

Measles Active and Passive Immunity in a Worldwide Perspective

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Contents

I. Introduction	1
II. Immunity to Measles	2
III. A. Measles Virus Immunogenicity	2
B. Methods for Measuring Measles Antibody	5
C. Durability of Measles Immunity and Antibody Titer	9
D. Secondary Immune Responses in Measles	11
III. Measles Herd Immunity	12
A. R_0 , the Transmission Potential of Measles	12
B. Potential Vaccine Efficiency	14
C. Sources of Vaccine Failure in the United States	16
D. Vaccination Programs in Less-Developed Countries	17
IV. Variation in Measles Passively Acquired Antibody	19
A. Geographic Differences in Maternal Measles Titers	19
B. Geographic Differences in Placental Transfer Efficiency	21
C. Geographic Differences in Passive Antibody Half-Life	22
D. Mechanism of the Effect of Income on Passive Antibody Half-Life	24
V. Summary	26
References	28

I. Introduction

Twice in the last 20 years officials at the Centers for Disease Control of the United States Public Health Service have put forward a program for elimination of measles from the United States [1, 2], and twice that program has failed. The failures have been reviewed from a public health point of view, and administrative solutions were proposed in a recent paper of this series by Mitchell and Balfour [3]. Here, I will examine

the biological and statistical bases of the elements on which those and all other proposals for measles control must rest: the nature of measles immunity, infectiousness of the virus, vaccine effectiveness, and interference by passively acquired immunity. When elimination was called for, it was thought that a vaccination program would raise levels of herd immunity to a point where the virus could no longer propagate itself. The failures were less a matter of the vaccine failing to yield the expected immunization rates, than an underestimation of the rates that were needed. Serological studies, using methods that were available in 1967, when the first call for eradication was issued, could have defined these requirements, had we known how to interpret the data.

II. Immunity to Measles

A. Measles Virus Immunogenicity

The essential components of the measles virus induced immune response can be measured simply, although the entirety of the measles immune reaction is, as usual, very complex. Various classes of T cells are activated, and B cells are stimulated to yield antibody of several classes and subclasses. Each type of T and B cell responds to several epitopes on each of several proteins or polysaccharides of the virus. In other infections, this plethora of individual responses is further complicated by modifications caused by prior experience of the host with antigens of taxonomically related organisms. The response to other agents also varies because the agents themselves are variable. Altogether, it is not usually realistic to try to draw a sharp line between those individuals who have that combination of immunities that will provide protection from reinfection and those who do not. Most of these immunological elements, however, are unimportant in protection from measles infection. An indication of this relative simplicity is the fact that maternally derived IgG, primarily IgG1, is sufficient to prevent initiation of infection, and this natural passive protection can be mimicked in older persons by injection of IgG.

Measles is caused by a virus that is extraordinarily uniform wherever it occurs around the globe. This statement is based less on direct comparisons of isolates, which have been few [4, 5], than on the absence of any evidence of regionally distinctive immunity. The paucity of evidence of symptom differences between epidemics, except differences attributable to nutritional status, other complicating infections, and age, also implies virus strain uniformity. In recent years much of the measles occurring in the United States has been due to the introduction of virus from diverse

countries [6], yet there has been no report of associated variations in the nature of the disease. Measles virus strains vary in their reactions with specific monoclonal antibodies, but they do not differ appreciably in their reaction with whole serum [7].

The uniformity of measles virus does not seem to be due to any unusual genetic stability. In the laboratory, the measles virus genome is highly mutable [8–10], like other RNA genomes. Rather, the virus has found a particularly deep ecological niche where any variant finds itself at a disadvantage relative to the parent strain, when propagating under natural conditions. An exception occurs when the virus establishes a persistent infection in neurological tissue. Then, mutants accumulate, but their progeny are not transmitted to new hosts. The niche seems to be defined by the use of a unique, relatively species-specific, host cell receptor. The use of this receptor provides a mechanism that makes the virus extraordinarily infectious. The failure of the virus to mutate, like influenza, to resistance to immune inactivation suggests that the attachment site is not protected within a pit, but that the epitopes which stimulate immune response are essential parts of the attachment organ.

Not only is measles virus uniform, but humans are not subject to infection with any related virus. The virus is a member of the relatively small *Morbillivirus* genus of the family *Paramyxoviridae* [11]. In terms of structure and replicative strategy, the genus is homogeneous, but there is little homology in amino acid sequences between *Morbillivirus* and the other genera [12, 13], and serological cross-reactions between genera have never been observed. This distinctive position of the morbilliviruses may evolve from their use of the cell receptor mentioned above. Their attachment to susceptible cells is not affected by neuraminidase and these viruses do not carry this enzyme [14]. On the other hand, attachment is inhibited by treatment of the cells with trypsin [15]. In spite of the key role of this receptor, and the fact that it was partially characterized by Norrby [15] 25 years ago, remarkably little is known about it. The measles virus receptor is found only on cells of the more evolved Old World primates, and although it is found on most types of nucleated cell in anthropoids, including humans, it is not present on erythrocytes of these species. Norrby characterized it as a lipoprotein on the basis of trypsin sensitivity and its solubility in more than 30% methanol, but Fenger and Howe [16], in the one subsequent biochemical study, associated it with a glycoprotein on the basis of reactivity with periodic acid-Schiff reagent. The latter study shows it as one of the smaller glycoproteins of the rhesus red cell stroma, but does not provide the basis for estimation of a specific molecular weight or further chemical characterization.

