

The Role of Herd Immunity in Control of Measles

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Measles vaccine cannot give high sero-conversion rates in developing countries. The high birth rates characteristic of these countries lead to infection at a very early age, thus making it difficult to vaccinate before exposure to the disease. Nevertheless, if given early in life, the vaccine can reduce the rate of virus circulation and thus raise the age at which children are infected. Once that is done, higher sero-conversion rates can be obtained by raising the age at vaccination. During the period when vaccine is given at an early age, the titers in responding children will be low, and this will leave children of the next generation with little protection. It is important, therefore, that if vaccine is used early the program be intensively and consistently applied to control virus circulation before the next generation is born.

Measles has been very largely controlled in the United States, but 13 percent of all 1981 cases were attributable to importations [1] and, unless these can be prevented, the disease cannot be eliminated. If the U.S. is to be freed of this disease, it cannot act alone, but must work toward worldwide control. At this date, however, it is not possible, with any available schedule of immunization, to protect a high proportion of the measles-susceptible population in a densely populated developing country (Fig. 1) [2-6]. In these countries, a large proportion of all measles cases occur early in life, and if one waits long enough for most children to become responsive to the vaccine by loss of maternal antibody, many will already have contracted the disease and many will have died of it (Fig. 2A). It is possible to do somewhat better in preventing measles cases than measles deaths, because the mortality is higher in the earlier cases. Data on the total number of cases from poorer areas such as Pernambuco are too unreliable to be used as an illustration, but the limitation on vaccine effectiveness is evident even in data from Rio Grande do Sul, one of the most developed parts of Brazil (Fig. 2B).

Re-vaccination at a later age is not a satisfactory solution to the problem of vaccine effectiveness in developing countries, because early vaccination inhibits the effect of a second dose [7-11], as well as because of the financial burden this places on limited public health budgets. If effective control of measles is to be attained in developing countries, a program must be designed to build on, and expand, herd immunity. Herd immunity, in the conventional sense of total protection of susceptible individuals by immunity in persons around them, is very difficult to establish against measles, because the virus is extremely contagious and a very high level of population immunity is required. However, population immunity affects the frequency of

