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–

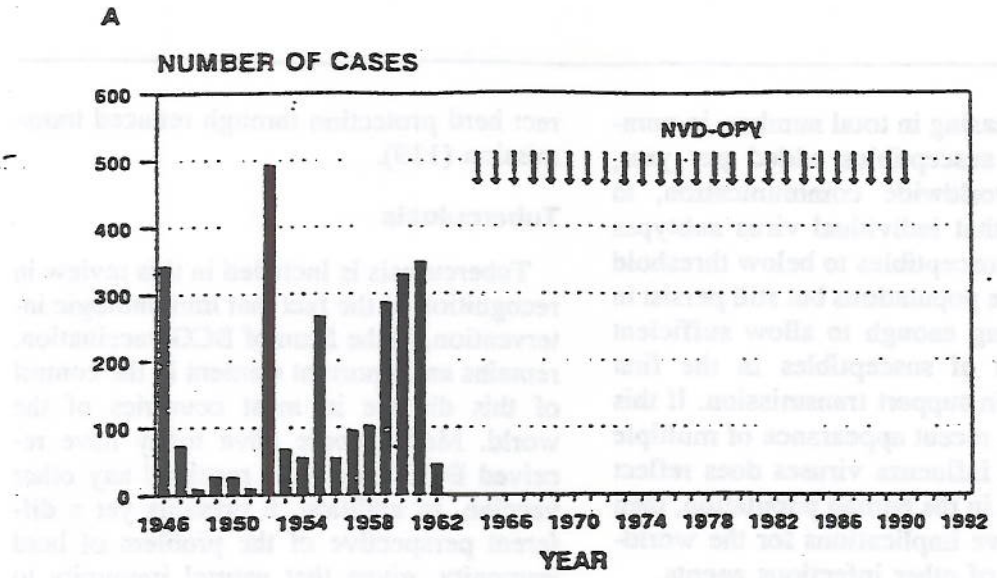
1985 was attributed to a type 3 virus different from that included in the vaccine (110). Outbreaks in the Netherlands have been restricted almost entirely to a religious community which refuses vaccination altogether, with no evidence of transmission in the population at large despite the presence of 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.

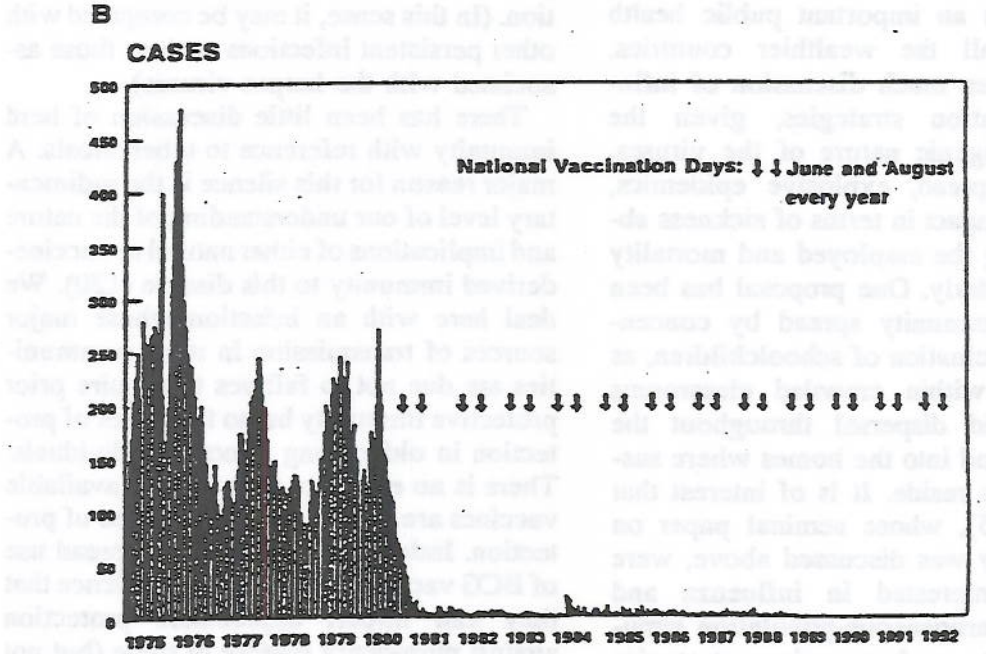
Influenza

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.