Most of the six proteins of measles virus (the L and F proteins are difficult to purify) elicit immune responses from both T cells [17, 18] and B cells [19, 20]. The T cell response usually declines below the detectable threshold within a few months of infection and hence tests for it do not give results indicative of immune status. The B cell response includes antibodies of the IgM [21] and IgA classes [22] as well as IgG, but the IgM is also transient. The IgA is not essential to protection as evidenced by the protection afforded by passive IgG, and it, too, wanes in a few years [23]. Monoclonal IgG antibodies to the measles P, NC and M proteins show some reactivity with analogous proteins of other viruses of the genus, that is, of canine distemper virus and rinderpest [24]. Comparable cross-reactions were not found with the H protein. The cross-reactions are of no epidemiological importance, because members of the genus *Morbillivirus*, other than measles virus, do not replicate in the human, and immune responses are not stimulated by the amounts of antigen that may be acquired by contact with infected animals [25]. When dealing with immunity to measles in populations, it is possible to focus on the IgG antibodies to measles H protein.

There is just one component of the immune response that may function independently of the anti-H antibodies and be of sufficient importance to determine immune status in a proportion of a population; this is antibody to the fusion (F) protein. Norrby [26] makes a strong case for the necessity for antibody to this protein as an essential component of effective measles immunity. However, except in persons who have been immunized with a killed virus vaccine [27], the amount of anti-F antibody has not been found to be a limiting factor. Salmi et al. [28] have also suggested that this antibody plays an enhanced role in multiple sclerosis, but that disease is rare enough not to be a significant factor in herd immunity. Strenuous efforts in our laboratory have not been successful in adapting the Salmi anti-F assay to a procedure that is suitable for large surveys as a measure of immunity. We therefore have no data on the relative prevalence and titer of this antibody in different populations.

Four epitopes have been identified on the measles hemagglutinin, but these overlap as if they are all part of one large active site [29, 30]. Mutation to resistance to particular monoclonal antibodies directed at these epitopes does not remove susceptibility to the hemagglutinin-inhibiting antibodies in normal sera. Tests designed to measure antibody to the hemagglutinin presumably measure a sum of the several idiotypes directed toward these linked sites. The correlation between hemagglutination inhibition (HI) and neutralization (NT) titer in the same sera is close enough to suggest that the two tests measure predominantly the same set of idiotypes (fig. 1). Both these titers correlate well enough with

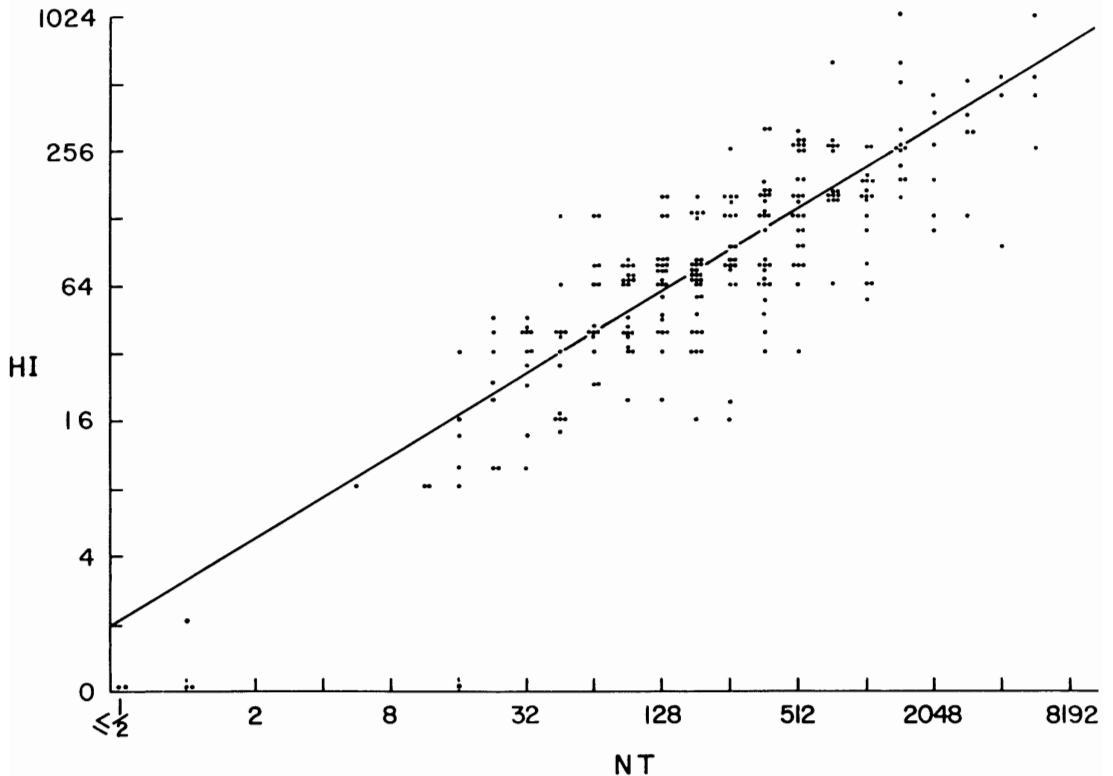


Fig. 1. Relationship between HI and NT titers in the cord blood of individual infants from New Haven, Conn.

immunity to infection [31] so that we are not in a position to choose one over the other as an index of susceptibility. Thus, any test that measures antibody to the H protein super-epitope seems to provide a reasonably adequate measure for estimating measles herd immunity.