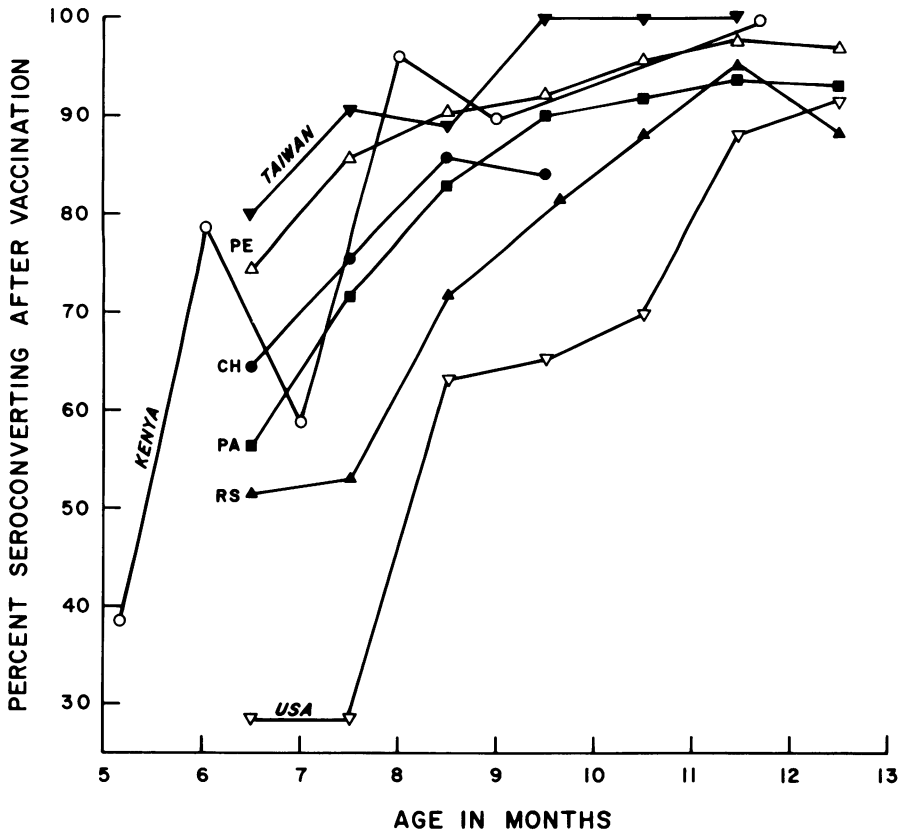


FIG. 1. Proportion of children of different ages who developed measles hemagglutinin-inhibiting antibody after vaccination. Sources: Kenya [1], Taiwan [2], Pernambuco (PE), Santiago, Chile (CH), Para (PA), and Rio Grande do Sul (RS) [3]; U.S.A. combined data from [4-6].

virus transmission and, hence, the age at infection; the purpose of this paper is to examine the significance of this phenomenon.

Immunity to measles derives from two sources: active immunization resulting from infection with wild or attenuated measles virus, and passive immunization by transplacentally acquired antibody. Active immunization makes the more important contribution to herd protection, but the duration of passive protection is quite variable, and it is important in providing protection during the most vulnerable age.

PARAMETERS OF MEASLES ENDEMICITY IN THE ABSENCE OF VACCINATION PROGRAMS

Reported cases of measles do not provide a satisfactory basis for calculating the extent of natural active immunization. It can be assumed that, prior to introduction of measles vaccine, everyone who lived more than a few years was infected with measles, in most societies. Yet, in the United States the reported number of measles cases was less than 10 percent of the number of births. In Mexico in 1972, it was only 3 percent, while in England and Wales, where reporting is possibly as good as anywhere, it was 37 percent of births in 1970-73. On the other hand, more than 95 percent of the adults in most populations have measles antibody, and the age at

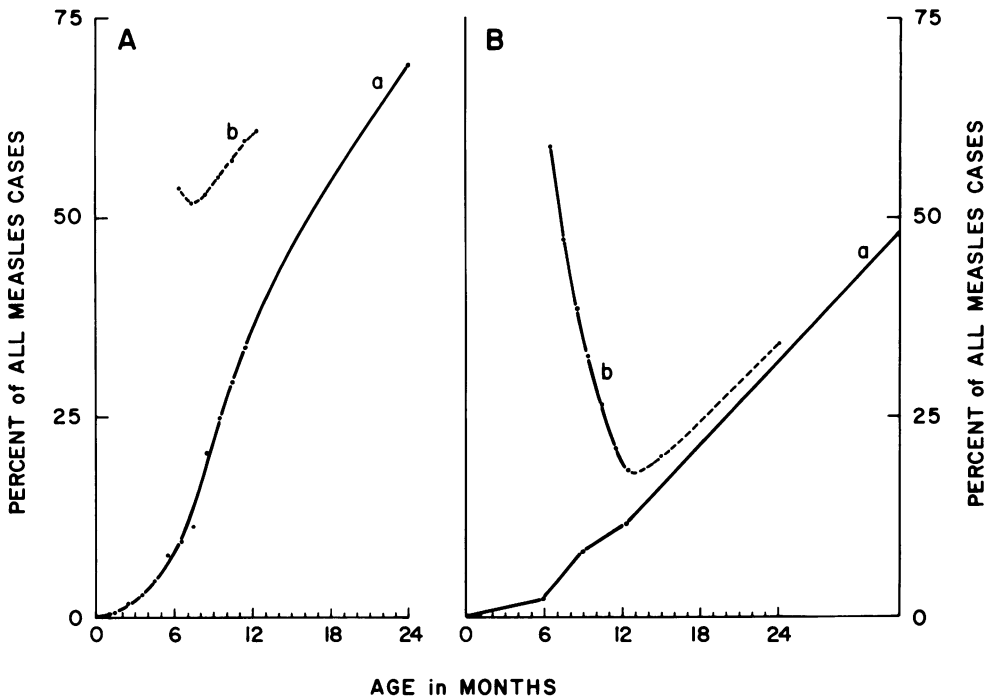


FIG. 2. **A:** Line *a*, reported measles mortality accumulated by age, and line *b*, proportion of measles deaths which could be prevented by vaccination at the indicated age. Data from Pernambuco, Brazil, 1979. **B:** Similar data for total reported measles in Rio Grande do Sul, an economically developed part of Brazil. The predicted protection rate is extended beyond 12 months vaccination age on the assumption of a 95 percent sero-conversion rate at age 15 months or more.

which this antibody is acquired provides a good indicator of the age at infection [12].

