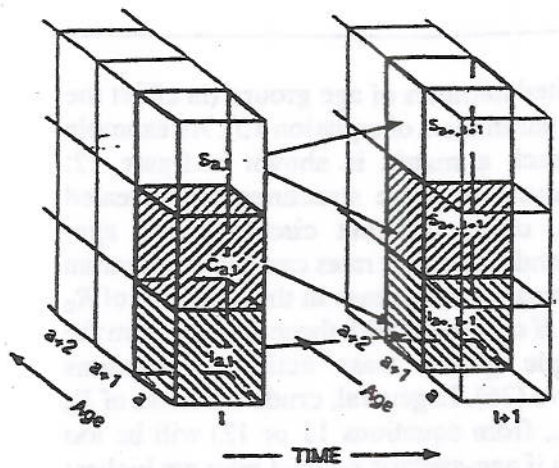

FIGURE 9. Schema for age-structured model, based on addition of age axes to figure 1. Simulation requires accounting susceptible ($S_{a,t}$), case ($C_{a,t}$), and immune ($I_{a,t}$) individuals over successive time periods. Such models generally include births, latent infections, and deaths (23).

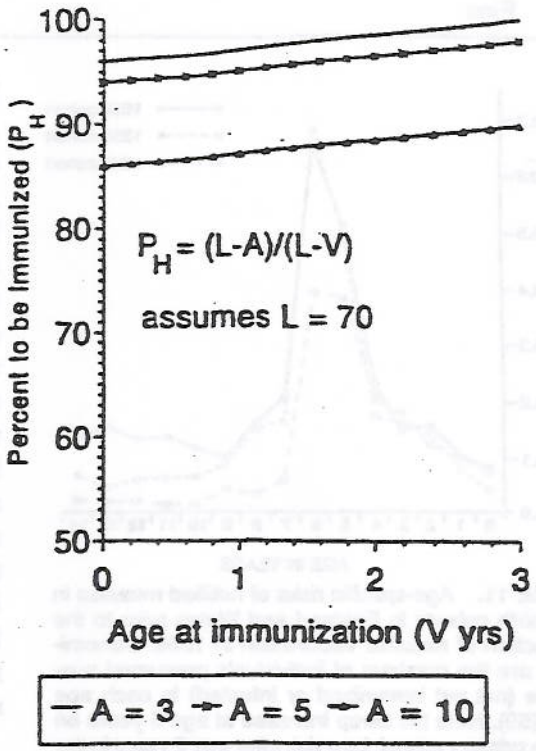

FIGURE 10. Relation between P_H (proportion of infants which must be immunized in order to attain herd immunity threshold), A (average age at infection), and V (age at immunization), assuming rectangular age distribution (equation 14). Illustrated solutions assume L = 70.

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

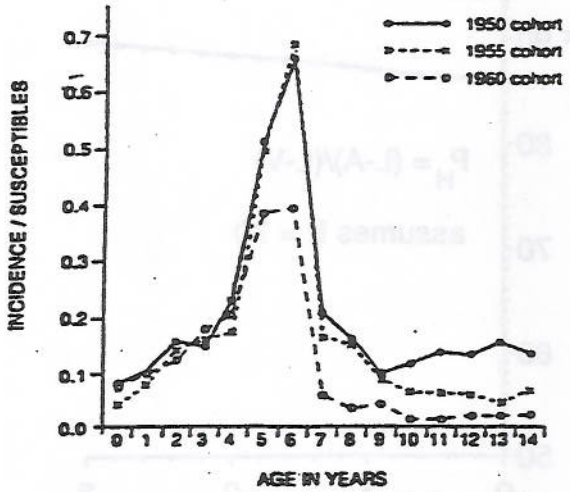

FIGURE 11. Age-specific risks of notified measles in three birth cohorts in England and Wales prior to the introduction of measles vaccination in 1968. Denominators are the numbers of individuals presumed susceptible (not yet immunized or infected) in each age group (55). Note the steep increase at age 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

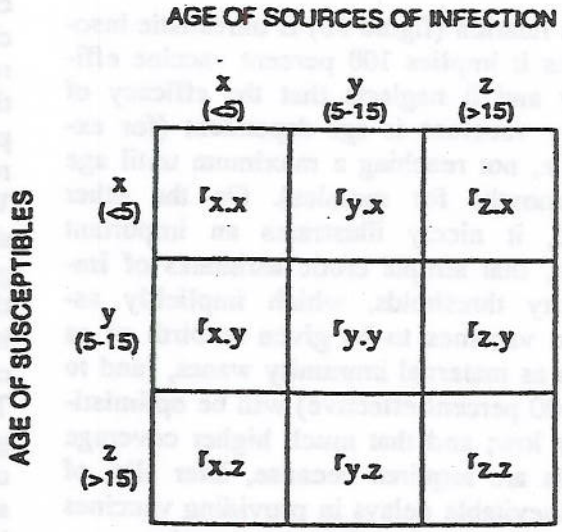

FIGURE 12. "WAIFW" (Who Acquires Infection From Whom) matrix of transmission parameters within and between three different age groups, preschool, school-age, and adult. Under most conditions such a matrix would be symmetric along the xx-yy axis, ($r_{xy} = r_{yx}$), though this need not necessarily be 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 [$R_0 = T/S_c$] 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