B. Methods for Measuring Measles Antibody

Two types of epidemiological information may be sought in using a serological test for measles. An appropriately standardized qualitative test will determine whether or not an individual has a level of immunity adequate to protect him- or her-self from infection. In the light of the considerations presented above, I believe that this level can be defined in practical terms as an amount of IgG specific for the super-epitope of the H protein of measles virus. When actively acquired, these antibody titers are quite stable and it need not be assumed that borderline levels of antibody will, at a later time, fall below the protective level. Alternatively, a quantitative measure of how many of these units are present may be needed to predict durability of protection, if the antibody is acquired pas-

sively. Whether the data are categorical or quantitative, the basic unit of antibody is the concentration that will prevent virus replication in a human.

If there were significant immunological variation between different strains of virus, this unit would be variable. Indeed, the Edmonston-Zagreb vaccine strain does infect in the presence of antibody that inhibits other vaccines and wild virus [110]. However, in diverse communities, the age at which the earliest natural infections are seen is very much the same as the age when children first respond to a standard vaccine. Thus, the level of passive antibody needed to give protection from naturally encountered doses of any wild virus, delivered to the respiratory tract, is similar to that needed to inhibit usually much larger doses of a standard attenuated virus injected into the tissues. The consistency of this relationship provides further evidence that the pathogenicity of wild virus strains does not vary greatly. We have no direct measure of the amount of antibody needed to prevent infection because deliberate infection with wild virus has been unethical since natural infection ceased to be inevitable, but there are adequate data on the amount of antibody that will prevent a response to vaccine, and this is our basic unit of immunity. Dabis et al. [32] have equated this to 0.1 International Reference Unit as contained in the WHO measles reference antiserum.

The most widely used method of measuring antibody to the H protein is the HI test [33] and a large body of data has been collected with it. Dispersal of measles antigen by sonication [33] or ether treatment [34] gives hemagglutinating particles that individually bind less antibody than the mixture of whole virus and infected cell debris that was originally used as antigen, and, hence, increased sensitivity. The use of red cells from the genera *Cercopithecus* or *Patas* instead of *Macaca* also increases sensitivity. When the challenge dose of hemagglutinin is held at two 100% hemagglutinating units, this test has sufficient sensitivity to detect one protective unit of antibody at a serum dilution of 1–5, or $2.3 \log_2$. Requisite pretreatment of serum to remove nonspecific inhibitors leads to an initial dilution of the serum that makes it inconvenient to measure titers lower than this. Nearly everybody whose serum does not react in a 1:5 dilution will respond to vaccination with a boost in titer [35], whereas those with titers of $2.3 \log_2$ or more will show, at most, an increase in IgG without IgM, when tested 3 weeks later [31]. This secondary response is not seen in persons who have titers below 5 of passively acquired antibody. The version of this test used at the US Centers for Disease Control is substantially less sensitive, presumably because of the use of a larger amount of hemagglutinin [36]. HI titer measurements made on different dates for the same serum have, in our laboratory, a standard deviation of

plus or minus $0.51 \log_2$. The variation between different sera is several-fold greater; it showed a standard deviation up to $1.83 \log_2$ [37] (table 1). The great practical limitation of this method is its requirement for fresh Old World monkey, preferably Cercopithecine, red blood cells. As we have striven for more humane animal care, the cost of keeping animals as a source of these cells has increased and potential suppliers have become few.

The optimal measles antibody test, with respect both to sensitivity and to reproducibility, is the plaque reduction test [36, 38], especially when its sensitivity is maximized by using low passage challenge virus and by aggregating virus antibody complexes with an antihuman antibody (EMPR test). Albrecht et al. [36] report that this test is 600-fold more sensitive than their HI test. They do not give a reproducibility estimate, but plaque reduction tests generally do very well in this regard. The difficulty, of course, is that an EMPR test is time consuming and expensive in materials. Its great sensitivity is not needed in determination of susceptibility to infection and it has, therefore, rarely been used in surveying large sets of sera.

In the more recent original work reported here, we have compromised by using a cytopathic effect neutralization test (NT) [37]. By using a low-passage virus and a challenge dose of only 10 plaque-forming units we can obtain a greater sensitivity than with our HI test, and because it is convenient to start this test with undiluted sera, it gives a generous margin between the minimal protective level and the minimum detectable level. Albrecht et al. [36] suggested that fresh virus isolates are more readily neutralized than high passage material. However, much of the difference in sensitivity can be eliminated if the standard strain is plaque purified within a few passages of its use. We interpret the problem with high passage virus as one caused by defective interfering particles which bind antibody, but do not register as independent cytopathic effect or plaques. By performing this test in duplicate 6-mm culture wells we get better reproducibility on retesting one serum than with the HI test (standard deviation = $0.39 \log_2$), but show more variation between sera (table 1).

The NT tests correlate closely with the HI (fig. 1), but the two tests do not measure exactly the same thing and the relation between the two titers varies slightly from one population to another (table 1). Where HI equivalents have been estimated from NT titers, this is simply based on the average for the populations on which both titers were determined. The slope of the line relating titers obtained by the two tests in New Haven sera is 0.76, indicating that the NT titers go up faster than the HI values. A possible explanation might be that the more strongly binding