Using serological data (Fig. 3) [12], we can estimate that the median age at infection was 6.0 years in New Haven, CT, in 1957, but only 2.0 years in Casablanca, Morocco, or Guatemala City in 1953 and 1957, respectively. Thus, half of all measles infections in the developing countries fell on children under two years old, whereas only 12 percent of the reported cases of measles in the U.S. occurred in children in this most vulnerable age group.

In some countries, differences in measles age-specific attack rates may be determined by differences in child-care practice, and consequent differences in frequency of exposure of infants to the larger community. However, the differences in measles age distribution, in the three areas mentioned above, are explicable simply on the basis of the proportion of the population in the lower age groups. Bartlett [13] and Griffiths [14] have shown that the number of measles cases per person in the population under consideration, N , is proportional to the product of three terms: the fraction of the population in the infectious stage of disease, I ; the fraction of the population susceptible to infection, S , and λ , a measure of the facility with which the virus is spread:

$$N = IS\lambda$$

We can calculate S , the proportion susceptible, by summing, for each age group,

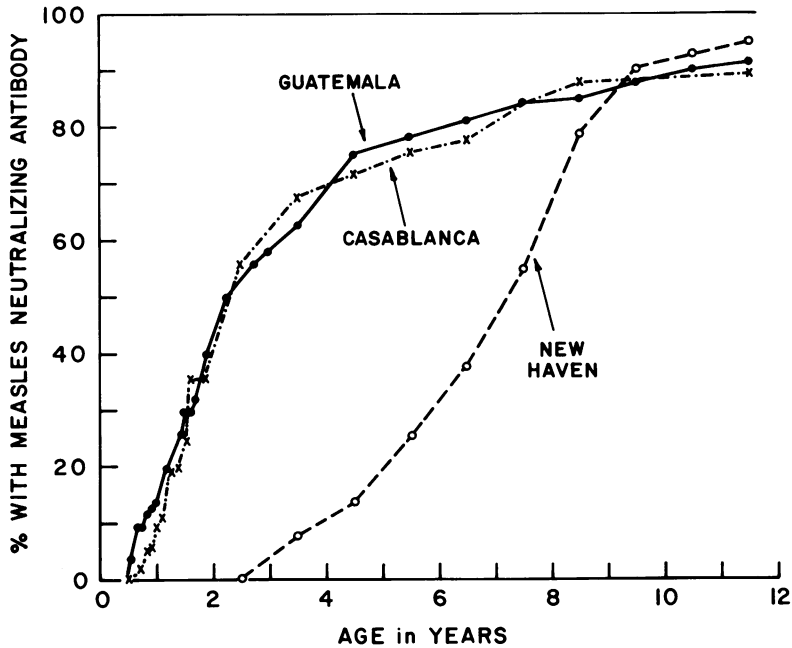


FIG. 3. Accumulated percent of population with measles-neutralizing antibodies in Casablanca, Morocco, in 1953, New Haven, CT, in 1957, and Guatemala City, Guatemala, in 1959.

the product of the fraction without measles antibody, times the fraction of the whole population in that age group. From this value one must subtract the number of children possessing passive immunity. On the basis of the age at which 50 percent sero-convert after vaccination (Fig. 1) the mean age at which children lose passive protection can be estimated to be eight months in the U.S.A., and 5.5 months in Kenya. The susceptible population in the developing countries is largely confined to age strata less than five years old, but nevertheless, the numbers in these lower cohorts are so great in Morocco and Guatemala, that the value of S , the proportion of the population susceptible, is only moderately lower than in the U.S.A., where susceptible individuals made up substantial proportions of all cohorts up to age ten or twelve (Table 1).

