and McKendrick (53). The principle may be illustrated by analogy with the physical concept of a "critical mass"—the epidemic threshold represents a critical mass (density per some area) of susceptibles, which, if exceeded, will produce an explosive increase in incidence of an introduced infection. The correspondence between the case and susceptible lines in figure 2 illustrates this relation.

Hamer and his successors used this logic to explain several aspects of the dynamics of measles and other childhood infections, such as cyclical epidemics, the persistence of susceptibles at the end of an epidemic, and the relation between the interepidemic interval and the time required for the number of susceptibles to reach the epidemic threshold (23, 43, 51, 52). Though it was not emphasized explicitly by the earlier authors, who dealt in numbers or "density," rather than proportions, of susceptibles, the epidemic threshold provides a simple numerical measure of a herd immunity criterion. If the *proportion* immune is so high that the *number* of susceptibles is below the epidemic threshold, then incidence will decrease. We can express this algebraically as:

$$H = 1 - S_e/T = 1 - 1/rT \qquad (4)$$

where T is the total population size, S_e is the epidemic threshold number of susceptibles for the population, and H is the herd immunity threshold, i.e., the *proportion* of immunes which must be exceeded if incidence is to decrease.

Figure 4 presents another way of illustrating the herd immunity threshold, i.e., in terms of the relation between the proportion immunized at birth and the ratio of the cumulative incidence during the postvaccination period to that during the prevaccination

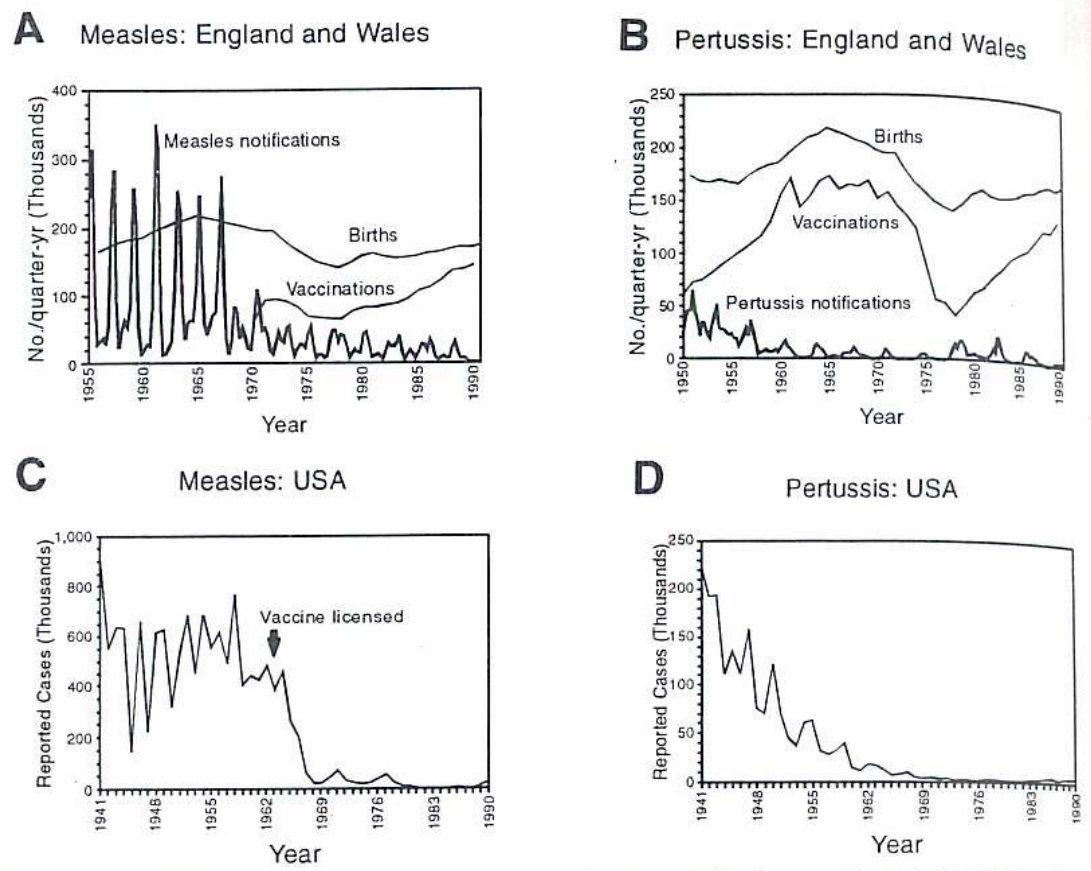


FIGURE 3. Reported incidence of common childhood vaccine-preventable diseases. Measles showed a tendency to biennial epidemics in England and Wales prior to vaccination (A). This pattern was less dramatic in data for the entire United States (C) because of the size and heterogeneity of the population (not all areas were in phase with one another). All areas showed a strong seasonal oscillation in addition to the biennial cycle. Pertussis shows a 3–4 year cycle with little obvious seasonality in the United Kingdom (B). This cycling is also seen in national data for the United States prior to 1970 (D). Notification efficiency was approximately 60% for measles in England and Wales prior to vaccination (55) but was considerably lower for pertussis and for both diseases in the United States.

period, either among those not immunized at birth (figure 4A), or in the entire population (figure 4B). Insofar as the immunization of individuals removes both susceptibles and potential sources of infection from the community, it will lead to a reduction in incidence rates and, hence, in cumulative incidence. If the proportion immunized at birth is maintained at or above the threshold, H, then the cumulative incidence is reduced to zero, indicating that the infection has been eliminated from the population.

It was only many years after Hamer that the wide use of vaccines meant that these epidemic and herd immunity thresholds could be considered as targets for intervention. If appropriate vaccination could prevent the number of susceptibles from reaching the epidemic threshold, then incidence should continue to decline, ultimately to extinction. Hamer's original principle implied the simplistic assumption of an homogeneous, randomly mixing population, like that of molecules in the ideal gasses for which the mass action principle was most appropriate. However, given the power of the analogy, elaboration of the theory was only a matter of time.

Case reproduction rates

If an infection is to persist, each infected individual must, on average, transmit that infection to at least one other individual. If

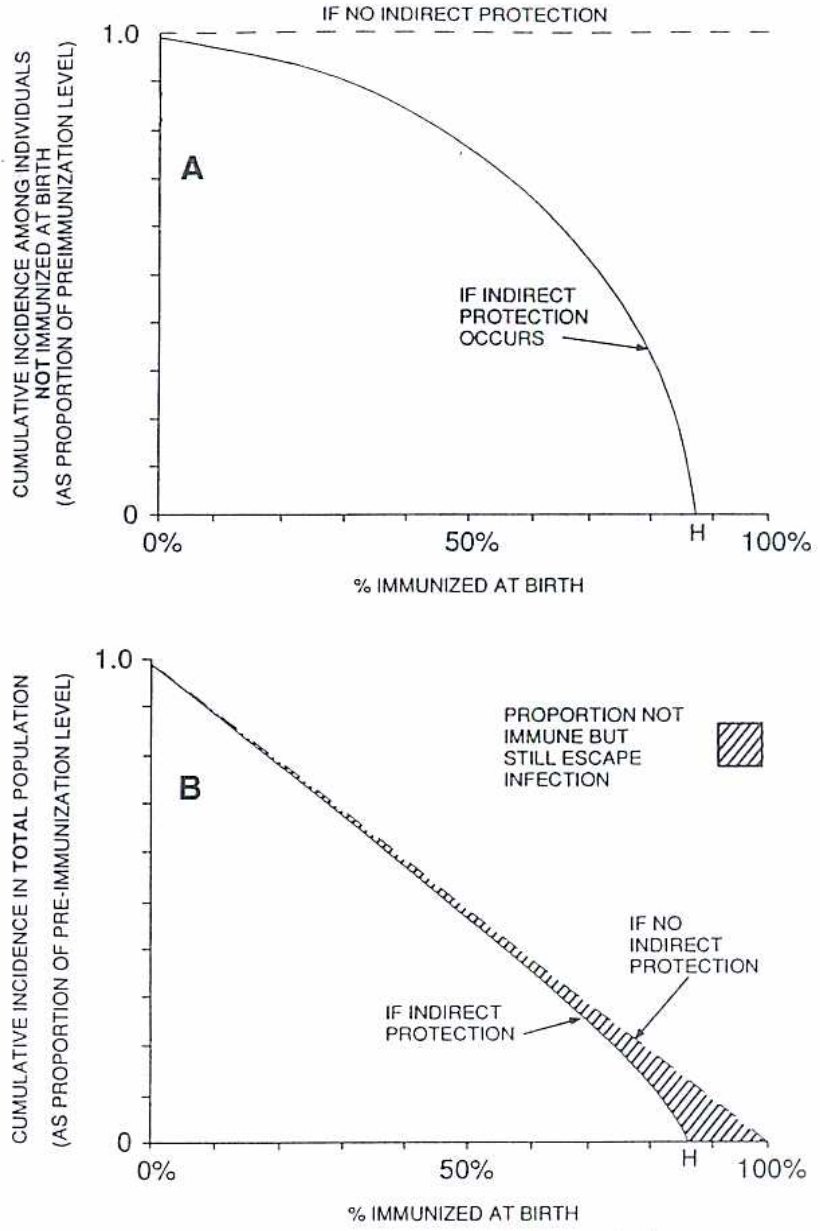


FIGURE 4. Cumulative incidence (e.g., per lifetime) of infection after a vaccination program as a proportion of prior cumulative incidence among individuals not immunized by the vaccine (A) and among the total population (B). In each diagram the *dotted line* refers to an infection for which the vaccine offers no indirect protection (e.g., tetanus vaccination of males) and the *solid line* refers to an infection for which the vaccine does impart indirect protection (e.g., measles). The vertical distance between the two lines reflects the nonimmunized individuals who escape infection as a proportion of all nonimmunized individuals (A) or of the total population (B).

this does not occur, the infection will disappear progressively from the population. This average number of actual infection transmissions per case is an extremely powerful concept, and has thus been discussed by many researchers. The fundamental statistic is one which was formulated originally by Macdonald (54), in the context of malaria studies, as the average number of secondary cases who contract an infection from a single primary case introduced into a totally susceptible population. He called this num-

ber the "basic case reproduction rate", by analogy with the demographic concept of the intrinsic reproduction rate, the average number of potential progeny per individual if there were no constraints to fertility (26). This definition can be translated directly into the mass action equation (equation 2) by letting $C_t = 1$ and $S_t = T$, to represent the single case introduced into a fully susceptible population. The number of secondary cases, C_{t+1}, is then equivalent, by definition, to the basic case reproduction rate (R_0):

$$R_0 = T r. \quad (5)$$

On reflection, we appreciate that this basic case reproduction rate describes the spreading potential of an infection in a population, and that it will be a function both of the biologic mechanism of transmission and of the rate of contact or interaction between members of the host population. Analogous or identical statistics have been defined by several authors, and given different names such as "expected number of contacts" (15), "contact number" (25), or "basic reproduction number" (26).[4] Examples of numerical values of this statistic, applicable to different infections and derived by methods described below, are shown in table 1. A simple way of illustrating the concept is presented in figure 5A.

Of course, in the real world there are constraints to unlimited infection transmission. For example, some of the "contacts" of an infected person may be individuals who are already infected or immune. As a result, the average number of *actual* infection transmissions per case, in a real population, will be *less* than the basic case reproduction rate, and has been defined, again first by Macdonald (54), as the "net reproduction rate" R_n. Other authors have called this the "actual" or "effective" reproduction rate (23). This is illustrated in figure 5B. It is clear from figure 5 that the net reproduction rate R_n should be equivalent to the basic case reproduction rate R_0 times the proportion susceptible in the population:

$$R_n = R_0 S_t/T. \quad (6)$$

This has interesting implications. If an endemic infection persists in a population of constant size, then R_n should, *on average*, over a long period of time, be equivalent to unity (i.e., each case leads on average to a single subsequent case). Therefore, "on average" from equation 6:

$$R_0 = T/average\ S_t = T/S_e. \quad (7)$$

In words, for endemic infections, the basic case reproduction rate should be equivalent to the reciprocal of the "average" proportion susceptible in the population. That the average number of susceptibles is equivalent to S_e should be evident from figure 2. An important implication of this relation is the prediction that the average proportion susceptible should remain constant in a population, even in the face of extensive and effective vaccination, as long as the infection remains endemic (and as long as the population remains of constant size). Analysis of data on measles has confirmed this relation (55).

Combination of equations 4 and 7 provides us with an expression for the herd immunity threshold in terms of R_0:

$$H = 1 - 1/R_0 = (R_0 - 1)/R_0. \quad (8)$$

This is illustrated graphically in figure 6 which shows the implications for persistence or eradication of infections depending on the proportion of immunes in the population.[5]

The Reed-Frost heterogeneous population simulation approach

The paper by Fox et al. (15) cited in the introduction has been one of the most fre-

[4]Different symbols have been used for the statistic by different authors. The original work by Macdonald (54) employed Z_0 for the basic reproduction rate. Several authors have noted that the statistic is not a proper rate, but that term is now imbedded in the literature (26).

[5]This important relation was published explicitly first by Dietz (18), in 1975, though it is implicit in some earlier work, in particular a graph published by Smith (56) in 1970.

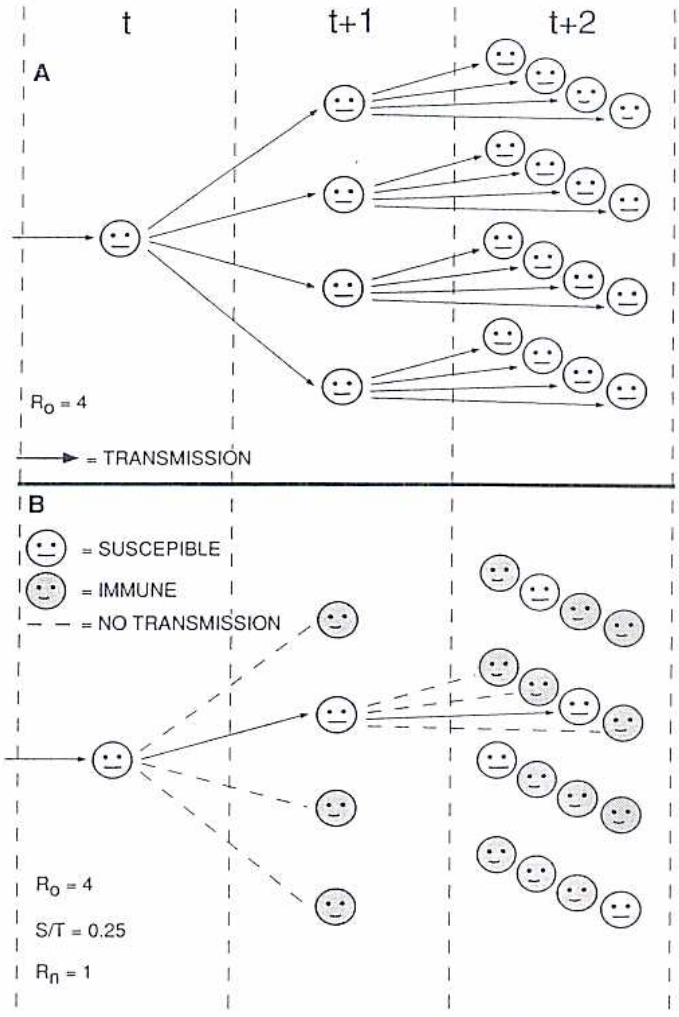


FIGURE 5. Cartoon illustrating implications of a basic reproduction rate $R_0 = 4$. In each successive time (serial interval, each individual has effective contact with four other individuals. If the population is entirely susceptible (A) incidence increases exponentially, fourfold each generation (until the accumulation of immunes slows the process) If 75% of the population is immune (B), then only $S/T = 25\%$ of the contacts lead to successful transmissions, and the net reproductive rate $R_n = R_0 (S/T) = 1$.

quently cited references on herd immunity. This paper is of historical interest, and also of interest because of its theoretical argument and conclusions.