Table 1. Maternal samples tested, percent positive, and mean HI and NT titers

Source of sera	Type of clinic ¹	Number tested	% positive	Geometric mean titer of positive samples	
				HI titer \pm SD	NT titer \pm SD
1. New Haven, Conn., 1982, born <1958	M	326	98.0	6.0 \pm 1.5	6.8 \pm 2.0
2. New Haven, Conn., 1982 born >1959	M	74	97.3	5.4 \pm 1.5	6.1 \pm 1.8
3. Kingston, Jamaica, 1986	M	221	100.0	7.3 \pm 1.8	7.7 \pm 1.8
4. Ecuador, 1982	P	125	98.4	6.0 \pm 1.2	
5. Para State (rural), Brazil, 1982	P	125	98.4	5.9 \pm 1.4	
6. Recife, PE, Brazil, 1982	P	99	100.0	6.3 \pm 1.4	6.1 \pm 2.1
7. São Paulo, SP, Brazil, 1982	P	100	100.0	6.1 \pm 1.5	
8. Porto Alegre, RS, Brazil, 1982	P	149	99.3	5.7 \pm 1.5	5.9 \pm 2.0
9. Copiapo, Chile, 1987	M	96	99.0	(6.1)	6.4 \pm 2.0
10. Santiago, Chile, 1982	P	218	100.0	5.3 \pm 1.2	
11. Accra, Ghana, 1987	M	307	100.0	(6.8)	7.1 \pm 1.9
12. Lagos, Nigeria, upper class, 1982	I	63	100.0	6.0 \pm 1.3	
13. Lagos, Nigeria, lower class, 1982	P	73	100.0	5.6 \pm 1.1	
14. Northern, Tanzania, 1987	M	119	100.0	(7.0)	7.3 \pm 1.5
15. Gazankulu, South Africa, 1983	M	98	100.0	7.6 \pm 1.6	7.2 \pm 1.9
16. Jordan, military families, 1985	M	100	92.0	5.4 \pm 1.3	
17. Vellore, India, 1984	M	270	100.0	4.8 \pm 1.3	
18. Yogyakarta, Indonesia, 1987	M	56	100.0	(5.8)	6.1 \pm 1.6
19. Taipei, Taiwan, 1977	I	123	100.0	4.6 \pm 1.3	
20. Taipei, Taiwan, 1984	M	175	100.0	4.4 \pm 1.3	
All, means of populations		2,917	99.2	5.83	6.84

Numbers under sources of sera are the key to map locations in figure 1. HI values in parentheses are estimates based on the NT titers.

¹Type of clinic where collections were made: I = infant immunization; M = maternity ward; P = prenatal clinic. Titers of samples collected in I and P clinics were adjusted by $-0.05 \log_2$ per month until term to equalize the effect of dilution by increased blood volume in pregnancy [37].

antibody clones are accentuated in a strong response and that a firm union between virus and antibody is more important to inhibition of infection than to inhibition of attachment. As a logical corollary of this relationship, the variation between individuals as measured by the NT test is greater ($1.5\text{--}2.2 \log_2$) than by the HI test.

An enzyme-linked immunosorbent (ELISA) test has been developed more recently [39], and the fact that measles ELISA kits are now commercially marketed makes this test convenient. The versions of this test that have been described utilize partially purified supernatant fluid from measles virus infected cultures as antigen, and hence measure the sum of antibodies to all viral protein. The presence or absence of antibody at a predetermined cutoff level can be measured. Newmann et al. [40] reported that all of 28 cases in a Canadian high school occurred in 37 of 238 children who were negative by the commercial ELISA test. Gustafson et al. [41] found a cutoff that correlates well, in secondary school children, with the failure to make IgM in response to a challenge with vaccine virus: an appropriate index of protection from disease. However, the mean absorbancy reported by Gustafson declined by one-third between ages 11 and 17. Extrapolation of this trend would suggest that half the population would lose protection by age 30, something that is not true. This decline is reminiscent of that seen with the complement fixation (CF) test [23, 25, 42] and may reflect a decline in titer of antibody to proteins other than the hemagglutinin. The ELISA test could be adapted to utilize purified envelope proteins as antigen, but even so quantitation would be complicated. The absorbancy values that are initially obtained from the test do not bear a linear relation to titer. Developing a standard curve and then using several wells to determine each titer makes this a much more elaborate procedure. Nevertheless, when this is done one obtains a measure of antibody that permits comparison of smaller titer differences than any method dependent on serial dilution.

The complement fixation test has been used to determine measles immunity in the past [42]. As usually performed, this test, too, measures the sum of antibodies to all viral proteins. These titers are less stable over time and, hence, less related to protection than tests depending on antibody to H protein. The test requires elaborate standardization of reagents and has fallen out of favor for research purposes.

C. Durability of Measles Immunity and Antibody Titer

An immunological test that is epidemiologically relevant must reflect the solidity and durability of the immunity that follows infection even with attenuated strains of virus. This durability is not altogether unique among viral diseases; persistent antibodies associated with lasting im-

munity have been demonstrated in yellow fever [43] and dengue [44] and the immunity to hepatitis A may be as solid [45]. However, measles is the best-known example of lifetime protection. Other diseases like poliomyelitis, which exhibit durable protection from disease after initial infection, do not in fact exhibit comparable protection from localized infection [46]. In rubella, too, repeated infections occur occasionally [47].

The immunity of measles came to be the model for durable protection as a result of the classic study by Peter Panum in the Faroe Islands in 1846 [48]. There had been an epidemic of measles in this North Atlantic archipelago in 1781 with high mortality and, when the virus was reintroduced in 1846, Panum and another young doctor were sent from Denmark to provide medical care. Panum made the mode of spread of the virus, and the epidemiological conditions that preceded it, his main focus of interest. In vivid prose he showed that those who, 65 years earlier, had had measles remained solidly immune although there could have been no interim boost of immunity.