TABLE 1
Demographic Parameters of the Endemic Measles Equilibrium in
the Pre-Vaccination Era

	New Haven, CT, U.S.A.	Casablanca, Morocco	Guatemala City, Guat.
Median age at acquisition of antibody	6.0	2.0	2.0
% of population with antibody at 2nd birthday	12	50	50
S , proportion of population susceptible	0.136	0.088	0.103
I , proportion of population infectious	0.00090	.00136	.00168
λ , relative transmission rate	1.0	1.02	0.71

We can also estimate I . If we assume that each case is infectious for two weeks, and that everyone gets measles, the mean value of I will be two fifty-seconds part of the annual birth rate, where that rate is expressed as a fraction of the total population. Because of the high birth rate in developing countries [15], the value of I will be high in those areas.

If we assume N was uniform in the several populations, because essentially everyone ultimately caught measles, we can now use these values of I and S to calculate relative values for λ , the frequency of effective contact between infectious and susceptible cases. The observed differences in λ are small but, if anything, measles seems to have spread less readily in Guatemala than elsewhere. These differences cannot account for the more than fivefold greater proportion of children infected at less than two years of age in the cities of developing countries. Rather, the differences in age-specific attack rates were chiefly a result of differences in birth rate.

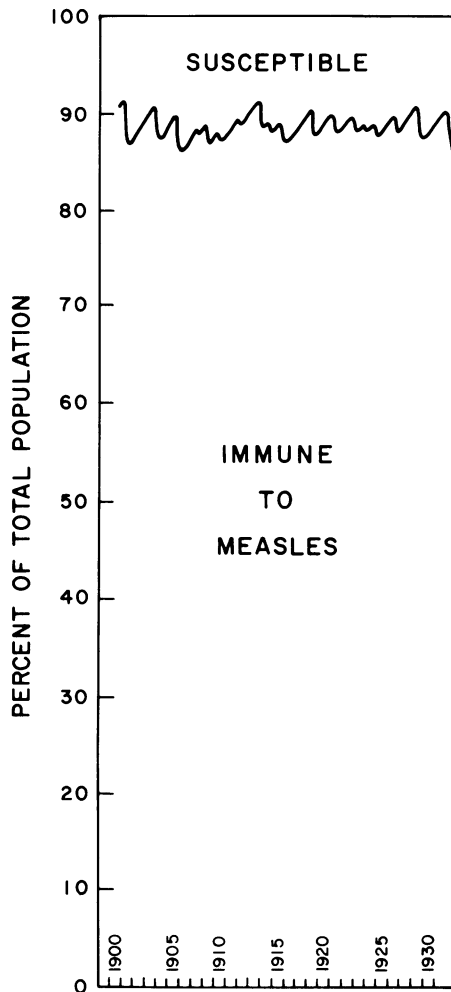
THE SHORT-TERM EFFECTS OF A VACCINATION PROGRAM IN A DEVELOPING COUNTRY

A vaccination program will have an immediate effect on the proportion of a population that is susceptible to measles. The chance of an infected person contacting a susceptible individual will then be reduced, and the rate of recruitment into the infectious group decreased. In 1933, Hedrick [16] showed that in an endemic situation, the change in S from the beginning to the end of a measles epidemic is quite small. The mean value at the beginning of an epidemic in Baltimore, during the early 1900s, was 12.6 percent of the whole population, and the epidemics ended when this value had fallen to 10.4 percent (Fig. 4). A limited vaccination campaign could easily effect this much change in the proportion susceptible and modify the normal sequence of measles epidemics. However, as pointed out earlier, vaccination programs in developing countries cannot confer protection on all children at risk. Even in relatively developed Rio Grande do Sul, the best response rate to be expected is 80 percent. It is probable that even a reasonably good campaign would miss 10 percent of the Rio Grandense children, leaving a total of 28 percent unprotected. With 28 percent of the annual births entering the susceptible pool each year, the proportion of the whole population susceptible will reach the level needed to sustain major epidemics again within a decade.