The appearance of the Fox et al. paper in 1971 was significant. Four years before, in 1967, the World Health Organization had declared its intention of eradicating smallpox from the world within 10 years, and the United States Public Health Service had declared its intention of eradicating measles from the United States within 1 year (57). Both of these tasks were to be achieved by the induction of herd immunity with vaccines. By 1971, the initial successes and failures of these programs were on record (e.g. figure 3C), and Fox et al. set out to explain them.

They based their theoretical argument not on the mass action arguments outlined above, but on an alternative approach rooted in the Johns Hopkins University School of Hygiene and Public Health (58). This model, named the Reed-Frost for its developers Lowell Reed and Wade Hampton Frost, assumes the same discrete time schema illustrated in figure 1 but proposes an alternative to the mass action equa-

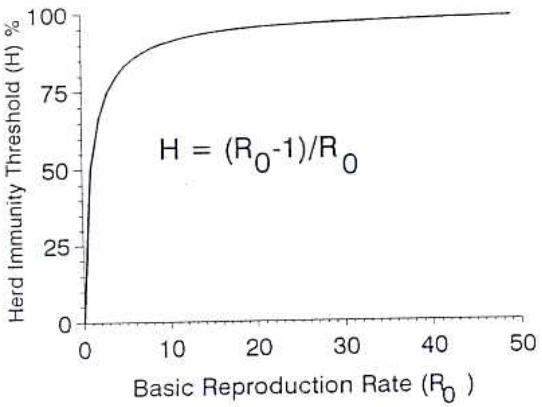


FIGURE 6. Relation between herd immunity threshold (H) and basic reproduction rate R_0, as in equation 8: $H = 1 - 1/R_0$.

tion (equation 2 above) as:

$$C_{t+1} = S_t\{1 - (1 - p)^{Ct}\} \qquad (9)$$

where p equals the "probability of effective contact," or the probability that any two individuals in the population have, in one time period (serial interval), the sort of contact necessary for transmission of the infection in question (58). The logic of this equation is such that the risk of infection among susceptibles is equal to the probability of having effective contact with at least one infectious case.[6] This model had traditionally been applied to simulate epidemics in closed populations (with no births or influx of susceptibles). Fox et al. continued this tradition, and thus calculated susceptibles for successive time periods as

$$S_{t+1} = S_t - C_{t+1}. \qquad (10)$$

This is important, as, by omitting any term for births (B_t in equation 3), the authors could only address questions relating to epidemics in closed populations.

Their first step was to explore these equations for simple randomly mixing populations. Table 2 presents a portion of the initial results, on the basis of which the authors concluded "... application of the Reed-Frost model ... demonstrates that, over a wide range of variations, the number of susceptibles and the rate of contact between them determine epidemic potentials in randomly mixing populations. If these are held constant, changes in population size and, therefore, in the proportion immune do not influence the probability of spread" (15, p. 182). The emphasis in this conclusion on *numbers* and *probability of spread* deserves comment. The perspective reflects the paper's focus on epidemic potential in closed populations rather than on infection persistence in open populations. Though the authors calculated statistics analogous to basic and net reproduction rates (see table 2), they neither used that terminology nor derived thresholds. Indeed, on the surface, their conclusion implies there is no threshold ("the proportion immune do not influence the probability of spread"), though this is a consequence of the assumption that "numbers of susceptibles and the rate of contact" are held constant. But, given the definition of the Reed-Frost contact rate as the probability that *any* two individuals have effective contact in one time period, it is unreasonable to consider alteration of population size without accepting its implications for some consequent change in contact probabilities. (For example, the probability for any two people *chosen at random* in a small community to meet, by chance, in 1 week, may be 0.1, but this probability will surely be smaller if they live in a very large population). Viewed from this perspective, the authors' first conclusion, as quoted above, appears almost spurious.

The paper then took a crucially important step. The authors explored an alternative to the basic assumption of homogeneous random mixing, which had been implicit in all

[6] If the same value is substituted for r in equation 2 and p in equation 9, the mass action predicts a higher number of successive cases than does the Reed-Frost for any given S_t and C_t. This is because the mass action equation does not correct for the fact that multiple infections on a single susceptible can lead to only a single subsequent case. It can be shown by the binomial expansion that the Reed-Frost model approximates the mass action if p is small, in which case the Reed-Frost p and the mass action r become the same statistic (59). This is reasonable in that as p is reduced, the probability of a susceptible contacting more than one case per serial interval (e.g., p^2 is the probability of contacting two cases, etc.) becomes vanishingly small.

TABLE 2. Extract from a table published by Fox et al. (15) to illustrate the behavior of infections in a randomly mixing population, as predicted by the Reed-Frost model

Initial population composition				"Probability of effective contact" (p)	Expected number of effective contacts by case in first interval		Probability of no spread $(1 - p)^{10}$‡
Susceptibles (S)	Cases (C)	Immune S (I)	Total (N)		With susceptibles pS*	Total $p(N - 1)$†	
10	1	0	11	0.2	2	2	0.11
10	1	5	16	0.2	2	3	0.11
10	1	5	16	0.133	1.3	2	0.23

* Analogous to the net reproduction rate, R_n.
† Analogous to the basic reproduction rate, R_0.
‡ The probability that all 10 susceptibles fail to have contact with the single index case.

modeling arguments to that time. They set up a structured community in which 1,000 individuals were separately assigned family, school, and social groupings, each of which had a different internal contact probability. By using Monte Carlo techniques, they simulated the consequences of introducing infections into such populations with and without opportunities for special mixing within and between the social groups. Table 3 presents a portion of the results of these simulations, which led the authors to conclude: "Free living populations of communities are made up of multiple and interlocking mixing groups, defined in such terms as families, family clusters, neighborhoods, playgroups, schools, places of work, ethnic and socioeconomic subgroups. These mixing groups are characterized by different contact rates and by differing numbers of susceptibles. The optimum immunization program is one which will reduce the supply of susceptibles in all subgroups. No matter how large the proportion of immunes in the total population, if some pockets of the community, such as low economic neighborhoods, contain a large enough number of susceptibles among whom contacts are frequent, the epidemic potential in these neighborhoods will remain high. Success of a systematic immunization program requires knowledge of the age and subgroup distribution of the susceptibles and maximum effort to reduce their concentration throughout the community, rather than aiming to reach any specified overall proportion of the population" (15, p. 186). While the argument that social structure is important in determining patterns of infection is compelling, two points in this con-

TABLE 3. Relative frequency distributions of epidemic sizes predicted by the Reed-Frost model, assuming different structures to a population of 1,000 persons. Data are based on 100 stochastic simulations under each set of conditions, as published by Fox et al. (15)

Mixing groups	Within group contact (p value)	Total number of cases per epidemic (%)										Mean epidemic size
		1	2	3	4	5–9	10–19	20–29	30–39	40–59	60–79	
Total community	0.002	82*	15	2	1							1.2†
Total community	0.002	22	18	34	8	17	1					3.3
Families, [62]‡	0.5											
Total community	0.002											
Families, [62]	0.5	11	6	26	23	23	9	1	1			5.6
Playgroups [24]	0.1											
Total community	0.002											
Families, [62]	0.5											
Playgroups [24]	0.1	23	4							28	45	45.0
Nursery school	0.1											

* Thus, 82 of the 100 epidemics simulated under these conditions (in this case a randomly mixing community with probability of effective contact, $p = 0.002$), terminated after a single case.
† The average total number of cases in all 100 simulated epidemics was 1.2.
‡ The numbers in brackets reflect the numbers of families, playgroups, and nursery schools in the simulated populations.

clusion are less clear. First, the statement that it is important to reduce the supply of susceptibles in *all* subgroups is not strictly supported in the paper's theoretical results; indeed, it is intuitively reasonable, and was later demonstrated in theory (see below), that targeting vaccination to groups with high contact probabilities can be more efficient (in the sense of minimizing the total number of vaccinations required) in reducing disease than is uniform coverage of an entire population. Second, the emphasis on curbing epidemic spread remains. Although Fox et al. considered their approach "... relevant to programs of systematic immunization ... which have as their ultimate goal elimination of the causative agent from the country" (15, p. 186), it was most relevant to epidemics in closed populations, as it had no provision for examining the implications of a constant influx of susceptibles into the population, as by birth.

The Fox et al. paper deserves its considerable influence. Its break from the tradition of random mixing populations was a crucially important development. Its theory was born of practical experience and disappointment with progress in measles control in the United States, and its tone was pessimistic and practical, compared with most of the past (and subsequent) literature on herd immunity, which has trended to emphasize simple thresholds. As we shall see, the paper still proves to be wise counsel.

Recent theoretical developments

The credibility of the simple formulations of herd immunity thresholds is weakened by the fact that the logic and formulae are based on obviously simplistic assumptions. In particular, the basic mass action models assumed that populations are homogeneous, with no differences by age, social group, or season, and that they mix at random. Mathematically inclined workers have taken these failings as a challenge to adapt the theory to more realistic assumptions.

The estimation of R_0. The centerpiece of research on herd immunity has been the linking of the mass action and basic case reproduction rate theories. The crucial insight appeared in a 1975 paper by Dietz (18) which demonstrated that, if one assumes a stable population in which the mortality rates and the incidence rates of infection are both independent of age, then

$$R_0 = T/S_e = 1 + L/A, \qquad (11)$$

where L is defined as the average expectation of life and A is the average age at infection.[7] Mathematical proofs of this relation have been presented by several authors (18, 23, 25, 27). The derivations assume an exponential distribution of the population by age and age-independent incidence rates of infection (figure 7A).[8] The relation can take an even simpler form if the population is assumed to have a rectangular age distribution (figure 7B), in which case

$$R_0 = L/A. \qquad (12)$$

This latter relation can be illustrated neatly if we recall that R_0 is equivalent to the reciprocal of the proportion susceptible at equilibrium ($(R_0 = T/S_e = 1/s_e)$, and assume that everyone is infected at exactly age A, the average age at infection, and dies at exactly age L, the average expectation of life (figure 7B). Assuming this rectangular age structure, the proportion susceptible is A/L; thus $R_0 = L/A$. On this basis, we might conclude that the higher crude estimates of R_0 implicit in equation 11 should in general be more appropriate for developing countries, with pyramidal or exponential age distributions (figures 7A and C), and the lower estimates of equation 12 for developed countries (figures 7B and D).

[7] This insight represents another contribution stemming from the traditions of the mathematics of vector-borne diseases (Dietz's paper (18) was on arthropod-borne viruses) and of physical chemistry (the assumption of an age-independent incidence rate is the basis of the so-called "catalytic models" (60)).

[8] In brief, if μ is the death rate and λ is the force (person-time incidence rate) of infection, then the average duration of life is $1/\mu = L$ and the average duration of susceptible life is $1/(\lambda + \mu)$. As $R_0 = 1/(\textit{proportion susceptible})$, $R_0 = (\lambda + \mu)/\mu = 1 + \lambda/\mu$. If μ is small compared to λ, then this expression is close to $1 + L/A$.

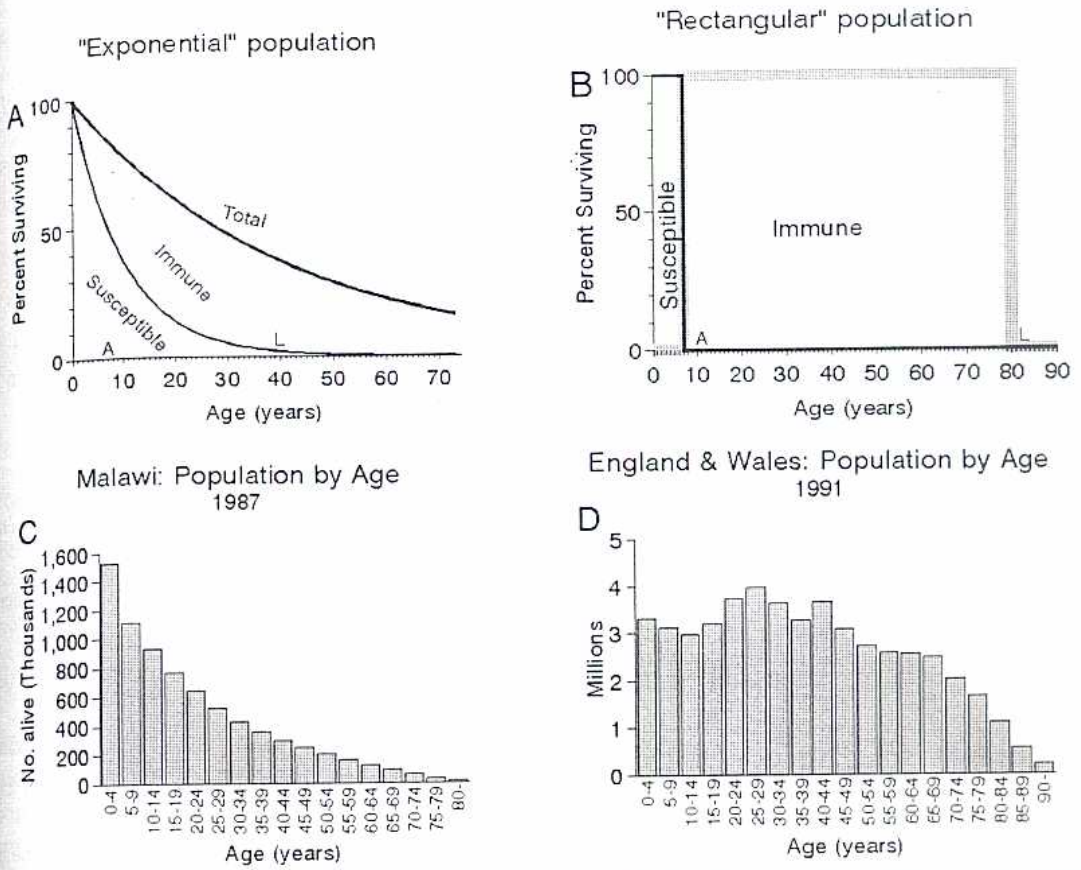


FIGURE 7. Schematic diagrams of exponential (A) or rectangular (B) age distributions compared with current population distributions in Malawi (C) and England and Wales (D). The exponential model (A) assumes infection and constant death rates at all ages. The average age at infection and average expectation of life are *A* and *L* years, respectively. In the rectangular model, all individuals are assumed to become infected at age *A* and to die at age *L*.