Studies in other island populations in Tahiti [25], the Pacific [49] and St. Helena [50] have shown that measles HI antibodies persist, if not altogether stably, with minimal change, for long periods in a high proportion of previously infected persons. In Tahiti a time period of 21 years had elapsed since exposure, yet the measles HI and NT titers were only slightly lower than those in persons 6 months after infection. The CF titer fell somewhat more rapidly.

The immunity induced by the vaccination with attenuated measles virus reaches lower peak titers than those induced by wild virus, but the subsequent curves are parallel [51]. We have followed the HI titers in persons living in Iceland [52] and in the Amazon [53] for up to 15 years after vaccination with no intervening exposure and found no significant change after a drop of two- to fourfold during the first year. (The referenced papers cover only part of the time interval that has now been studied.) More recently, Pedersen et al. [23] reported detailed studies carried out in a population of 1,000 Eskimo who live along Scoresbysund in East Greenland. These Eskimo have never been exposed to measles, but were vaccinated in 1962. The results are complicated by the finding of an HI titer boost in 4 individuals between 1970 and 1972, 2–4 years after vaccination. Pedersen et al. attribute this boost to reexposure, although they make no reference to any other evidence of the introduction of measles virus. On the basis of the data presented, there is no evidence that this was an exogenously stimulated titer fluctuation. It is unlikely that some other morbillivirus provided the stimulus, because the only known possibility, canine distemper virus, did not affect human antibody titers during a massive outbreak in Tahiti [25] and would doubtlessly

have been recognized and reported if it had occurred in this isolated, but medically well served, community. These fluctuating titers were a minority in Scorsbysund. More prominent is the fact that titer measured by any method declined very slowly, the NT and HI titers more slowly than the others and sufficiently slowly that, extrapolated at a uniform rate, the mean value would remain above the minimum required for protection throughout a 70-year lifetime.

The Scorsbysund data point to one of the major persistent questions regarding measles immunity: Is it maintained by cells that were activated by the initial infection or is it repeatedly boosted by antigen produced by a latent virus? Current immunological thinking implies that activated IgG producing B cells have a limited life span, but that a proportion of the cell clones selected for specific antibody production are relegated to a hibernating status. These 'memory' cells can be rapidly activated to produce a secondary immune response on new contact with the antigen. In Tahiti and Scorsbysund such stimuli could only have come from endogenous viruses. Evidence for latent measles virus is, however, very limited. Measles virus does persist latent or at most slowly growing, for several years during the interval between overt measles and subsequent subacute sclerosing panencephalitis (SSPE). SSPE cases are rare, however, and it seems a major extrapolation to use them as a model. Haas et al. [54] have reported finding RNA that hybridizes with a measles probe in brain from measles-experienced persons. Whether this is a truly persistent measles genome, and, if so, whether it can function to produce measles antigens, remains subject to question. The possibility that memory cells are gradually reactivated without specific stimulus, although equally without supporting evidence, offers the simplest hypothetical mechanism for antibody maintenance in disease with durable immunity. For the present, the main point is that antibody to the H protein exhibits a stability and durability comparable to immunity to disease.

D. Secondary Immune Responses in Measles

Although it is not known whether periodic secondary immune boosts play a role in maintaining measles titers, secondary responses have been observed in more specialized situations. When minimal levels of passive antibody persist at the time of immunization, primary immune sensitization may occur without the production of measurable antibody titer. When children immunized under these circumstances are revaccinated they mount a rapid immune response without IgM production [31, 55, 56]. Titers induced by such secondary responses do not persist like the primary response titers [31]. Contrary to published speculation [57], these secondary responses do not prevent the characteristic symptoms of measles

infection [56, 58–60], although under these circumstances the disease is usually mild measles. In Hungary, 23% of all measles cases, occurring in persons with a vaccination history, were associated with failure to produce IgM [59]. Presumably, the same type of inadequate immunity may be elicited by natural infection in the presence of minimal passive antibody titers. This has never been directly demonstrated, but it may explain the very rare instances of relatively well-documented repeated measles infection [61].

III. Measles Herd Immunity

A. R_0 , the Transmission Potential of Measles

The term R_0 has been defined as the number of secondary cases of disease to be expected, in the absence of disease-induced immunity, from contact with 1 primary case [62]. It is necessary to reduce, and hold, this value below 1.0 if transmission of the disease is to be halted. Vaccine-induced immunity may be used in doing this, but immunity induced by natural disease must be excluded, because the latter effect will approach zero in the ultimate stages of control. Direct measurement of R_0 is generally impractical. There is significant disease-induced immunity in all except a few rare communities, such as Julianahaab, in Greenland, at the time Manasse returned there from Denmark and initiated 250 secondary cases of measles [63]. Generalizing from these exceptional instances is not good science – it happened that the night after Manasse arrived in Greenland there was a big party in Julianahaab.

There is a more generally applicable method for calculating R_0 . In a stable population, $R_0 = L/A$ where L is the average life span and A is the average age at first infection [64]. In the case of a disease like measles where a single infection confers lifelong immunity, and in a numerically stable population, this implies that R_0 approximates the total number of persons in a population divided by the number who have never been infected, or, in the absence of vaccine-induced immunity, the reciprocal of the fraction of the population without antibody. Substantial data applicable to this determination were collected before the measles vaccine was used. Anderson and May [65] estimated the value at 16 for England and Wales. A similar value can be calculated from the classic paper by Hedrick [66] on measles in Baltimore, if his data are transposed from exclusively children to represent proportions of the total population. On this basis, a measles vaccine that is 94% effective should be adequate, if universally administered, to reduce R_0 below 1.0 and, ultimately, to eliminate the disease. Mitchell and Balfour [3], in their earlier review,

found that the vaccine can meet this standard and proceeded to emphasize problems of vaccine coverage.