There would be one important difference when the epidemics resumed: 28 percent, instead of all the population, would experience measles. At the new equilibrium, there would be only 28 percent of the previous number of infectious individuals in the community. Whereas, now the median Rio Grandense becomes susceptible to measles at five months of age and is infected 19 months later, the median child could then expect to escape measles for six years. With this reduced intensity of virus transmission, a smaller proportion of the children would be infected while still in the most vulnerable age group, and the time of vaccine administration could be raised to an age level when there would be less interference from residual maternal antibody. It would then be possible to obtain much better response rates and a successful long-term measles control program could be initiated.

LONG-TERM HAZARDS OF A POOR VACCINATION PROGRAM

I believe, that in this way, a consistent, well-orchestrated vaccination program could control measles in any land. However, an erratic or inadequate program could actually increase measles mortality. When a child is vaccinated while he still has



Redrawn
from
Hedrich
Am J Hyg
1933

FIG. 4. Proportion of the population susceptible to measles in Baltimore, 1900 to 1931. Modified from data of Hedrich to show proportion of the whole population instead of proportion of children.

marginal levels of maternal antibody, the effect of the vaccine is suppressed, but not totally negated. We have recently studied the effect of re-vaccination in a group of 81 children who had first been vaccinated at six to twelve months of age without apparent immunological response. All of 21 who were tested three weeks after re-vaccination developed moderate titers of anti-measles IgG antibody, although all but one were without IgM. However, when we tested these children three to eighteen months after re-vaccination, their IgG levels had fallen precipitously, and in one out of three the antibody titer was less than that which we usually find necessary to confer protection. These data confirm similar findings made in the U.S.A. by Linneman et al. [10]. Confirmation of the hypotheses that re-vaccination of initially prematurely vaccinated children may fail to protect, was seen in the recent measles epidemic in Westchester County, New York [11]. There, three of sixteen serologi-

cally confirmed cases occurred in children who had been vaccinated twice, the first time when they were less than thirteen months old.

We need not only be concerned about those children who may be made refractory to re-vaccination by too early an attempt at immunization. Even when low residual levels of passive antibody permit production of protective levels of immunity, this antibody may still so inhibit the reaction to the vaccine, that titers of actively produced antibodies are suppressed. These low titers will protect the vaccine recipient, but they may cause trouble for the next generation, because they will confer only short-lived protection on the children of current vaccinees. I have already drawn attention to the data which indicate that children in less developed areas generally become responsive to measles vaccine sooner than children of most economically privileged countries [1-3]. This early responsiveness is due to early loss of passive protection, and it is indicative of early susceptibility to infection with wild measles virus. The early age at acquisition of susceptibility is an important element in the high measles mortality in less developed countries.

In the Greenland epidemics of 1951 to 1962 [17-18], maternal antibody was lacking in all infants because the adults had not had measles. Data from these epidemics can, therefore, be used to compare innate vulnerability to measles in the lower age strata. We find that the case fatality rate in infants less than one year old, 3.8 percent, was more than six times that in babies one to two years old and 53 times as high as in older children (Table 2). Data from virgin-soil epidemics in South American Indians suggest that even among children less than one year old, there is a vulnerability gradient with the youngest at greatest risk [19-20]. Because of this gradient in case fatality rate, earlier susceptibility in children of vaccinated mothers will leave them at substantially increased risk.

The early loss of passive antibody, observed in developing countries, could be due either to lower initial levels or to an increased rate of destruction. In Taiwan, a country in which measles vaccine response rates are characteristic of developing lands, the mean measles antibody titers of mothers of small children were substantially lower than in the United States (Table 3). These Taiwan women have less antibody to pass to their babies and the babies would, therefore, become susceptible to measles sooner. On the other hand, the rate of passive antibody decay observed in Kenya, a 39-day half-life, is not more rapid than the rates suggested for the developed countries [21-22].

TABLE 2
Age-Specific Measles Case Fatality Rate
in Greenland 1951-1962

Age	No. of Cases*	Deaths	Rate/1000
0-1	795	30	37.7
1-2	696	4	5.7
2-14	5628	4	0.7
14-34	5208	11	2.1
35-55	2713	24	8.8
55+	1150	44	38.3

*In distributing cases by age group it has sometimes been necessary to assume that this distribution was the same as in that of the population as a whole.