Equations 11 and 12 may be combined with the basic herd immunity expression (equation 8) to give relations between crude basic reproduction rates, herd immunity thresholds, and average age at infection, as shown in figures 8A–8D. The availability of such expressions has made it a straightforward matter to estimate crude basic reproduction rates and herd immunity thresholds for a variety of diseases of childhood (see table 1). Beyond that, they have opened the way to explorations of more realistic (and complicated) sets of assumptions.

Age-related effects. The simple mass action and Reed-Frost models make no provision for the fact that individuals pass through periods of different infection risk as they age. The inclusion of this factor requires compartmentalization of the population by age groups as well as by infection status (i.e., with maternal immunity, or susceptible, or latent, or infectious, or with active immunity). Assumptions must then be made as to how the risk of infection, within each age group in each time period, is a function of the prevalence of infectious cases in the same and other age groups at that time. A general scheme for this approach is presented in figure 9. Several investigators have tackled the problem and have thus been able explore the effects of different age-specific contact patterns, and vaccination strategies, within simulated populations (7, 19, 23, 36). Not surprisingly, the simple elegance of the basic mass action model has been lost, and the results have

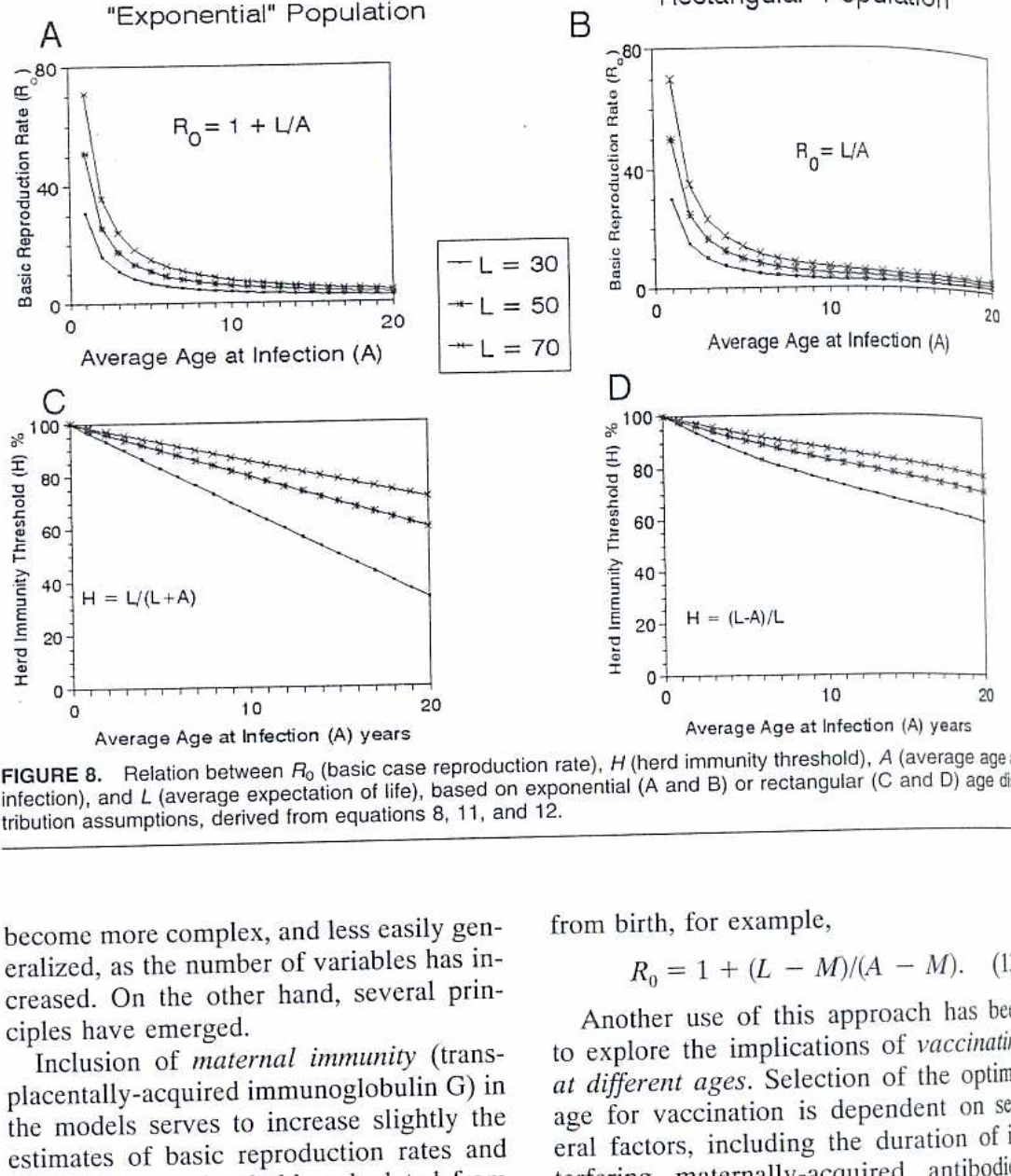


FIGURE 8. Relation between R_0 (basic case reproduction rate), H (herd immunity threshold), A (average age at infection), and L (average expectation of life), based on exponential (A and B) or rectangular (C and D) age distribution assumptions, derived from equations 8, 11, and 12.

become more complex, and less easily generalized, as the number of variables has increased. On the other hand, several principles have emerged.

Inclusion of *maternal immunity* (transplacentally-acquired immunoglobulin G) in the models serves to increase slightly the estimates of basic reproduction rates and herd immunity thresholds calculated from equations 11 and 12 (23). This is intuitively reasonable in that, as far as an infectious agent is concerned, an individual does not really enter the population until he or she has lost maternal antibody protection (and, thus, the A and L parameters in equations 11 and 12 are, in effect, overestimates). The basic equations can thus be adapted to adjust ages as though they were calculated from the average age of losing maternal immunity, M (on the order of 0.5 years for measles but less for many other infections), rather than from birth, for example,

$$R_0 = 1 + (L - M)/(A - M). \quad (13)$$

Another use of this approach has been to explore the implications of *vaccinating at different ages*. Selection of the optimal age for vaccination is dependent on several factors, including the duration of interfering maternally-acquired antibodies, logistic requirements of the health services, and the need to protect children prior to exposure to risk. The issue is complicated further insofar as vaccination itself may reduce infection risks, and, hence, expand the "window" period prior to any given level of cumulative incidence. On the other hand, age at vaccination is related inversely to the reduction of susceptibles in the population, and, hence, affects estimates of herd immunity thresholds. This is easily described in terms of the

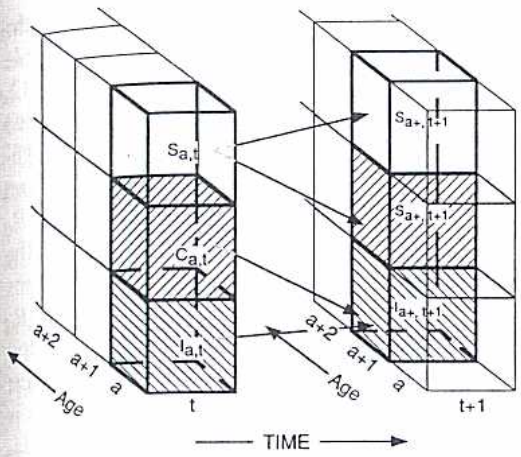


FIGURE 9. Schema for age-structured model, based on addition of age axes to figure 1. Simulation requires accounting susceptible ($S_{a,t}$), case ($C_{a,t}$), and immune ($I_{a,t}$) individuals over successive time periods. Such models generally include births, latent infections, and deaths (23).

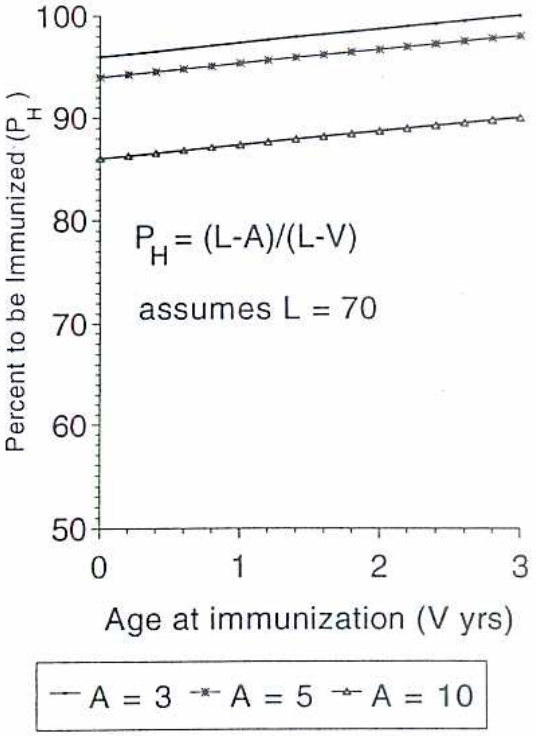


FIGURE 10. Relation between P_H (proportion of infants which must be immunized in order to attain herd immunity threshold), A (average age at infection), and V (age at immunization), assuming rectangular age distribution (equation 14). Illustrated solutions assume L = 70.

rectangular age distribution (figure 7B). By seeking the proportion P_H of a population which must be vaccinated at age V, in order to produce an overall proportion of immunes in the population equivalent to $(L - A)/L$ (see figure 7B), we find directly (23, 28):

$$P_H = (L - A)/(L - V). \qquad (14)$$

This relation (figure 10) is unrealistic insofar as it implies 100 percent vaccine efficacy and it neglects that the efficacy of many vaccines is age-dependent (for example, not reaching a maximum until age 15 months for measles). On the other hand, it nicely illustrates an important point, that simple crude estimates of immunity thresholds, which implicitly assume vaccines to be given at birth or as soon as maternal immunity wanes, (and to be 100 percent effective) will be optimistically low; and that much higher coverage levels are required because, inter alia, of the inevitable delays in providing vaccines to some members of the community.

The assumption of *variations in infection risk by age* has even more complicated and important effects on herd immunity threshold estimates. It is common knowledge that certain age groups are at special risk for childhood infections, and it is intuitively reasonable that this should be so considering the implications of aggregation in schools in particular. Figure 11 shows annual *risks* of reported measles by age in England and Wales prior to introduction of vaccination, showing the dramatic effect of the aggregation of children in primary schools from the age of 5 years. Very few children made it to their eighth birthday without having contracted infection with the measles virus! The actual *risks* of infection in any age group (a) are a consequence of "contact" not only within that group, but also between that age group and each of the other age groups in the community. The simple mass action formulation can be generalized to define the incidence of infection in age group a as the sum of infections acquired from contact within age group a, and between that and

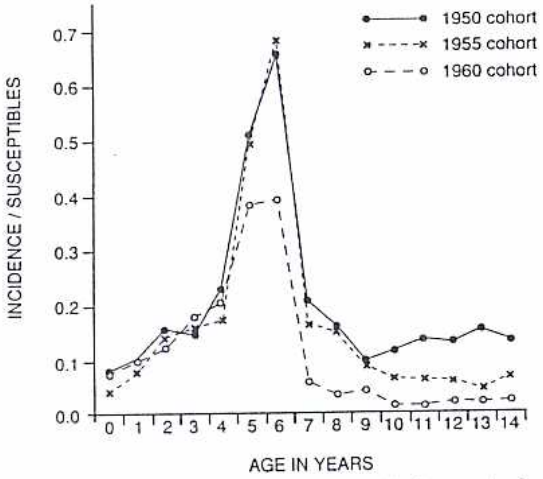


FIGURE 11. Age-specific risks of notified measles in three birth cohorts in England and Wales prior to the introduction of measles vaccination in 1968. Denominators are the numbers of individuals presumed susceptible (not yet immunized or infected) in each age group (55). Note the steep increase at age 5 years on entry to primary school. Low risk after age 6 years in the 1960 cohort reflects reduced transmission after introduction of vaccination.

each of the other age groups ($i = 1,2,3 \ldots a \ldots n$) to be considered:

$$C_{a,t+1} = \sum_{i=1}^{n} S_{a,t}\, C_{i,t}\, r_{a*i}. \qquad (15)$$

Here, the a subscripts refer to separate age groups and r_{a*i} stands for the contact or transmission parameter between age groups a and i. Reiteration is based on recalculation of numbers of susceptibles and cases in each age group at each successive time period, taking into account transitions from one age group to the next.

Exploration of the effects of this additional structure is hampered by the difficulty (perhaps impossibility) of obtaining appropriate data defining the contact parameters within and between different age groups in any population (let alone that any such parameters would vary between different populations and change over time). The theoretical implications of such age structure were thus explored by Anderson and May (36) in the context of simplified "WAIFW" ("Who Acquires Infection From Whom") matrices defining contact between limited numbers of age groups (in effect the r_{a*i} parameters of equation 15). An example of such a matrix is shown in figure 12. Analysis of these structures has revealed that, under different circumstances, age-dependent contact rates can lead to either an increase or a decrease in the estimates of R_0 and H compared with those derived from the simple global mass action assumptions above (36). In general, crude estimates of R_0 (e.g., from equations 11 or 12) will be too high if age-specific contact rates are highest among the young and fall with age. This is reasonable as older susceptibles will be relatively less relevant insofar as they are less likely to have the sort of contact necessary for transmission. In contrast, crude estimates of R_0 will be too low if contact rates rise with age.

Season and other periodic changes. Most of the common vaccine-preventable diseases are seasonal. The most obvious example of this is the seasonal increase in measles which follows the annual opening of primary schools in many countries (61). It was recognized long ago that this had implications for the mass action theory as it

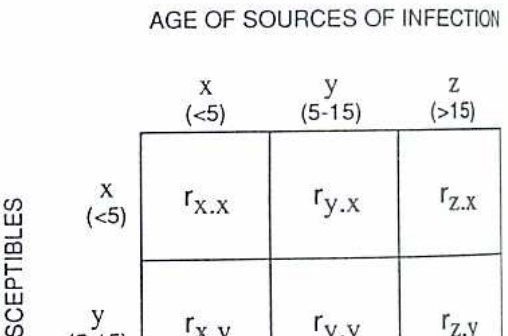


FIGURE 12. "WAIFW" (Who Acquires Infection From Whom) matrix of transmission parameters within and between three different age groups, preschool, school-age, and adult. Under most conditions such a matrix would be symmetric along the *xx-yy* axis, ($r_{xy} = r_{yx}$), though this need not necessarily be the case (e.g., the hygiene habits of younger children may be different making them particularly efficient at transmitting some infections, in which case, for example, $r_{xy} > r_{yx}$).

meant that there must be seasonal changes in the transmission parameter r (and in the basic reproduction rate) (51). Some early authors tried to mimic these changes by attaching trigonometric functions to the contact rates in their models (51, 62), but more recent authors have taken more pragmatic approaches.