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After the honeymoon in measles control

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Do we face yet another obstacle in the way of measles control? In this issue Mulholland draws our attention to several problems on the horizon. Cohorts of young women are approaching child-bearing age with low levels of antibodies against measles and pertussis. Their children will in turn have lower, faster-waning immunity to these infections. Such babies present a challenge to vaccination campaign strategists since they will be especially vulnerable if caught up in post-honeymoon-period epidemics.

The honeymoon refers to the period of very low incidence immediately following the introduction of a mass vaccination programme. This happens because susceptibles accumulate much more slowly in a vaccinated community, so it takes a long time to reach the threshold number required for a new epidemic. The honeymoon effect is most pronounced immediately after the introduction of a mass cohort vaccination programme when very high levels of immunity already exist among older cohorts—a legacy of the efficiency of natural transmission. Because of these high levels of immunity among older individuals, the initial impact of a vaccination programme will look very promising. However, this striking short-term reduction in measles incidence is not an accurate reflection of the longer term impact of the control programme. After the initial period of very low incidence, epidemics restart, albeit with lower incidence than in the pre-vaccination era. This phenomenon was predicted by use of mathematical models in the 1980s,[1,2] and such patterns of incidence have recently been documented in Hong Kong,[3] Burundi,[4] and other settings cited by Cutts[5] and Mulholland.

A campaign targeted across all vaccinated cohorts, and those a few years older (who are especially likely to have been neither vaccinated nor naturally infected), is the obvious way to avert such an accumulation of susceptibles. The mass campaign of vaccination against measles conducted late last year in Britain aimed to prevent just such an epidemic.[6,7]

Now Mulholland observes a second effect of the ageing of vaccinated cohorts: women with vaccine-induced immunity have low levels of antibody to transfer across the placenta.[8] Consequently they will have babies who start life with low levels of antibody and who will therefore become susceptible to infection at very young ages. There have been cases of measles among very young babies in recent US epidemics. In developing countries the measles case-fatality rate in infants can exceed 20%.[9] Exposed to post-honeymoon-period epidemics in poor countries, such babies will be at very high risk of disease-related mortality, which will be most serious among the youngest for both measles and pertussis.

What can be done? Since one can vaccinate pregnant women and young babies against pertussis, the problem, though well worth highlighting, seems reasonably tractable. For measles, it is harder to choose the best course of action. There are two ways to stop susceptible babies from catching measles: *(a)* stop them from being susceptible; or *(b)* ensure that they are not exposed to measles.

Mulholland, while advocating vaccination of adolescents to boost immunity among young adults and hence their offspring, acknowledges that this strategy might not work. Revaccination seems to confer sustained high antibody levels in only about half the recipients.[10] Mulholland's base in The Gambia offers an obvious setting in which to determine whether revaccination of adolescents is an effective way to protect their young babies. Arya[11] advocates categorising neonates into groups receiving early or late immunisation according to antibody levels in cord blood.

Policies aimed at preventing exposure to measles (by preventing epidemics) can be of two types: mass campaigns across all cohorts with suspected low immunity) or two-stage policies with the second dose in early childhood. In practice, the real dilemma is when to give the second dose of a two-dose strategy. Should this be done in adolescence (to protect babies with maternally derived antibody) or in childhood (to prevent epidemics)? A recent report in a biomathematical journal evaluates the trade-offs.[12] Rouderfer and co-authors used a measles transmission model to find two-stage policies that minimise the total number of cases. An attractive option would be to modify that model to search for regimens that diminish cases among the very young (and hence lessen case-fatalities). Mulholland's paper serves as a timely warning that policies designed to minimise the number of cases may leave the most vulnerable unprotected.

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