I believe, however, that there is a flaw in this reasoning that explains the failures of CDC's campaigns to eliminate measles. The flaw lies in ignoring the inhomogeneity of human populations and the possibility that the disease may persist in some subpopulations where the chance of virus transmission is higher than elsewhere. The fact that Manasse may have met a thousand people in 1 day of contagiousness is not really unusual; many people in any of our larger communities, particularly those in colleges and the military, may come into contact with that number on a routine day. Younger children, and the elderly, tend to move in smaller groups with fewer daily contacts. In the prevaccine era, most susceptible persons were preschoolers and the value of R_0 calculated from data collected at that time reflects their situation. Recently, the bulk of cases has shifted to adolescents and young adults, because they have more social contacts, a large R_0 value, and are thus better able to maintain virus transmission [67]. It is the R_0 of this group that must be reduced below 1.

There have been many reports of measles outbreaks in schools and colleges [40, 41, 59, 68–75]. This blizzard of reports on the same general topic has been publishable because the phenomenon comes as a surprise to many reviewers who thought that herd immunity levels were amply high. In some instances it was shown that 98% or more of the population had valid immunization records [41, 69–71]. In one study an epidemic occurred where 96% had protective levels of antibody [41]. Clearly 94% immunity does not confer herd protection where large groups of persons gather together.

If vaccination is to attain levels of herd immunity comparable to those given by wild virus, it must have a very low failure rate. This is demonstrated by the data in table 1. The geographic distribution of the sites listed in table 1 are shown in figure 2. To some extent these sites were chosen for opportunistic reasons, but they are broadly representative of developing and less-developed parts of the globe. Only the Jordanian sample includes a substantial proportion of women without measles antibody. It was drawn from dependents of the military and probably included a large proportion of Bedouin who shelter their women more than most cultural groups. The other populations did not differ significantly from one another and only 16 of 3,036 women, or 0.5%, lacked protective levels of antibody.

A value for R_0 cannot be calculated from these data alone, because this high immunity rate was probably attained in contact with a younger population who included more susceptible persons, but it does serve to emphasize the pervasiveness of measles infection. If we hope to stop the

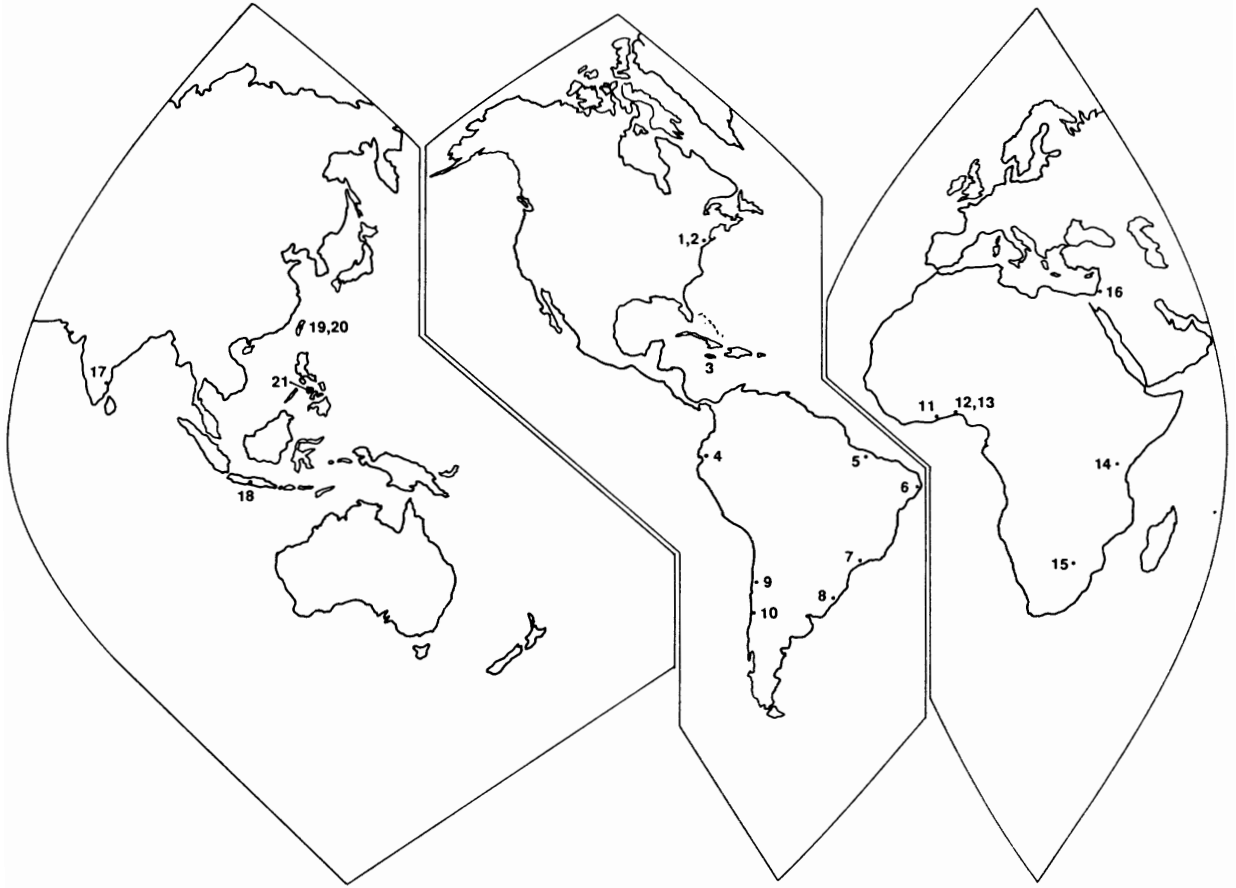


Fig. 2. Geographic sources of populations studied. See table 1 for key to numbers.

spread of measles, we must work on the premise that the relevant value for R_0 is at least 50, and that more than 98% vaccine efficiency is needed.