Yorke et al. (63) discussed the implications of seasonality for eradication strategy employing the simple mass action approach. Though these authors did not argue in terms of herd immunity thresholds or basic case reproduction rates per se, they noted that transmission is most tenuous (i.e., R_0 is minimal) just before, or during, seasons of lowest incidence, and that it should be easiest to break transmission at these times. (Though they did not so express it, the implication was that the herd immunity threshold is lowest during such periods, and, thus, that a vaccine coverage level which is not high enough to "interrupt transmission" in peak seasons may nonetheless be sufficient to do so during the annual low.)

The implications of periodic aggregation of children in schools was explored by Schenzle (7) who constructed a compartmental model for measles simulation which included both age structure and appropriate changes in the transmission parameters to mimic the periodic aggregation of successive cohorts of children in schools. His results are of particular interest in that they provide a closer approximation to observed measles trends and the impact of vaccination (in England and in Germany) than has been achieved by any other published model. As with the other models incorporating age structure and a declining contact rate with age, Schenzle's simulations suggested a herd immunity threshold for measles which was appreciably lower than that predicted by the simple homogeneous mixing model. In his own words: "The quantity $[R_0 = T/S_e]$ has no meaning at all in the presence of age-dependent contact rates, where infectives of differing ages are assigned different infectious potentials. These have to be weighted appropriately in order to determine a 'maximum initial infection reproduction rate,' R_{max}, which quantity must be used in defining conditions of herd immunity. . . . As a consequence the present model implies herd immunity against measles with substantially lower immunization rates than are predicted from global mass action theory. Here the calculated critical immunization coverage would be 76 per cent if protection by vaccination could be achieved in newborns" (7, pp. 187–8). The extent to which Schenzle's surprisingly low estimate of measles herd immunity might have been attributable to his assumptions of annual changes in transmission (low R_0 values during the summer months), in addition to the assumed age structure and age-dependent contact rates, is unclear.

Timing of interventions. The Schenzle paper cited above, and work by others (64) have shown that the predicted impact of an intervention can also vary according to the timing of its introduction into a population. Though it has been proposed that certain situations can lead to "chaotic" results (65), it is unclear to what extent such effects are relevant to actual programs, given that real life includes many structured perturbations (such as school year calendar variation and holiday-dependent delays in notification) beyond the scope of the assumptions of simple mathematical models. On the other hand, such work lends another perspective to the interpretation of irregular incidence patterns.

Social and geographic clustering. The disparity between the homogeneous mixing assumption of basic models and the heterogeneity in structure and mixing of real human populations is obvious. The importance of social aggregations such as families, play groups, neighborhoods, and schools, and geographic distinctions between towns and urban and rural areas, mean that human populations are partitioned in a complex set of interlocking patterns with inevitable implications for the transmission of infections. Fox et al. (15) showed great insight in tackling this problem in their original paper on herd immunity. Since then, though several

subsequent investigators have attempted to build models with social or geographic structure, few useful generalizations have arisen (7, 20, 22, 23, 29). In one sense, social and geographic partitioning of populations just represents an extension of the sort of partitioning represented by age. All individuals belong to many different subgroups in society, and the transitions from one subgroup to another (by aging, migration, etc.), as well as the contact rates within and between all subgroups, will vary according to many different factors, many of which will, in turn, be confounded with one another (socioeconomic status, political, social, and historical context, behavior, hygiene level, crowding, season, mode of infection transmission, etc.). In an effort to describe just the most superficial level of such complexity, May and Anderson (29) formulated a set of general equations describing populations broken into several groups with two different within and between group (high and low) transmission characteristics. They found that eradication could be achieved with fewer overall vaccinations if they were distributed primarily to the high contact rate groups (e.g., cities) than if they were distributed uniformly to the overall population (but see also (22)). Beyond this intuitively sensible qualitative result, that it may be advantageous to target interventions at high risk groups, we are left with the conclusion of Fox et al. (e.g., table 3) that social structure can have profound effects on the likelihood and patterns of infection transmission and, hence, upon herd immunity thresholds.

Overall implications of additional variables. Implications of the various supplemental assumptions which have been explored in recent theoretical work on herd immunity are summarized in table 4. The difficulty of making precise estimates of herd immunity thresholds in any particular context is evident for each of the various influences even without considering the in-

TABLE 4. Implications of different assumptions for theoretical estimates of the herd immunity threshold (H), with reference to simple global estimates as obtained by equation 8, 11, and 12

Variable + assumption	Implications for herd immunity	References
Maternal immunity	If vaccines not effective until maternal immunity wanes, crude H estimates will be too low; this may be corrected by considering that a child is not born until maternal immunity disappears (equation 13)	(23)
Variation in age at vaccination	Herd immunity effect greatest (H threshold lowest) when vaccination occurs at earliest possible age; delayed vaccination implies threshold coverage level will be *higher* than simple estimates	(8, 28)
Age differences in "contact" rates or infection risk	Implications vary with relation between age and contact rate; falling contact rate with age implies true H may be *lower* than simple global estimate	(7, 36)
Seasonal changes in contact rates	Seasonality may imply *lower* true herd immunity threshold if seasonal change is marked, and fade out can occur during low transmission period	(7, 63)
Geographic heterogeneity	In theory, geographic differences in contact rates may permit elimination with lower overall vaccine coverage than that implied by H based on total population by targeting high risk groups	(20)
Social structure (nonrandom mixing)	Social structure can have complicated implications as it implies group differences in vaccination uptake and/or infection risk; existence of vaccine-neglecting high contact groups means true H will be *higher* than simple estimates	(15)

evitable interactions between them (i.e., different age groups have different social structures and seasonal patterns of aggregation).

PRACTICE

This section examines the relation between theory and experience of herd immunity with reference to particular vaccine-preventable diseases.

Smallpox

The historic elimination of smallpox was one of the important stimuli behind the recent interest in herd immunity. The initial World Health Organization encouragement toward global eradication of smallpox came in a resolution passed by the 12th World Health Assembly in 1959, which stated that "... eradication of smallpox from an endemic area can be accomplished by successfully vaccinating or revaccinating 80 percent of the population within a period of four to five years, as has been demonstrated in several countries" (66). The wording is of interest in its explicit stipulation of a herd immunity threshold and also in its implication that waning vaccine-derived immunity might pose an obstacle to achieving the threshold (thus the call for revaccination).

The disappearance of smallpox from many regions despite the continued presence of large numbers of unvaccinated susceptibles was evident from the historical record (as had been noted by Farr (41) more than a century ago). This is consistent with relatively low estimates of household secondary attack rates, basic reproduction rates and, hence, herd immunity thresholds for smallpox (table 1) (67). It is notable that the 1959 World Health Organization recommendation implied an R_0 of 5. Though this is consistent with more recent theory-derived estimates, it was based originally upon experience alone, having been made prior to the development of the elegant herd immunity theory discussed above. On the other hand, the validation of such estimates, however derived, remains difficult. In practice, the severity of smallpox, in particular variola major, was such that outbreaks generally led to active intervention, in effect to different forms of quarantine and ring vaccination, and, hence, it is not always clear to what extent the disappearance of the disease from different populations was due to the general or to the selective vaccination.

Arita et al. (68) assembled data on crude population densities and smallpox vaccination coverage in African and Asian countries during the late 1960s and early 1970s. Despite inevitable problems of nonuniform distributions of populations and of vaccinations, let alone the inaccuracy of vaccination statistics themselves, these data indicate that smallpox disappeared early from countries in which the crude density of susceptibles (unvaccinated individuals) fell below 10 persons per km^2 (corresponding to 80 percent coverage in populations with crude population density less than 50 persons per km^2. The infection persisted in more densely populated regions, however, in particular Nigeria (54 persons per km^2), Pakistan (83 persons per km^2), India (175 persons per km^2), and Bangladesh (502 persons per km^2). Whether or not continued reliance upon population-wide vaccination programs might ultimately have been sufficient to eliminate smallpox from the more densely populated nations of Africa and Asia is now a moot point. If the 10 susceptibles per km^2 threshold is a guide, then 98 percent vaccination coverage would have been necessary for Bangladesh, and such coverages were impracticable. However, it was recognized by 1970 that variola virus could be eliminated from populations more effectively by a policy of active case detection, contact tracing, and the breaking of individual chains of transmission by quarantine and ring vaccination than by relying entirely upon herd immunity from mass vaccination programs (69). In effect, the focus of prevention activity shifted from the population back to the individual. The success of this policy is now a matter of record (67).

Among the major lessons from the smallpox program was the inadequacy of relying too heavily upon reported vaccine uptake statistics and herd immunity predictions for disease eradication. Many experiences illustrated that reported data could be extremely unreliable, and that implicit assumptions of uniform or random coverage with vaccines were misleading. High coverage statistics often obscured the fact that important segments of a population were inadequately vaccinated and could serve to maintain and transport the infection for long periods and distances (67, 68).[9] The disappearance of smallpox from many populations prior to the intensive campaigns of the final elimination program are consistent with herd immunity and indirect protection of unvaccinated susceptibles having contributed importantly to the overall decline of this disease. Beyond that, the persistence of the disease in densely populated third world countries despite apparent vaccination coverages far in excess of the World Health Organization's recommended 80 percent herd immunity threshold probably reflects two important factors: 1) that R_0 varies importantly *between* populations and is a function of population density, and 2) that it varies importantly *within* populations as a consequence of complex social patterns.

The smallpox experience is thus salutary in demonstrating both the validity and the limits of herd immunity in practice. It should also be appreciated that several features of the natural history of smallpox favored the shift in strategy away from the emphasis upon herd immunity, in particular the high case-to-infection ratio and characteristic pathology (which facilitated detection of cases) and the relatively low transmissibility (see table 1) (which facilitated control by identification of contacts and ring vaccination). Without these characteristics, much greater emphasis would have had to be placed on raising general herd immunity levels in order to achieve eradication of this disease.

[9]It was such experiences which led to the naming of the World Health Organization's Expanded Programme on Immunization, the intent being to increase *immunizations*, not just vaccinations (R. H. Henderson, World Health Organization, Geneva, Switzerland, personal communication, 1993).

Measles

No disease has been studied more intensely with reference to herd immunity than has measles (3, 4, 6, 7, 27, 28, 43, 51, 55, 57, 61, 70). There are two reasons for this: 1) measles has long been a favorite subject for theoretical modeling, because of its frequency, its regular behavior, and the high quality of available data, and 2) there has been serious discussion ever since 1967 of the possibility of eliminating measles both nationally and internationally (57, 71–74). These discussions have relied heavily on perceived estimates and implications of herd immunity.

Table 5 lists published estimates of herd immunity thresholds for measles, with notes commenting on the assumptions upon which each was based. The earliest cited estimate, explicit in the published declaration that measles would be eradicated from the United States during 1967, was derived from a combination of intuition, epidemiologic experience, and bold interpretation of a classic paper by Hedrich (75). Hedrich had analyzed measles notifications in Baltimore, Maryland, between the years 1900 and 1931 and showed, by cumulating age-specific notifications, that measles epidemics appeared when the proportion immune among children (under 15 years of age) fell below 55 percent (76). The 1967 US Public Health Service prediction of measles elimination was based upon this figure as an estimate of the herd immunity threshold, *neglecting the population over 15 years of age* because in unvaccinated populations such older age groups were then not involved in measles transmission. In retrospect, we see two problems with this threshold estimate. First, as soon as vaccination is introduced, transmission is reduced, and the mean age of cases increases, and given that all age groups are

TABLE 5. Measles herd immunity thresholds H^* as predicted in the published literature

H (%)	Situation (assumptions)	References
55	Based upon Hedrich's (75) analysis of Baltimore, Maryland, data indicating that epidemics began when less than 55% of children under 15 years were immune; invalid because older individuals were neglected	(57)
70	Compartmental model, assumptions not clear from publication but may have included inappropriate parameter values (23)	(6)
76	Compartmental mass action model with age and season; data from England and West Germany	(7)
85	Stochastic simulation of a West Africa situation; measles elimination predicted if 85% of susceptibles immunized every year	(136)
94–96	Compartmental mass action model with age, but no season	(8)
95	Simple discrete time mass action with season but no age	(63)
Not specified	Reed-Frost model simulation of population with social structure but no consideration of age, season, or introduction of susceptibles	(4, 15)

* H, herd immunity threshold defined as the minimum proportion to be immunized in a population for elimination of infection.

potentially able to participate in measles virus transmission, the total population should be included in the denominator. Indeed, if everyone aged greater than 15 years were immune, then the estimate of 55 percent immunes among those aged less than 15 years corresponds roughly to 90 percent immunes among the total population, and is thus consistent with the theory discussed above and the simple estimates of R_0 and H shown in table 1. The second problem is the implicit assumption of homogeneous mixing.

The 1967 US Public Health Service prediction has been discussed by Langmuir in several lectures and publications (3, 77). These discussions are of particular interest in that they reflect the influence of early modeling theory upon the formulation of public health policy. Langmuir states that he was influenced strongly by his exposure to the Reed-Frost model while at the Johns Hopkins University School of Hygiene and Public Health during the 1940s, and that this was important in encouraging the 1967 prediction. It is thus ironic that it was, in part, the failure of this prediction (see figure 3C) which led to the work of Fox et al. in applying the Reed-Frost model explicitly to the problem of herd immunity (15). Fox et al.'s conclusion differed from Langmuir's, but was no less dogmatic. Twelve years after the original publication, Fox (4) reiterated his views with direct reference to measles, and in effect argued that herd immunity did not apply because of heterogeneity of contact within populations.

Though Fox was reticent (perhaps because of his experience) or unable (because of the modeling approach he used) to give a precise estimate of the proportion immune required to stem transmission of the measles virus, his pessimism was not shared by several modelers who subsequently published predictions based on variations of the mass action model approach (table 5). The range of these estimates, from 70 to 96 percent, is itself instructive in showing the implications of different sets of assumptions. Indeed, the range is such that those responsible for setting vaccination strategy may find that Fox's conclusion, though less precise (he provided no threshold estimates) and less apparently rigorous in its mathematical base, is the most useful of them all! In general, simple theoretical approaches provide crude estimates of R_0 in excess of 10 for measles in developed countries (except for some rural

area populations), and, hence, imply herd immunity thresholds in excess of 90 percent (table 1). The extremely low estimate provided by Cvjetanovic et al. (6) was based upon simulations that may have been logically flawed (23).

The comparison of theory with experience is complicated by the nature of the available data. Measles elimination has been declared policy in several countries, e.g., Canada, Czechoslovakia, Sweden, and the United States, and more recently the European and Caribbean regions of the World Health Organization. The strategy in each country is different, in terms of the number and timing of vaccine doses, and has changed over time. The United States experience is informative in its complexity because of the size of the population and the aggressiveness with which the elimination goal has been pursued. Given that global eradication is still impracticable and the consequent inevitability of measles importations, the United States has phrased its measles elimination target pragmatically, as a level of population immunity and of program capacity such that indigenous transmission of measles virus does not persist and that no more than two generations of transmission occur subsequent to any importation (74).