TABLE 3
Maternal Protection in Taiwan and in Connecticut

Age of Women (yr)	Number	G.M.T.	80% of Titers Less Than:	Age with 80% Response	
				Expected (mo)	Observed (mo)
Taiwan					
25-38	75	47.5	160	7.6	
19-24	42	50.4	160	7.6	6.5
Connecticut					
24-29	50	226	640	10.2	
13-19	50	143	320	9.2	10.6

Table 3 also gives mean titers for younger New Haven women. Those who were born from 1961 to 1967 span the cohort in which the major immunizing agent changed from wild to attenuated virus. Their titers are about half those of the older age group. If half of them were immunized with vaccine and half by wild virus, this would indicate that the vaccine-induced titers are only one-quarter of those elicited by wild virus. This estimate coincides well with the shorter term difference between titers induced by these agents [23]. On this basis, we can expect that the children of vaccinated mothers in this country will, in the future, be susceptible to measles two months sooner than has been the case. It may be well to move the recommended age for vaccination forward to 13 months of age, but as long as measles is controlled at the present level, this situation should not present any serious problem.

When vaccine is given to age groups in which residual maternal antibody is sometimes a problem, the titers in responding children are lowest in the youngest (Fig. 5). The practice of vaccination at seven months of age, as was done in Rio

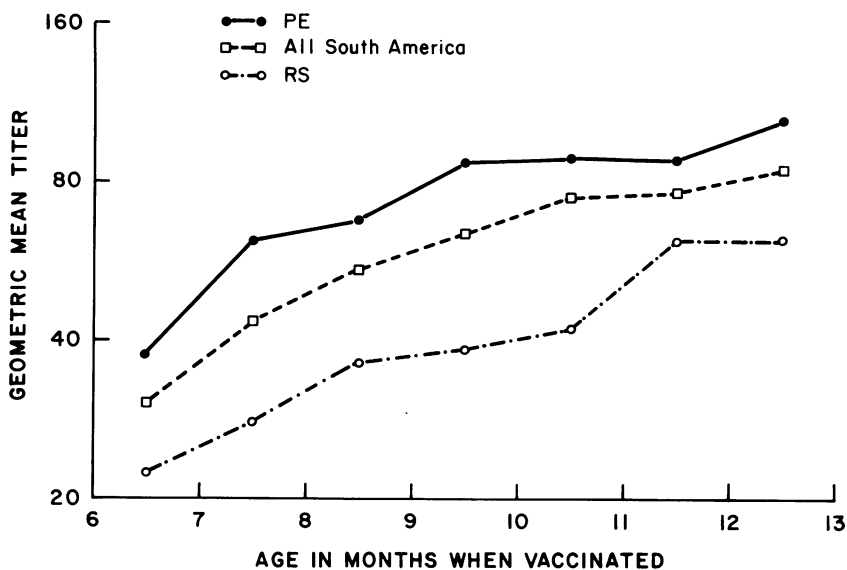


FIG. 5. Measles H.I. antibody titers in Latin American children four weeks after vaccination. PE = Pernambuco, Brazil; RS = Rio Grande do Sul, Brazil.

Grande do Sul, results in a peak post-vaccinal titer of 25, one-quarter of that attainable after the first birthday, and a fortieth of that commonly seen after wild virus infection. These low titers are not due to immunological immaturity, but individually correlate inversely with the mother's titer [3]. Hence, they are probably caused by very low residual levels of passively acquired antibody. When the girls who are now being vaccinated in Southern Brazil grow to have babies of their own, they will be able to confer protection on their offspring for only two or three months, on the average. Many children will become susceptible even sooner. If the circulation of measles virus has not been severely curtailed by that time, we must expect a serious increase in measles mortality.

In summary, a measles vaccination campaign can greatly reduce the toll exacted by measles in developing countries, even when it is not possible to reach a high proportion of susceptible children, provided the effect of herd immunity in raising the age-specific attack rate is exploited. However, care must be taken, lest such a program be inconsistently followed, and very young infants be left without either maternal or herd immunity in the next generation.

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