Measles outbreaks were a problem in the military in the prevaccine era [76]. These epidemics occurred even though prevalence of immunity was very high. The serological tests available at that time were slightly less sensitive than modern tests. Nevertheless, in the United States 98.8% of military recruits had demonstrable immunity. It is thus probable that in the unique circumstances of a military recruit base, measles can spread in populations that are close to 99% immune and that there the measles R_0 is close to 100.

B. Potential Vaccine Efficiency

If at least 98% antibody positivity is needed for herd immunity, one may well wonder whether this is an attainable goal with the currently

Table 2. Seroconversion rates in populations free of pre-existing antibody

	Number vaccinated and tested	Number sero- converting	%
Iceland, 1962	576	572	99.3
Iceland, 1965	156	155	99.4
Brazil Tiriyo, 1966	110	110	100.0
Brazil Xikrin, 1970	110	107	97.2
Brazil Mekranoti, 1972	141	138	97.9
All	1,093	1,082	99.0

available live attenuated vaccine. Most vaccine efficacy studies have been content with ascertainment of greater than 95% seroconversion rates. To measure differences within that last 5% requires large numbers of subjects and near total freedom from errors of subject identification and bookkeeping. If the test is carried out in babies one must be sure that subjects with any residual passive immunity are excluded, and, if in older age groups, one must be careful to avoid all individuals with immunity derived from prior experience.

We have carried out two sets of studies in isolated populations whose members were old enough to have no chance of retaining passive protection and whose prior experience with the virus had been very limited [77–80]. The results are given in table 2. In rural Iceland there had been a series of measles outbreaks, but each had been restricted geographically and their timing and extent had been recorded carefully. The individuals whom we vaccinated were keenly aware of their own histories. The other trials were carried out in Brazilian Indians among who there had been no measles epidemics, and where measles antibody was found only in a few individuals who had travelled outside the tribal territories. In Brazil, however, there were record-keeping problems in that there was a double language barrier and the subjects did not read or write. All subjects were tested and found negative for measles antibody before vaccination and all were retested 3–10 weeks afterwards. In this series of more than 1,000 vaccinations only 1.3% failed to develop protective postvaccinal titers. Most of the failures were in the Brazilian groups where clerical errors were anticipated.

In the ultimate test of routinely administered vaccine, protection in the face of an epidemic, McCormick et al. [81] and Davis et al. [75] found vaccine efficacy rates of 97.5%. Thus, at least at its best, vaccine efficiency in the United States is near that required to establish herd immunity.

C. Sources of Vaccine Failure in the United States

Although the measles vaccine is capable of providing the requisite levels of immunity under ideal conditions, it is apparent that it often fails to do so. As noted above, the proportion of a population found to be immune is often substantially lower than the proportion with a record of immunization. This problem has recently been reviewed by Frank et al. [82]. Frank and his co-authors, however, consider 95% 'very high vaccine efficiency' and, finding that this is commonly achieved, focus on problems of vaccine coverage. As stated above, I believe that 95% is inadequate, and that we should seek to attain a vaccination success rate of 98% or better.

Early studies suggested that mishandling of the vaccine was to blame for many of the failures [83]. This may have played a role, but the cited major study by Krugman et al. [83] does not reveal any very common or serious problem in vaccine stability. Four of 20 lots tested had lost more than one \log_{10} activity, but it would take a titer loss of 2–3 logs to seriously affect immunogenicity. It is also probable that the currently available product is more stable than those tested by Krugman. WHO standards now stipulate that vaccine lose no more than 1 log in potency after 1 week at 37°C. The Tiriyo tribe listed in table 2 with 100% seroconversion was immunized with vaccine that had been lost for 3 weeks in transit in the tropics. This lot retained a titer greater than 10^3 when tested after the misadventure. Holding vaccine for an extended time after rehydration would be more damaging.

Wassilak et al. [84] found that a malfunctioning jet injector accounted for a series of vaccine failures. However, most children in the US are injected by syringe.

Many studies that have measured vaccine failure have adhered to CDC practice in considering any child vaccinated after 12 months of age as appropriately immunized, even though the general recommendation calls for vaccination at 15 months of age [85]. It is known that interfering levels of passive antibody may persist beyond a year of age [38], and a slightly higher vaccine failure rate in children vaccinated between 12 and 15 months than those vaccinated later has been noted [41, 59]. Other studies have failed to distinguish between failures in children who were vaccinated appropriately and those who were first vaccinated too early and then revaccinated. As already noted, such revaccination is not as effective as initial vaccination at an appropriate age.

Another gap in our herd immunity is caused by a coverage problem, although cases resulting from this gap are classified as 'nonpreventable' by the CDC. This is reflected by the proportion of cases of measles that occur in children less than 15 months old. The fraction of all reported

cases that occur in this age group has increased steadily to reach 16% in 1986 [86]. It seems probable that this trend is due to an increasing proportion of mothers who were themselves immunized with vaccine and who have less antibody to pass to their children [87]. Within the next decade we will move to a position where nearly all babies born of North American mothers will get only this lower level of protection. At this time one can predict that the average child will become susceptible at 5 months of age [86]. That is not to say that vaccine should be given when the average becomes susceptible, but unless the age for vaccination is lowered from the current 15 months, 1% of our population will be susceptible to measles as a result of this one gap. The effect is somewhat mitigated by the fact that this age group does not associate in large numbers, and they, by themselves, will not be enough to breach herd immunity.