It is difficult to describe the immunity profile of a large nation such as the United States, because of several factors: 1) underreporting of measles cases (this has lessened in recent years, but was considerable during the 1960s), 2) the fact that measles cases were not reported by precise year of age until 1982, 3) the absence of precise age-year-specific vaccination uptake data, 4) variations in the estimates of measles vaccine efficacy, 5) absence of representative serologic data, and 6) controversies over the interpretation of different serologic assays (78), let alone the sheer size and heterogeneity of the population. It is evident that the incidence of measles in the United States has fallen by approximately 99 percent since the introduction of vaccination in 1963, even accepting the resurgence which began in 1989, despite the fact that a smaller percentage of individuals have been immunized. (Though approximately 98 percent of children in the United States have been *vaccinated* by school entry in recent years, an appreciable proportion escape vaccination until they approach school age, and it is known that only some 95 percent of vaccinations succeed in immunizing the recipients; thus, the proportion of the preschool population effectively immunized is probably less than 90 percent.) This in itself is indicative of a certain degree of indirect protection of nonimmunes by the presence of immunes and, hence, a form of herd immunity. However, despite the decline, measles transmission persists in the United States. Analyses of surveillance data suggest that transmission has been continuous in several large urban populations, in particular those with large poor inner city populations (New York, New York, Los Angeles, California, etc.) and only sporadic through the remainder of the country (5). It is likely that current immunity levels are high enough to prohibit continued transmission throughout most of the country but are insufficient in these urban areas, where special initiatives will be required to attain the high coverage requisite for interruption of transmission. Unfortunately, these urban centers present an extremely difficult challenge to public health providers, as the social conditions are least conducive to high vaccine uptake in the very areas where the highest uptake is required. Given the extent of population movement in such a nation, it is not surprising that the measles virus repeatedly escapes from urban centers into schools and communities throughout the land.

Faced with this situation, the Advisory Committee on Immunization Practice to the US Public Health Service recommended in 1989 that all American children receive two doses of measles vaccine, at 15 months of age and at school entry (79). It is hoped to increase overall coverage and to reduce the number of primary and secondary vaccine

failures from approximately 5 percent to less than 1 percent by this procedure.

Sporadic outbreaks of measles in highly vaccinated populations have raised another problem for herd immunity. Some authors have implied that such events challenge the concept of population protection by a high prevalence of immunes (3–5). This is too pessimistic an appraisal. The fact that indirect protection fails to occur in some communities or small populations (perhaps because of a chance aggregation of vaccine failures or an exceptionally high exposure intensity) does not invalidate that it generally does occur, just as the failure of a vaccine in one individual does not refute its effectiveness in most. That said, experience does suggest that most theoretically-derived estimates of vaccination uptake and herd immunity thresholds have been optimistically low because they do not cater for important heterogeneity within real populations.

Rubella

Though the basic transmission dynamics of rubella are similar to those of measles, it raises different questions relating to herd immunity. Public health concern with rubella is concentrated on the congenital rubella syndrome and, thus, upon infections occurring in women in their reproductive years (30). Control can in theory be brought about in two ways, either by reducing the proportion susceptible among women or by reducing their risk of infection. Different vaccination strategies have emphasized these two approaches to different degrees. Vaccination of adolescent girls, as practiced in the United Kingdom between 1971 and 1988, emphasized the reduction of susceptibles by ensuring a maximum percentage of females would acquire either natural or vaccine-derived immunity prior to their reproductive years. On the other hand, vaccination of boys and girls in their second year of life, as practiced in the United States since 1971 and in the United Kingdom since 1988, also leads to reduction of circulation of rubella virus and, hence, to the reduction of risk of infection for any remaining susceptibles in the adult female population. The herd immunity implications of these two policies are paradoxical as this is a situation in which low coverage vaccination (a little induced herd immunity) can be "worse" than none at all. Low vaccination coverage of young children of both sexes can, in theory, have a detrimental effect by reducing the transmission of rubella virus to such a degree that the proportion of women of reproductive age still susceptible to the virus, and the number of consequent cases of congenital rubella syndrome, actually increase. Several investigations have concluded that the threshold vaccination coverage which must be achieved and maintained in young children of both sexes, in order for the incidence of congenital rubella syndrome to decrease in the long term, is in the region of 50 to 80 percent (25, 30–32). The higher the initial intensity of transmission in the population, the higher the threshold of vaccination coverage required among young children in order to avoid increasing the incidence of congenital rubella syndrome. Given that vaccination uptake rates in the early 1970s in the United States and the United Kingdom were on the order of 90 and 50 percent, respectively, each nation's strategy was probably appropriate under the circumstances. As incidence rates of rubella infection are extremely high in some third world countries (e.g., The Gambia, which is one of the few populations with appropriate data), it would be unwise for them to introduce measles-mumps-rubella vaccine until they can confidently ensure and maintain coverage levels over 90 percent (23).

According to current estimates, rubella is less transmissible than is measles, and, thus, a lower herd immunity threshold should be required for its elimination (table 1). Given that measles and rubella vaccines are commonly combined in a single preparation, the strategy and success of the measles eradication efforts will have interesting implications for herd immunity to rubella and, thus, for herd immunity theory in general. It may be that rubella will disappear as a conse-

quence of measles elimination activities with no special additional efforts such as outbreak containment (e.g., school exclusion as is practiced as part of measles control in the United States). Such a disappearance would confirm the theoretical predictions of rubella R_0 levels and would demonstrate the power of herd immunity alone to dictate eradication of an infection.

Mumps

Mumps is similar to measles (both are paramyxoviruses maintained by respiratory spread) but is less transmissible in household settings and has a lower crude R_0, and, hence, a lower herd immunity threshold (table 1) (33). Mumps vaccine was licensed in the United States in 1968 but not recommended by the Advisory Committee on Immunization Practice until 1977. In the United Kingdom, mumps vaccine was not introduced until 1988. Routine mumps surveillance began in the United States in 1968. These data indicate that the incidence of the disease fell sharply over the 9 years between licensure and universal use of the vaccine in children. Mumps notifications have now fallen by more than 95 percent since the introduction of vaccination. Given that vaccine uptake has only recently reached that level among school entrants, that uptake among preschoolers is far below that level, and that mumps vaccine efficacy is probably below 90 percent (73, 80, 81), this decline in incidence is appreciably greater than would be predicted by direct protection alone. Assuming that the decline in reported cases reflects incidence and not a decline in notification efficiency, then this is evidence for indirect protection of susceptibles by herd immunity.

Only Sweden has thus far declared an intent to eradicate mumps (73). However, the routine administration of mumps along with measles antigens, coupled with the lower herd immunity threshold of mumps, indicates that it may disappear from several countries as a consequence of efforts directed at measles elimination. Indeed, if this does *not* occur, it will be of interest as an indication of special population heterogeneity relevant to mumps virus transmission.

Pertussis

Whooping cough is an ubiquitous disease of childhood. Responsible for considerable morbidity and mortality in the past, it has been a target for routine vaccination programs in many countries since the 1940s. These programs have been successful in reducing the burden of disease due to pertussis, and it is probable that herd immunity, in the sense of indirect protection, has played a role in this effect. For example, the protection of older children by vaccination has probably reduced the risk of infection for younger siblings who are at highest risk of severe complications of whooping cough. On the other hand, there has been little serious discussion of eradicating *Bordetella pertussis* (82). There is good reason for this reticence (83).

The cyclical pattern of pertussis provides a classic example of mass action dynamics (compare figures 2 and 3B) (34, 84). The crude basic reproduction rate of *B. pertussis* has been estimated to be approximately 15 for developed countries in recent decades (table 1). This is similar to measles and implies a crude herd immunity threshold of 93 percent. Consideration of age-dependent transmission has suggested a slightly lower estimate, 88 percent, assuming no waning of immunity (34). Given that these herd immunity estimates are higher than most estimates of the protective efficacy of a complete course of pertussis vaccine (85), and that there is evidence of waning vaccine-derived protection (85, 86), it appears that eradication of this infection is not currently possible by childhood vaccination alone.

Immunity to pertussis is extremely difficult to define, either in individuals or in populations. There is as yet no good serologic or other immunologic correlate for protective immunity (85, 87); history of disease is neither highly sensitive nor highly specific as an indicator of past infection and, hence, natural immunity; and there is considerable controversy over the efficacy of

available pertussis vaccines (85, 87). In addition, there is evidence that pertussis vaccines provide greater protection against pertussis disease than they do against infection with *B. pertussis*, and that adults may participate in transmission of the infection without manifesting characteristic signs of the disease (37, 84, 85, 87). Given all these unknowns, we are not able to make convincing predictions of the global herd immunity thresholds for this disease.

Diphtheria

Diphtheria is one of the success stories of public health. Though vaccine-induced herd immunity probably played a role in this success, the role was not straightforward and serves to illustrate additional complexities of herd immunity processes.

Diphtheria was a major cause of morbidity and mortality in Europe and North America during the last century. Incidence fell from the early years of this century but the decline accelerated along with introduction of widespread toxoid vaccination in the United States and the United Kingdom during the 1940s. As vaccination of less than 90 percent of children has led to more than 99.99 percent fall in disease, it appears that the herd immunity threshold against diphtheria was achieved in these populations. But what was the threshold, and how did it work?

One of the earliest published estimates of a herd immunity threshold for any disease was by Godfrey (88) who, in 1933, predicted that vaccination (three doses of diphtheria toxoid) of 30 percent of infants and children 0–4 years old and 50 percent of children 5–14 years old would be sufficient to eliminate diphtheria. Later authors proposed higher figures, on the order of 70–90 percent (89, 90) based on experience in developed countries, and application of simple theory gives an estimate of approximately 85 percent (17). Estimates aside, the *actual* proportion of diphtheria immunes in today's populations is an elusive quantity. Vaccine uptake is difficult to define as at least three doses are recommended, though one or two doses provide some protection (91). The protection imparted by diphtheria toxoid vaccines has never been evaluated in formal trials, but observational studies provide estimates ranging from 55 to 90 percent (11, 91, 92). Serologic studies have shown that vaccine-induced antitoxin titers decline with time or age (93), but may in some populations be lower among individuals born in recent decades, perhaps because they have not been boosted by exposure to natural infections (90). Surveys carried out in developed countries have shown a wide range in prevalence of "protective" antitoxin levels among adults, from 50 to 80 percent, leading to recommendations that adults should receive booster doses of diphtheria vaccine (90).

An even more fundamental issue relates to the nature of immunity induced by diphtheria toxoid vaccines and how it may differ from infection-attributable immunity. In the sense that herd immunity implies indirect protection, it requires immunity against *infection*. However, given that diphtheria toxin is not a normal constituent of *Corynebacterium diphtheriae*, the immunity induced by toxoid vaccination may not provide protection against infection at all. This view has been expressed by numerous authors; e.g., ". . . immunization with diphtheria toxoid is protective only against the phage-mediated toxin, and not against infection by the *C. diphtheriae* organism" (94, p. 1396). Some studies which have attempted to measure these two different types of immunity have found results consistent with this prediction (11, 92). However, if diphtheria toxoid vaccines did not impart *any* protection against infection, then one might predict that there should have been no change in the incidence of *C. diphtheriae* infection in the community and no change in the risk of *disease* in unvaccinated individuals. In effect there should be no evidence of herd immunity, a prediction which is inconsistent with the extremely low rates of diphtheria in recent years. Resolution of this paradox is probably related to the fact that transmission of the diphtheria bacillus is much more ef-

ficient from clinical cases than from subclinical carriers (95); thus, the vaccines protect against infection transmission, not (or more than) against infection receipt! Resolution of the implications of the various forms of immunity to diphtheria would require a major research effort. It is unlikely that this will ever be accomplished, given that the disease is no longer a major public health problem.

Tetanus

Tetanus is not directly communicable between hosts, and, thus, vaccination cannot lead to indirect protection in the source-reduction sense implied in many definitions of herd immunity. Strict adherence to the definition quoted by Fox et al. (15) (see above) would mean that herd immunity is not relevant to tetanus at all. Certainly there is no threshold proportion of immunes, below 100 percent, which can ensure total absence of tetanus from a community.

There is little doubt that the introduction of routine tetanus toxoid vaccination in the 1940s had an impact upon trends and patterns of the disease. However, the fact that the incidence of tetanus was declining prior to widespread vaccination, because of decreasing exposure (fewer people in contact with soil and animal feces which are the main reservoirs of the tetanus bacillus) and the widespread use of tetanus toxoid in wound management make it difficult to assess the precise extent to which the prophylactic vaccination has contributed to the decline in tetanus morbidity.

Despite the noncommunicability of tetanus, vaccination of certain individuals does impart indirect protection to others in the community. Antitetanus immunity of mothers is transmitted across the placenta, and two doses of toxoid during pregnancy can protect a woman's offspring against neonatal disease (96). This is extremely important in that the public health importance of tetanus on a global scale is attributable largely to neonatal disease. In 1989, the World Health Assembly declared an initiative to *eliminate* neonatal tetanus by 1995 (2). Though the intervention will include efforts to improve birth practices, it will be based largely upon provision of tetanus toxoid vaccine to girls and women (97). If "elimination" were to be interpreted as reduction to zero, then this initiative requires 100 percent effective vaccination coverage of 100 percent of the target population.

Poliomyelitis

The issue of herd immunity in polio has been debated for more than 3 decades. The debate has been notable for its partisan fervor and confusing for its shifting focus to and from different types of herd immunity induction by different types of polio vaccines (12–14, 98). The ecology and herd immunity characteristics of polioviruses are heavily dependent upon levels of hygiene. Serologic surveys carried out in the past among unvaccinated populations revealed that the average age at infection ranged from less than 2 years in nonhygienic environments in developing countries to more than 10 years in developed countries (99–101). Interpretation of such values in the context of equations 8, 12, and 13 suggests that the basic reproduction rate ranges from 5 to 30, and that the herd immunity threshold ranges from 80 to 97 percent depending on the level of hygiene.

The polio herd immunity controversy has been part of a broader argument concerning the relative advantages of killed, inactivated polio vaccine versus live oral polio vaccine. Among the arguments favoring the live vaccines has been the claim that they provide much greater herd immunity than do inactivated polio vaccines (12, 14). Two points are embedded in this claim. The first is that live vaccines impart greater intestinal (local, immunoglobulin A-mediated) immunity, and, hence, impart greater protection against *infection* than do the killed vaccines (which induce protection more directly against tissue invasion and *disease*). To the extent that this is so, then recipients of killed vaccines may be protected effectively against disease but still be susceptible to enteric wild poliovirus infection, and thus provide little or

no indirect protection to their unvaccinated neighbors. If this were so in the extreme, then herd immunity thresholds would be invalid for such vaccines, and only 100 percent inactivated polio vaccine coverage of a population would suffice to protect it from disease. However, this argument has sometimes been overstated. Though there is evidence that prior live oral polio vaccine recipients excrete less virus in their feces than do prior recipients of inactivated polio vaccine, after subsequent challenge with live polio vaccine virus strains, it has also been demonstrated that fecal and oropharyngeal virus excretion is reduced among prior inactivated polio vaccine recipients compared with unvaccinated individuals (102, 103). Thus, inactivated polio vaccines do provide some protection against infection transmission. The greater propensity of inactivated polio vaccine to reduce oropharyngeal excretion of virus might be particularly important in populations with high levels of sanitation, in which respiratory transmission of poliovirus is more important than in areas with poor sanitation conditions, where transmission is overwhelmingly by the fecal-oral route (14).

The second argument for greater herd immunity induction by live oral rather than inactivated polio vaccine is based upon the fact that live polio vaccine virus is excreted in the feces and the oropharynx in sufficient quantities for it to be transmitted to contacts. This unique attribute of live oral polio vaccine provides a special mechanism for indirect protection of nonvaccinees, in effect by vaccinating them surreptitiously. The frequency of such live oral polio vaccine spread is dependent on hygiene behavior and intimacy of contact, and varies greatly between populations. Studies carried out in the 1950s in Louisiana and in the Seattle, Washington, virus watch program, showed that oral polio vaccine virus was transmitted to 35–80 percent of child contacts of live oral polio vaccine recipients within low socioeconomic group households, though less frequently within better-off households, and that considerable transmission also occurred beyond the confines of households (104, 105). This means that the proportion *immunized* in a population receiving live oral polio vaccine is a function of three factors: vaccine uptake, vaccine efficacy, and vaccine virus transmission. The advantage inherent in this unique attribute of the live polio vaccines is tempered only by the fact that the live oral polio vaccine virus may rarely undergo reversion to virulence, and, hence, a small proportion of the contacts of vaccine virus may actually contract paralytic disease (this risk has been estimated to be of the order of one such case per million vaccine doses administered) (106).

It appears that wild polio viruses ceased to circulate in most of the United States by 1970, at which time only some 65 percent of children were receiving a complete course of live oral polio vaccine (14). However, given the complex history of previous inactivated polio vaccine and then live oral polio vaccine programs in the country, and the propensity of live oral polio vaccine viruses to circulate in the community, the overall level of immunity in the population is unknown. Given the evidence for disappearance of wild polio viruses from the United States (107), it is probable that the prevalence (or subpopulation-specific prevalences) of immunity was (were) considerably above whatever herd immunity threshold(s) might have been in force.

In addition to the virologic evidence for reduced fecal excretion of virus in inactivated polio vaccine recipients, there is epidemiologic evidence for indirect protection by killed polio virus vaccines. An analysis of surveillance data from the United States suggested that polio incidence fell by a greater degree during the years 1955–1961 (when only killed vaccines were in use) than could be explained by the direct protection of vaccinees alone (108, but see also 14). More convincingly, countries which have used only killed vaccines (e.g., Sweden, Finland, and the Netherlands) have experienced virtual elimination of circulating wild polio viruses for long periods of time (109, 110). An outbreak of 10 cases in Finland in 1984–

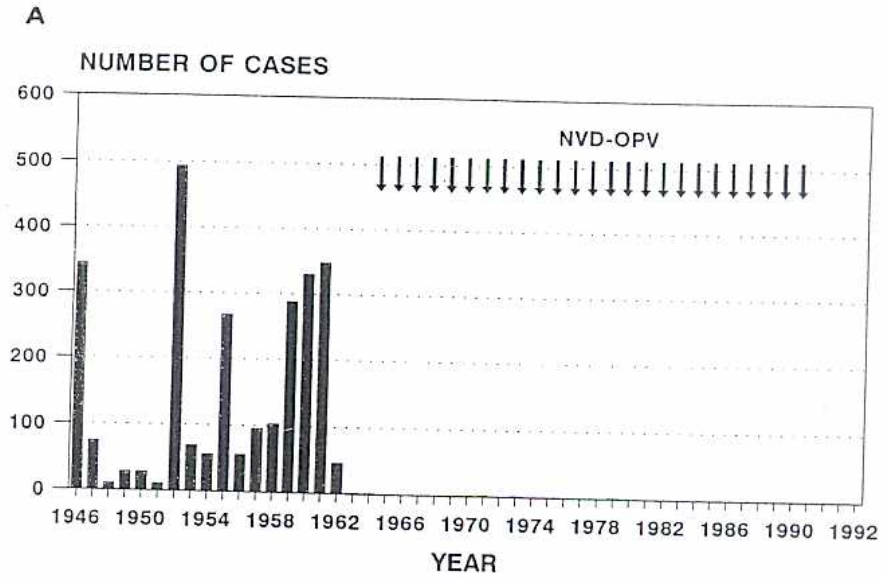
1985 was attributed to a type 3 virus different from that included in the vaccine (110). Outbreaks in the Netherlands have been restricted almost entirely to a religious community which refuses vaccination altogether, with no evidence of transmission in the population at large despite the presence of at least 400,000 individuals who have never been vaccinated at all (98, 111).

Current efforts at global eradication of polio highlight the importance of herd immunity. Given the low case-to-infection ratio of polio (probably less than 1 percent of infections are recognizable clinically) and the potential of poliovirus to spread through sewage, water, and foodstuffs, case finding and outbreak containment will be less efficient in controlling poliovirus spread than they were against smallpox and might be against measles. There will thus be a greater reliance upon high levels of herd immunity in the strategy for eradication of polio than for these other diseases. This has been recognized in the use of mass live oral polio vaccine campaigns, first in Cuba, then in Brazil, and more recently throughout Latin America (112). By providing live oral polio vaccine to large segments of the population (e.g., all children under 5 years of age) simultaneously, this approach ensures flooding of the environment with live oral polio vaccine virus to such a degree that very few individuals escape direct or indirect vaccination (figure 13). Though the approach has been manifestly successful in eliminating wild polio virus from Latin America, questions remain over its applicability in Africa and Asia because of greater logistic difficulties and evidence that the efficacy of live oral polio vaccine may be lower in these areas than in other parts of the world (98, 113). It is possible that the lower efficacy could also indicate lower indirect transmission of live oral polio vaccine in some environments, as both may be impeded by the high prevalence of other enteric virus infections. This and related concerns have led to continued debates over inclusion of combined inactivated-live oral polio vaccine regimens in the strategy. The population implications of all these environmental, vaccine type, and vaccination strategy variables are complicated. Given the pace of the global program in the face of its year 2000 target, it is unlikely that there will be sufficient time and research to comprehend fully the herd immunity mechanisms of polio control, unless the strategies fail and resources are diverted back from operations to research.

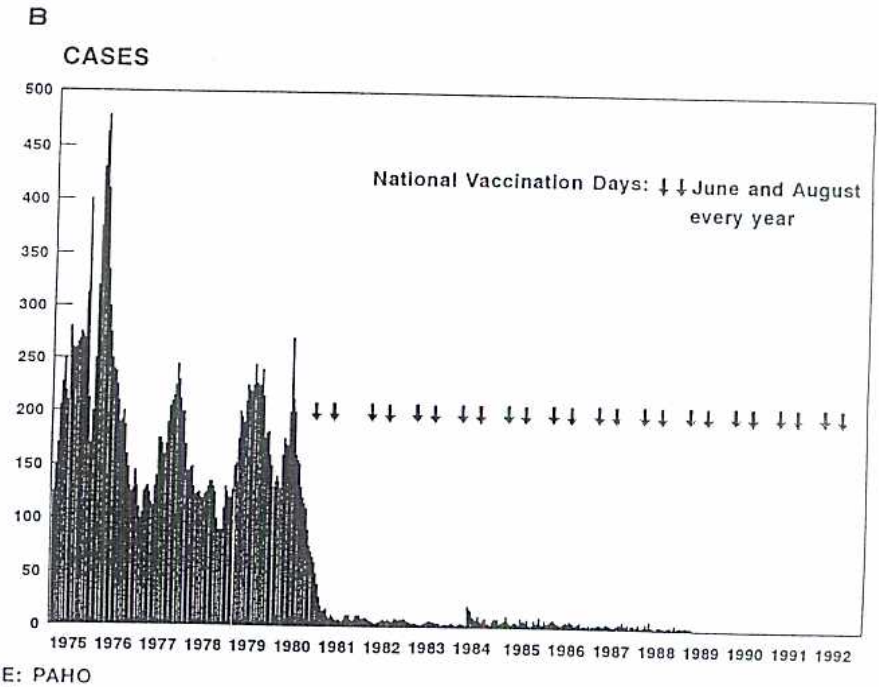
Influenza

Type A influenza viruses present yet another set of herd immunity problems. Given the genetic lability of these viruses, as manifested in frequent major (shift) and minor (drift) antigenic changes of their hemagglutinin (H) and neuraminidase (N) antigens, and their persistence in many different vertebrate species, there is no prospect of their total eradication. On the other hand, herd immunity has frequently been invoked in the literature as an explanation for the changing profile of influenza viruses in human populations and the successive disappearance of specific antigenic subtypes (35, 114). The argument is that increasing proportions immune to each individual influenza subtype, and varying degrees of cross protection provided between subtypes, should provide a selective pressure favoring the spread of new antigenic variants. Though such a mechanism appears to fit the available evidence, it does not lend itself to precise numerical description, given the complicated immunologic relations between virus subtypes, the possibility that immunity to influenza may be less durable than immunity to many other viruses, and the unpredictable nature of the antigenic changes of these viruses.

The hypothesis that herd immunity to influenza viruses has been a driving force in the selection of new predominant strains in the human population has another interesting feature. One of the peculiarities of influenza epidemiology is the observation that, although prior to 1977 only a single major virus (shift) subtype was found circulating in the human population worldwide at any time, more recent years have wit-



SOURCE: COUNTRY REPORTS TO PAHO



SOURCE: PAHO

FIGURE 13. Notified cases of polio in Cuba (A) and Brazil (B) in recent decades showing the effect of national vaccination days (*arrows*). PAHO, Pan American Health Organization.

nessed the cocirculation of different subtypes (e.g., H_1N_1 and H_3N_2) simultaneously in the same populations (115). Why this should have occurred in unclear. If the observation is correct, and does not reflect changes in virologic surveillance, then the recent appearance of cocirculating viruses may indicate one of two possibilities: 1) either the viruses are now different, perhaps providing less cross-subtype (e.g., H_3N_2 versus H_1N_1) protection than in the past, or 2) the human population has changed, per-

haps by increasing in total number, in number of new susceptibles added per year, and/or in worldwide communication, to such extent that individual virus subtypes may reduce susceptibles to below threshold levels in some populations but still persist in others for long enough to allow sufficient accumulation of susceptibles in the first group to again support transmission. If this is so, and the recent appearance of multiple cocirculating influenza viruses does reflect such changes in the human population, then this could have implications for the worldwide control of other infectious agents.

Though eradication of type A influenza viruses is not possible, their control by immunization is an important public health activity in all the wealthier countries. There has been much discussion of influenza vaccination strategies, given the changing antigenic nature of the viruses, their rapid spread, explosive epidemics, and serious impact in terms of sickness absences among the employed and mortality among the elderly. One proposal has been to reduce community spread by concentrating on vaccination of schoolchildren, as transmission within crowded classrooms leads to rapid dispersal throughout the community, and into the homes where susceptible adults reside. It is of interest that Fox et al. (15), whose seminal paper on herd immunity was discussed above, were particularly interested in influenza and used their heterogeneous-population simulation model to explore various strategies of influenza control, including selective vaccination of schoolchildren (116). A comparison of influenza spread between two communities in Michigan, one with and one without schoolwide vaccination, provided evidence of the effectiveness of this selective herd immunity approach (117), and the strategy has been national policy in Japan for many years (118). Despite such theory and evidence, the national policy for influenza control in the United States (and most other wealthy countries) has emphasized direct protection of high risk individuals and not indirect herd protection through reduced transmission (119).

Tuberculosis

Tuberculosis is included in this review in recognition of the fact that immunologic intervention, in the form of BCG vaccination, remains an important element in the control of this disease in most countries of the world. More people alive today have received BCG than have received any other vaccine. In addition, it presents yet a different perspective of the problem of herd immunity, given that natural immunity to tuberculosis is generally associated with persistent, rather than self-limited, infection. (In this sense, it may be compared with other persistent infections such as those associated with the herpes viruses).

There has been little discussion of herd immunity with reference to tuberculosis. A major reason for this silence is the rudimentary level of our understanding of the nature and implications of either natural or vaccine-derived immunity to this disease (120). We deal here with an infection whose major sources of transmission in most communities are due not to failures to acquire prior protective immunity but to the losses of protection in older, long infected, individuals. There is no evidence thus far that available vaccines are able to prevent this loss of protection. Indeed, despite the widespread use of BCG vaccines and the good evidence that they can impart appreciable protection against pulmonary disease in some (but not all) populations (121), there is no convincing evidence that the use of BCG vaccines has reduced the risk of infection with the tubercle bacillus in any population (122). In the absence of greater basic understanding of the nature and implications of the immune response to tuberculosis, it is of questionable utility to ponder its theoretical herd implications.

Malaria

Though malaria is not generally included among the vaccine-preventable diseases, it deserves mention here because it illustrates

yet another set of problems related to herd immunity. Considerable effort is now being devoted to the development of malaria vaccines which may ultimately provide means for manipulating the immunity of human populations against these pathogens. The concepts of a basic reproduction rate, and of an eradication threshold, were formulated with reference to malaria before being applied to any other infection (54). The calculation of R_0 is different with reference to vector-borne than to directly communicable infections, as the contact parameter (r or p in the simple mass action or Reed-Frost formulations) is a function of the density, survival rate, and feeding behaviors of the vector populations (23, 54). Studies in various regions of the world have provided estimates of R_0 for malaria in the range from 5 to 100, which would imply herd immunity thresholds from 80 to 99 percent. These reflect tremendous regional variations in the epidemiology of malaria and have been interpreted as indicating that vaccines alone will never be sufficient to eliminate malaria, in particular from the holoendemic regions of Africa. However, recent studies on the antigenic diversity of *Plasmodium falciparum* indicate that multiple genotypes of the parasite may cocirculate in endemic areas. If these reflect independent populations, then previous estimates of R_0, which have implicitly assumed a single population of parasites, may have been too high (S. Gupta et al., Imperial College London, manuscript in preparation). These new results suggest that *individual* genotypic populations each have R_0 values on the order of 7, and, hence, might be amenable to elimination by high vaccine coverage (>87 percent), and raise new questions about the genetic diversity and stability of the parasite population.

Another unusual feature of malaria relating to herd immunity is the fact that several different types of malaria vaccines are under development, and these may have different individual as well as population actions. The simplest vaccines, based on sporozoites or merozoites, would, in theory, provide protection against infection in the recipient and, hence, work like most conventional vaccines. However, there are also vaccines against the transmissible stages (gametocytes), which would, in theory, provide no protection against initial phases of the infection or against disease in the individual recipients, but only against the transmissibility of the infection (123, 124). We thus have the potential for a new possibility, vaccines which protect against transmissibility but *not* against disease! Apart from the ethical problems (is it acceptable to give a vaccine which imparts no direct protection to the recipient?), this raises new strategic questions concerning the appropriate deployment of such reagents in order to optimize their impact.

DISCUSSION

This brief review of various infections reveals numerous complexities to the measurement and interpretation of functional herd immunity. The concept is simplest in the context of the nontransmissible infections, such as tetanus, in which it refers only to the direct protection of that proportion of the population actually immune (though complicated in this particular example by the important passive transfer of maternal antibodies which can protect infants from neonatal disease). It becomes more subtle with reference to directly transmitted viral infections such as measles, rubella, and mumps. Infection with these (wild or attenuated-vaccine) viruses leads to long-lasting immunity against subsequent infection, and we can expect that the risk of infection in individuals still susceptible will vary in some inverse fashion with the proportion of such immunes in a population. Further complexities are introduced by the fact that both vaccination and contact behavior have highly clustered distributions in real populations, and these distributions will determine the net effect of the presence of immunes. For many other infections, exemplified in this review by pertussis, diphtheria, poliomyelitis, tuberculosis, and malaria, the complexity is much greater yet, as a consequence of the fact that vaccines can pro-

vide various sorts of immunity, i.e., which may act against infection, or against disease, or against transmission, or which may decline with time or age, or which may be transferred indirectly to unvaccinated individuals. Our understanding of the implications of population immunity in all these latter infections is seriously hindered by our incomplete understanding of the full implications of immunity in individuals.

There is also a sense in which our understanding of immunity in individuals is dependent upon that in populations. Measures of vaccine efficacy—in effect the proportion with protective immunity among those who have been vaccinated—may be exaggerated if vaccination coverage is not random in a population. If vaccinated individuals are clustered in community groups, then they benefit both directly, from individual receipt of the vaccine, but also indirectly, from reduced transmission in their neighborhoods (because of the herd immunity associated with the concentration of vaccinated individuals). In such circumstances the vaccinated and unvaccinated individuals are not equally exposed to infection, and derived efficacy estimates will overestimate the immunizing capacity of the vaccine among individual recipients (85, 125). This is a particular problem in observational studies of vaccines, but may also affect trials in which randomization is by group and not by individual.

Much of the literature on herd immunity to various infections emphasizes the estimation of theoretical threshold proportions of immunes which, if reached and sustained (e.g., by vaccination), should supposedly lead to progressive elimination of the infection from the population. Such estimates provide a rough ranking of the probable levels of natural and vaccine-derived immunity required for eradication of these infections. On the other hand, their validity should not be accepted uncritically; for, as shown in table 5, they vary greatly dependent upon their assumptions, and even the most elaborate derivations omit important features of the immune response and of the practical logistics and nonuniformity of populations and of vaccination programs. In addition, their relevance is mitigated by the fact that most public health programs aim at "control," rather than elimination or eradication of infections. Even if the goal is eradication, the practical approach will not be to just attain some threshold and sustain it, but to aim for *and sustain* the highest possible coverage, in theory 100 percent, as this will maximize the rapidity of the disappearance of the infection in question. Merely achieving a herd immunity threshold does not mean immediate disappearance of the infection, it only starts a downward trend.

Such caveats are not to argue that herd immunity is not a valid and a useful concept. That indirect protection occurs is obvious, both in logic and in observation. Prevention of a communicable infection in any individual reduces by one the potential sources of infection—and, hence, the potential risk (which is a probability, by definition) of infection—for that individual's peers. That is indirect protection and a form of herd immunity. The observation of apparent exceptions, small communities in which infections appear to be transmitted despite very high levels of vaccination coverage, do not refute this principle, just as the failure of a vaccination in some individual recipients need not refute an overall high efficacy of the vaccine.

The herd immunity threshold concept provides an important epidemiologic attribute with which to characterize and understand any particular infection. Though precision may not be possible, even crude estimates are themselves of use in giving a rough guideline for predicting the impact of a vaccination program and at least the potential for eradication. As experience grows, we will come to appreciate better how the various subtleties of the epidemiology of different infections (e.g., those attributable to the nature of the immune response and to the social structure of populations) imply greater or lesser biases in the estimates derived from simple models. Those authors who would discuss fully the eradicability of

any infection must deal with the herd immunity issue. Finally, and perhaps most important, the theory of herd immunity is useful in the context of teaching. It is part of the basic science of infectious disease epidemiology, and, like all the basic sciences, provides an essential background for understanding the real world.

The emphasis upon elimination thresholds in the herd immunity literature distracts from important dynamic implications of changing patterns and levels of immunity in populations over time. A vaccination intervention entails a massive disruption of the previous "natural" balance and can destabilize epidemiologic patterns for many years. For example, the introduction of an effective vaccination program among children may reduce infection incidence to such a degree that a large number of susceptibles can accumulate among those individuals born just too early to receive the vaccinations, and who thus escape both the natural infection and the benefits of vaccination. The accumulation of such susceptible groups may lead to changes in the age distribution of cases in the future, as has been reported for measles, mumps, and pertussis in recent years (126–129). Discussion of such changes is sometimes confused by presentation in terms of proportions of cases in different age groups, as it is possible, for example, for the proportion of measles cases among adults to increase dramatically even though their absolute number decreases. Prediction of such effects requires simulation with models which take into account differences in contact within and between age groups. Schenzle (7), and Anderson and May (36) have made an important contribution to this subject in the exploration of matrices to describe different age-dependent patterns of contact. The stipulation of correct matrices, and the derivation of correct transmission parameters, present major logical difficulties (23, 36). Many different matrices will be consistent with any given age distribution of immunity. The only way to derive convincing descriptions is by the accumulation of detailed analyses of age specific data over time, preferably before and after a vaccine intervention.

The growth of emphasis upon vaccination programs, and the recognition of the complexity of their implications, highlight the importance of immunologic monitoring of populations. Only by accumulating such data will we ultimately be able to understand the dynamics of herd immunity and the full effects of vaccine interventions. In addition, such monitoring should enable detection of accumulating pockets of susceptibles and, hence, the prediction of delayed epidemics such as have been observed after a period of vaccine-program-attributable low incidence (126, 127, 130). A further example of the long-term implications of vaccine interventions is the recent evidence for lower levels of passive immunity among children of mothers who received measles vaccine compared with those whose mothers had experienced measles infection (131). Recognition of this trend may lead to lowering of the recommended age for vaccination.

Current measles and polio programs are destined to enlarge greatly our understanding of herd immunity. The continued effort to eliminate measles in the United States has led to repeated changes in policy: changes in the recommended age for vaccination, changes in policy of revaccination, and the formulation of special recommendations for dealing with outbreaks and with inner city populations (5, 79). These changes have occurred in response to growing understanding of the subtleties of measles epidemiology, i.e., the recognition of long-duration maternal antibody, appreciation of the implications of changes in vaccine formulation, evidence for extremely high potential transmission risks in high school populations, the difficulty of achieving high vaccination coverage in inner city areas, and the possibility that vaccine-derived immunity to measles may wane with time (5, 132). Despite the inadequacy of the data at any point in time, the public health policy has had to be decisive. If measles is ultimately eliminated from the United States, it will be unclear whether two doses of vaccine were really

necessary, whether intensive outbreak control was really essential, or whether merely shifting some of the resources to urban areas would have been sufficient. In that sense, we will never know just what part herd immunity played in the success. Ironically, we may learn more about herd immunity by observing what happens to mumps and rubella, as a consequence of the measles elimination effort, than by observing measles itself. If mumps or rubella do disappear, it will be attributable largely to the passive effects of indirect protection, to herd immunity alone.

Even more aggressive attempts at measles elimination are currently underway in the Caribbean and in Latin America, based on mass campaigns targeted at all children aged from 9 months to 15 years (133). Early impressive results indicate cessation of measles virus transmission over broad areas, but the long-term implications in terms of preventing importations, and follow-up vaccination strategy, have yet to be defined. The issue of herd immunity thus expands from the protection of individuals by vaccination of other individuals, to the protection of populations through vaccination of other populations.

The goal of polio eradication from the world by the end of this decade raises additional herd immunity problems. It now appears that wild polio viruses no longer circulate in the New World as the last confirmed case attributed to continued transmission had onset in August 1991. This success was achieved by mass live oral polio vaccine campaigns and was no doubt assisted by the spread of live oral polio vaccine strains within the populations involved. This advantage of live oral polio vaccine must be balanced against the lower efficacy of these vaccines, relative to inactivated polio virus, as measured in Africa and in Asia (113, 134). Insofar as one of the reasons for the low efficacy of live oral polio vaccine may be the presence of other enteric infections, there may be a complicated relation between the efficacy of these vaccines in individual recipients, and their tendency to spread in the population. Prediction of the overall effect of a strategy will thus be difficult for any given population, and optimal strategies may require the combination of inactivated and live oral polio vaccines. Whatever the strategy may be, there will be a need to maintain high levels of herd immunity in the New World to prevent reintroduction of polio viruses until full global eradication has been achieved.

This review has avoided emphasizing any single definition of herd immunity, rather, accepting the varied uses of the term by different authors. This is in keeping with the first published use of the term which posed the problem of herd immunity as the problem of how to distribute any given amount of immunity (antibodies, vaccinations, etc.) so as best to protect a population from disease (38). The mechanisms will be several: direct protection of vaccinees against disease or transmissible infection and indirect protection of nonrecipients by virtue of surreptitious vaccination, passive antibody, or just reduced sources of transmission and, hence, risks of infection in the community. And the solutions will likewise depend on many factors: the nature of the population, the infection, the vaccine, and the health services. The population and the infection are generally given, the vaccine we may try to improve, but the distribution of that vaccine is up to the public health community. How to optimize that distribution remains, in the broadest sense, the problem of herd immunity.

ACKNOWLEDGMENTS

This review began during a period as visiting scientist in the Immunization Division at the Centers for Disease Control and Prevention in Atlanta, Georgia. The author is indebted to the London School of Hygiene and Tropical Medicine, London, England, and the Centers for Disease Control and Prevention for having facilitated that arrangement, and to colleagues in both institutions for many hours of discussion of the material presented here. Susan Ashayer and Joel Almeido helped greatly with the document.

REFERENCES

1. Last JM. A dictionary of epidemiology. 2nd ed. New York, NY: Oxford University Press, 1988.
2. World Health Assembly. Handbook of resolutions and decisions of the Forty-second World Health Assembly and the Executive Board. Geneva, Switzerland, World Health Organization, 1989:42.32.
3. Langmuir AD. Changing concepts of airborne infection of acute contagious diseases: a reconsideration of classic epidemiologic theories. Ann N Y Acad Sci 1980;353:35–44.
4. Fox JP. Herd immunity and measles. Rev Infect Dis 1983;5:463–6.
5. Markowitz LE, Preblud SR, Orenstein WA, et al. Patterns of transmission in measles outbreaks in the United States, 1985–1986. N Engl J Med 1989;320:75–81.
6. Cvjetanovic B, Grab B, Dixon H. Epidemiological models of poliomyelitis and measles and their application in the planning of immunization programmes. Bull World Health Organ 1982;60:405–22.
7. Schenzle D. An age-structured model of pre- and post-vaccination measles transmission. IMA J Math Appl Med Biol 1984;1:169–91.
8. Anderson RM, May RM. Directly transmitted infectious diseases; control by vaccination. Science 1982;215:1053–60.
9. Klock LE, Rachelefsky GS. Failure of rubella herd immunity during an epidemic. N Engl J Med 1973;288:69–72.
10. Gremillion DH, Gengler RE, Lathrop GD. Epidemic rubella in military recruits. South Med J 1978;71:932–4.
11. Miller LW, Older JJ, Drake J, et al. Diphtheria immunization: effect upon carriers and the control of outbreaks. Am J Dis Child 1972;123: 197–9.
12. Melnick JL. Advantages and disadvantages of killed and live poliomyelitis vaccines. Bull World Health Organ 1978;56:21–38.
13. Salk D. Eradication of poliomyelitis in the United States. II. Experience with killed poliovirus vaccine. Rev Infect Dis 1980;2:243–57.
14. Fox JP. Eradication of poliomyelitis in the United States: a commentary on the Salk reviews. Rev Infect Dis 1980;2:277–81.
15. Fox JP, Elveback L, Scott W, et al. Herd immunity: basic concept and relevance to public health immunization practices. Am J Epidemiol 1971;94:179–89.
16. Dorland's illustrated medical dictionary. 24th ed. Philadelphia, PA: WB Saunders, 1965.
17. Anderson RM. The concept of herd immunity and the design of community-based immunization programmes. Vaccine 1992;10:928–35.
18. Dietz K. Transmission and control of arbovirus diseases. In: Ludwig D, Cooke KL, eds. Epidemiology. Philadelphia, PA: Society for Industrial and Applied Mathematics, 1975:104–21.
19. Katzmann W, Dietz K. Evaluation of age-specific vaccination strategies. Theor Popul Biol 1984;25:125–37.
20. Anderson RM, May RM. Spatial, temporal and genetic heterogeneity in host populations and the design of immunization programmes. IMA J Math Appl Med Biol 1984;1:233–66.
21. Anderson RM, May RM. Vaccination and herd immunity to infectious diseases. Nature 1985; 318:323–9.
22. Hethcote HW, Van Ark JW. Epidemiological models for heterogeneous populations: proportionate mixing, parameter estimation and immunization programs. Math Bioscience 1987; 84:85–118.
23. Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford, England: Oxford University Press, 1991.
24. Nokes DJ, Anderson RM. The use of mathematical models in the epidemiological study of infectious diseases and in the design of mass immunization programmes. Epidemiol Infect 1988;101:1–20.
25. Hethcote HW. Measles and rubella in the United States. Am J Epidemiol 1983;117:2–13.
26. Dietz K. The estimation of the basic reproduction number for infectious diseases. Stat Methods Med Res 1993;2:23–41.
27. Farrington CP. Modeling forces of infection for measles, mumps and rubella. Stat Med 1990;9: 953–67.
28. Nokes DJ, Anderson RM. Measles, mumps and rubella vaccine: what coverage to block transmission? Lancet 1988;2:1374.
29. May RM, Anderson RM. Spatial heterogeneity and the design of immunization programmes. Math Bioscience 1984;72:83–111.
30. Knox EG. Strategy for rubella vaccination. Int J Epidemiol 1980;9:13–23.
31. Anderson RM, May RM. Vaccination against rubella and measles: quantitative investigation of different policies. J Hyg 1983;90:259–325.
32. van Druten JAM, de Boo T, Plantinga AD. Measles, mumps and rubella: control by vaccination. Dev Biol Stand 1986;65:53–63.
33. Anderson RM, Crombie JA, Grenfell BT. The epidemiology of mumps in the UK: a preliminary study of virus transmission, herd immunity and the potential impact of vaccination. Epidemiol Infect 1987;99:65–84.
34. Grenfell BT, Anderson RM. Pertussis in England and Wales: an investigation of transmission dynamics and control by mass vaccination. Proc R Soc London [Biol] 1989;236:213–52.
35. Fine PEM. Herd immunity. In: Selby P, ed. Influenza models: prospects for development and use. Lancaster, England: MTP Press, 1982: 189–94.
36. Anderson RM, May RM. Age-related changes in the rate of disease transmission: implications for the design of vaccination programmes. J Hyg 1985;94:365–436.
37. Knox EG, Shannon HS. A model basis for the control of whooping cough. Int J Epidemiol 1986;15:544–52.
38. Topley WWC, Wilson GS. The spread of bacterial infection. The problem of herd immunity. J Hyg 1923;21:243–9.
39. Greenwood M, Hill AB, Topley WWC, et al. Experimental epidemiology. Medical Research Council special report, series no. 209. London,

England: His Majesty's Stationary Office, 1936.
40. Greenwood M. Epidemics and crowd-diseases. London, England: Williams and Norgate, 1935.
41. Farr W. Second annual report of the Registrar-General of Births, Deaths and Marriages of England and Wales, 1840.
42. Brownlee J. Certain considerations of the causation and course of epidemics. Proc Roy Soc Med (Epidemiol Sect) 1909;2:243–58.
43. Hamer WH. Epidemic disease in England—the evidence of variability and of persistency of type. Lancet 1906;1:733–9.
44. Fine PEM. John Brownlee and the measurement of infectiousness: an historical study in epidemic theory. J R Stat Soc [A] 1979;42: 347–62.
45. Jenner E. The origin of the vaccine inoculation. London, England: Shury, 1801.
46. Dubos R, Dubos J. The white plague: tuberculosis, man, and society. New Brunswick, NJ: Rutgers University Press, 1952.
47. Ross R. Report on the prevention of malaria in Mauritius. London, England: J and A Churchill, 1909.
48. World Health Assembly. Handbook of resolutions and decisions of the Eighth World Health Assembly and Executive Board. Geneva, Switzerland: World Health Organization, 1955: 8.30.
49. World Health Assembly. Handbook of resolutions and decisions of the Eighteenth World Health Assembly and the Executive Board. Geneva, Switzerland: World Health Organization, 1965:18.38.
50. Hope Simpson RE. The period of transmission in certain epidemic diseases: an observational method for its discovery. Lancet 1948;2: 755–60.
51. Soper HE. The interpretation of periodicity in disease prevalence. J R Stat Soc 1927:92: 34–73.
52. Bailey NTJ. The mathematical theory of infectious diseases and its applications. 2nd ed. London, England: Charles Griffin and Company, 1975.
53. Kermack WO, McKendrick AG. A contribution to the mathematical theory of epidemics. Proc R Soc 1927;A115:700–21.
54. Macdonald G. The epidemiology and control of malaria. London, England: Oxford University Press, 1957.
55. Fine PEM, Clarkson JA. Measles in England and Wales. II. The impact of the measles vaccination programme on the distribution of immunity in the population. Int J Epidemiol 1982; 11:15–25.
56. Smith CEG. Prospects for the control of infectious disease. Proc R Soc Med 1970;63:1181–9.
57. Sencer DJ, Dull HB, Langmuir AD. Epidemiologic basis for eradication of measles in 1967. Public Health Rep 1967;82:253–6.
58. Frost WH. Some conceptions on epidemics in general. Am J Epidemiol 1976;103:141–51.
59. Fine PEM. Applications of mathematical models to the epidemiology of influenza: a critique. In: Selby P, ed. Influenza models: prospects for development and use. Lancaster, England: MTP Press, 1982:15–85.
60. Muench H. Catalytic models in epidemiology. Cambridge, MA: Harvard University Press, 1959.
61. Fine PEM, Clarkson JA. Measles in England and Wales. I. An analysis of factors underlying seasonal patterns. Int J Epidemiol 1982;11: 5–14.
62. Costa Maia JDO. Some mathematical developments on the epidemic theory formulated by Reed and Frost. Hum Biol 1952;24:167–200.
63. Yorke JA, Nathanson N, Pianigiani G, et al. Seasonality and the requirements for perpetuation and eradication of viruses in populations. Am J Epidemiol 1979;109:103–23.
64. Aron JL. Multiple attractors in the response to a vaccination program. Theor Popul Biol 1990; 38:58–67.
65. Gleick J. Chaos: making a new science. New York, NY: Penguin Books, 1987.
66. World Health Assembly. Handbook of resolutions and decisions of the twelfth World Health Assembly and Executive Board. Geneva, Switzerland: World Health Organization, 1959: 12.54.
67. Fenner F, Henderson DA, Arita I, et al. Smallpox and its eradication. Geneva, Switzerland: World Health Organization, 1988.
68. Arita I, Wickett J, Fenner F. Impact of population density on immunization programmes. J Hyg 1986;96:459–66.
69. Henderson DA. Epidemiology in the global eradication of smallpox. Int J Epidemiol 1972; 1:25–30.
70. Black FL. The role of herd immunity in the control of measles. Yale J Biol Med 1982;55: 351–60.
71. Hopkins DR, Hinman AR, Koplan JP, et al. The case for global measles eradication. Lancet 1982;1:1396–8.
72. Henderson DA. Global measles eradication. Lancet 1982;2:208.
73. Fahlgren K. Two doses of MMR vaccine—sufficient to eradicate measles, mumps and rubella? Scand J Soc Med 1988;16: 129–35.
74. Hinman AR, Kirby CD, Eddins DL, et al. Elimination of indigenous measles from the United States. Rev Infect Dis 1983;5:538–45.
75. Hedrich AW. The corrected average attack rate from measles among city children. Am J Hyg 1930;11:576–600.
76. Hedrich AW. Monthly estimates of the child population "susceptible" to measles, 1900–1931, Baltimore, MD. Am J Hyg 1933;17: 613–36.
77. Langmuir AD. The territory of epidemiology: pentimento. J Infect Dis 1987;155:349–58.
78. Chen RT, Markowitz LE, Albrecht P, et al. Measles antibody: reappraisal of protective titres. J Infect Dis 1990;162:1036–42.
79. Advisory Committee on Immunization Practices. Measles prevention: recommendations of the Immunization Practices Advisory Committee. MMWR 1989;262:1443–4,1456.
80. Kim-Farley R, Bart S, Stetler H, et al. Clinical

mumps vaccine efficacy. Am J Epidemiol 1985;121:593–7.
81. Sullivan KM, Halpin TJ, Marks JS, et al. Effectiveness of mumps vaccine in a school outbreak. Am J Dis Child 1985;139:909–12.
82. Kendrick PL. Can whooping cough be eradicated? J Infect Dis 1975;132:707–12.
83. Fine PEM. Epidemiological considerations for whooping cough eradication. In: Wardlaw AC, Parton R, eds. Pathogenesis and immunity to pertussis. New York, NY: John Wiley and Sons, 1988:451–67.
84. Fine PEM, Clarkson JA. The recurrence of whooping cough: possible implications for assessment of vaccine efficacy. Lancet 1982;1: 666–9.
85. Fine PEM, Clarkson JA. Reflections on the efficacy of pertussis vaccines. Rev Infect Dis 1987;9:866–83.
86. Farrington CP. The measurement of age-specific vaccine efficacy. Int J Epidemiol 1992; 21:1014–20.
87. Ad Hoc Group for the Study of Pertussis Vaccines. Placebo controlled trial of two acellular pertussis vaccines in Sweden—protective efficacy and adverse events. Lancet 1988;1: 955–60.
88. Godfrey ES. Practical uses of diphtheria immunization records. Am J Public Health 1933; 23:809–12.
89. Zalma VM, Older JJ, Brooks GF. The Austin, Texas, diphtheria outbreak. JAMA 1970;211: 2125–9.
90. Simonsen O, Kjeldsen K, Bentzon MW, et al. Susceptibility to diphtheria in populations vaccinated before and after elimination of indigenous diphtheria in Denmark: a comparative study of antitoxic immunity. Acta Pathol Microbiol Immunol Scand 1987;95:225–31.
91. Jones EE, Kim-Farley RG, Algunaid M, et al. Diphtheria: a possible foodborne outbreak in Hodeida, Yemen Arab Republic. Bull World Health Organ 1985;63:287–93.
92. Marcuse EK, Grand MG. Epidemiology if diphtheria in San Antonio, Texas, 1970. JAMA 1973;224:305–10.
93. Lau RCH. Antibody level of New Zealand children immunized with the triple vaccine DPT (diphtheria-tetanus-pertussis). Epidemiol Infect 1988;101:405–10.
94. Chen RT, Broome CV, Weinstein RA, et al. Diphtheria in the United States, 1971–81. Am J Public Health 1985;75:1393–7.
95. Doull JA, Lara H. The epidemiological importance of diphtheria carriers. Am J Hyg 1925;5: 508–29.
96. Newell KW, Duenas Lehman A, LeBlanc DR, et al. The use of toxoid for the prevention of tetanus neonatorum. Final report of a double-blind controlled field trial. Bull World Health Organ 1966;35:863–71.
97. Expanded Programme on Immunization. A vision for the world: global elimination of neonatal tetanus by the year 1995. Geneva, Switzerland: World Health Organization, 1989.
98. Beale AJ. Polio vaccines: time for a change in immunisation policy? In: Modern vaccines: current practice and new approaches. London, England: Edward Arnold, 1990:59–66.
99. Paul JR, Horstmann DM. Etude des anticorps antipoliomyelitiques chez les habitants du Maroc francais. Maroc Med 1956;35:3–10.
100. Hillis A. A mathematical model for the epidemiologic study of infectious disease. Int J Epidemiol 1979;8:167–76.
101. Melnick JL, Ledinko N. Development of neutralizing antibodies against the three types of poliomyelitis virus during an epidemic period: the ratio of inapparent infection to clinical poliomyelitis. Am J Hyg 1953;58:207–22.
102. Henry JL, Jaikaran ES, Davies JR, et al. A study of polio vaccination in infancy: secretion following challenge with live virus by children given killed or living polio vaccine. J Hyg 1966;64:105–20.
103. Dick GWA, Dane DS, McAlister J, et al. Vaccination against poliomyelitis with live virus vaccine. 7. Effect of previous Salk vaccination on virus excretion. Br Med J 1961;2:266–9.
104. Fox JP, Hall CE. Viruses in families: surveillance of families as a key to epidemiology of virus infections. Littleton, MA: PSG Publishing Company, 1980.
105. Gelfand HM, Potash L, LeBlanc DR, et al. Intrafamilial and interfamilial spread of living vaccine strains of polioviruses. JAMA 1959; 170:2039–48.
106. Melnick JL. Live attenuated polio vaccines. In: Plotkin SA, Mortimer EA Jr, eds. Vaccines. Philadelphia, PA: WB Saunders, 1988:115–57.
107. Strebel PM, Sutter RW, Cochi SL, et al. Epidemiology of poliomyelitis in the United States one decade after the last reported case of indigenous wild virus-associated disease. Clin Infect Dis 1992;14:569–79.
108. Stickle G. Observed and expected poliomyelitis in the United States, 1958–1961. Am J Public Health 1964;54:1222–9.
109. Bottiger M. A study of the sero-immunity that has protected the Swedish population against poliomyelitis for 25 years. Scand J Infect Dis 1987;19:595–601.
110. Hovi T, Cantell K, Huovilainen A, et al. Outbreak of paralytic poliomyelitis in Finland: widespread circulation of antigenically altered poliovirus type 3 in a vaccinated population. Lancet 1986;1:1427–32.
111. Schaap GJ, Bijkerk H, Coutinho RA. The spread of wild polio virus in the well vaccinated Netherlands in connection with the 1978 epidemic. Prog Med Virol 1984;29:124–40.
112. de Quadros C, Andrus JK, Olive J-M, et al. Polio eradication from the Western Hemisphere. Ann Public Health 1992;13:239–52.
113. Patriarca PA, Wright PF, John TJ. Factors affecting the immunogenicity of oral poliovirus vaccine in developing countries: a review. Rev Infect Dis 1991;13:926–39.
114. de St Groth SF. The control of influenza. Bull Schweiz Akad Med Wissensch 1977;33:201–9.
115. Thacker SB. The persistence of influenza A in human populations. Epidemiol Rev 1986;8: 129–42.

116. Elveback LR, Fox JP, Ackerman E, et al. An influenza simulation model for immunization studies. Am J Epidemiol 1976;103:152–65
117. Monto AS, Davenport FM, Napier JA, et al. Modification of an outbreak of influenza in Tecumseh, Michigan by vaccination of schoolchildren. J Infect Dis 1970:22:16–25.
118. Dowdle WR, Millar JD, Schonberger LB, et al. Influenza policies and practices in Japan. J Infect Dis 1980;141:258–64.
119. Advisory Committee on Immunization Practices. Prevention and control of influenza. Part I, vaccines. MMWR 1993;42(RR-6):1–14.
120. Fine PEM. Immunities in and to tuberculosis: implications for pathogenesis and vaccination. In: Porter JDH, McAdam KPWJ, eds. Tuberculosis: back to the future. London, England: John Wiley and Sons, 1993 (in press).
121. Fine PEM. The BCG story: lessons from the past and implications for the future. Rev Infect Dis 1989;11(suppl 2):S353–9.
122. Styblo K, Meijer J. Impact of vaccination programmes in children and young adults on the tuberculosis problem. Tubercle 1976;57:17–43.
123. Medis KN. Malaria vaccine research—a game of chess. In: Targett GAT, ed. Malaria: waiting for the vaccine. New York, NY: John Wiley and Sons, 1991:183–96.
124. Halloran ME, Struchiner CJ. Spielman A. Modeling malaria vaccines. II: Population effects of stage-specific malaria vaccines dependent on natural boosting. Math Bioscience 1989;94: 115–49.
125. Halloran ME, Haber M, Longini IM Jr, et al. Direct and indirect effects in vaccine efficacy and effectiveness. Am J Epidemiol 1991;133: 323–31.
126. Measles—United States, 1989 and first 20 weeks of 1990. MMWR 1990;39:353–6, 361–3.
127. Sosin DM, Cochi SL, Gunn RA, et al. Changing epidemiology of mumps and its impact on university campuses. Pediatrics 1989;84:779–84.
128. Kaplan KM, Marder DC, Cochi SL, et al. Mumps in the workplace. Further evidence of the changing epidemiology of a childhood vaccine-preventable disease. JAMA 1988;260: 1434–8.
129. Miller E, Vurdien JE, White JM. The epidemiology of pertussis in England and Wales. Comm Dis Rep 1992;2:R152–4.
130. Ukkonen P, von Bonsdorff C-H. Rubella immunity and morbidity: effects of vaccination in Finland. Scand J Infect Dis 1988;20:255–9.
131. Pabst HF, Spady DW, Marusyk RG, et al. Reduced measles immunity in infants in a well-vaccinated population. Pediatr Infect Dis J 1992;11:525–9.
132. Markowitz LE, Preblud SR, Fine PEM, et al. Duration of live measles vaccine-induced immunity. Pediatr Infect Dis J 1990;9:101–10.
133. Hospedales CJ. Update on elimination of measles in the Caribbean. West Indian Med J 1992;41:43–4.
134. Robertson SER, Traverso HP, Drucker JA, et al. Clinical efficacy of a new, enhanced-potency, inactivated poliovirus vaccine. Lancet 1988;1:897–9.
135. Benenson AS, ed. Control of communicable diseases of man. 15th ed. Washington, DC: American Public Health Association, 1990.
136. Foege WH. Measles vaccination in Africa. Proceedings, International Conference on the Application of Vaccines against Viral, Rickettsial and Bacterial Diseases of Man. Washington, DC: Pan American Health Organization, 1971: 207–12. (PAHO scientific publication no. 226).