The size of these problems must be kept in perspective. They have been sufficient to foil efforts to eliminate measles, but we should not lose sight of the fact that the current vaccination program has reduced the impact of measles in the United States to a very small part of its former weight. I do agree with Frank et al. [82] that a major continuing problem is the importation of cases from outside the country. It is in the less-developed countries that measles has always taken its greatest toll, but it is there that vaccination programs have had the poorest record. If we could define and rectify the problems in those countries, we would not only make the greatest impact on human suffering, but we would also greatly facilitate measles control in the United States.

D. Vaccination Programs in Less-Developed Countries

The reason for the high measles mortality rates in less-developed countries has not been entirely clear. The most obvious association is with malnutrition, but a number of studies [35, 60, 88, 89] have failed to show a relationship between severity of measles and the usual indices of protein-calorie malnutrition: weight for age, weight for height, or mid-arm muscle circumference. Recent studies reported on by WHO and UNICEF [90] suggest that the effect is specifically attributable to vitamin A deficiency. A particularly interesting aspect of this report is the association between measles, vitamin A deficiency and delayed death. The theorem that measles may trigger a long downward slide in generally malnourished children has been prominent since the work of Mata [91] in Guatemala.

Measles surveillance data from less-developed countries is inherently poor. Any effort to improve the efficiency of reporting will readily discover more cases and yield a spurious increase in the statistic. It is therefore not generally possible to measure the progress of measles control cam-

paigns in these areas in terms of number of reported cases. Although mortality data are more stable, the number of measles deaths does not provide a good index of measles incidence, because so many deaths are due to combined causes of measles and other infection or measles and malnutrition [92]. The effect of measles vaccine on mortality extends far beyond the cases directly attributed to measles. Hospital admission data have been used with success by Davis [89], and by others for short-term comparisons, but they do not give a good basis for comparisons between different countries or over extended time periods. I have favored using the shift in age-specific attack rate as the most reliable index of vaccine effectiveness [93], although age-specific data must often be collected specifically for this purpose. Fifty percent successful vaccine coverage would reduce the number of infectious persons by 50%, as well as the number susceptible by the same proportion. One would then get, in the next round, only a quarter of the previous number of effective contacts, and the time between the age when a child first becomes susceptible and first encounters the virus would be extended fourfold. (At a later time, the number susceptible would build up, and one would fall back to a level of reduction proportional to the number actually immunized.) The total number of social contacts probably increases with age even in young children in less-developed countries, diminishing this effect, but because of the second power term this should provide a sensitive test. In fact, the effect of vaccination campaigns on the age of subsequent cases has been small [32, 94, 95]. This indicates that something is seriously wrong with the programs, probably that they miss large congruent segments of the population where measles endemicity can continue largely unaffected.

The problem that most concerns us here with regard to Third World measles vaccination programs is determination of the optimal age for vaccine delivery. Virus transmission is so efficient, and the danger of measles at an early age is so great, that one must deliver the vaccine very soon after children lose maternal protection. There is some hope that the use of massive doses of a more potent strain of vaccine will permit immunization even in the face of maternal antibody [96, 97]. Unless and until this can be done, it remains imperative to closely define the age at which children first become responsive to vaccine. This varies from one geographic area to another and, curiously, these differences show a statistically significant, although not universal, correlation with regional per capita product: children in the poorer countries become susceptible sooner (fig. 2). There must be some biological connection between income and persistence of passive antibody and we have set out to define this.

IV. Variation in Measles Passively Acquired Antibody

There are three possible explanations of geographic variation in persistence of passive protection: (1) the women of different countries have different amounts of measles antibody to pass to their children; (2) there are genetic or environmentally determined differences in the efficiency of the placenta in transporting IgG; or (3) there are differences in the rate at which children lose passively acquired antibody. We have found variation in all three of these characteristics.

A. Geographic Differences in Maternal Measles Titers

Comparisons of measles titers in different serum collections poses a problem in standardization. In practical terms it is not possible to standardize either the HI or the NT test so as to get consistent titers in tests performed on different occasions. In the HI test the hemagglutinating antigen tends to aggregate on storage so as to reduce sensitivity and different lots of monkey red blood cells differ in agglutinability. In the NT test different batches of virus differ in fraction of interfering defective particles and the tissue culture system varies from day to day in its susceptibility. For the comparisons in table 1, and the following, these factors were minimized by holding virus aliquots at -60°C and thawing one for each test and, in the NT test, by using tissue culture cells propagated according to a standardized routine. Tests were collected into a relatively few very large day's runs, each of which included sera from several collections intermixed with one another. Maternal, cord and infant serum sets were always tested in the same run, but never in adjacent positions where the titer of one might influence the determination of the titer of the others. Finally, at least 10, and usually 20 standard sera were repeated in each test and the individual serum titers adjusted to account for any variation in the mean value of these standard specimens.

Inspection of table 1 will reveal a $3 \log_2$ (8-fold) range in maternal titers ranging from 4.4 or 4.6 in Taiwan to 7.6 in Gazankulu, a South African 'homeland'. If we use a 45-day half-life for antibody persistence in the infant as an approximate average of the values described below, this would account for a 4.5 month difference in the mean age when vaccine would be effective. Lee et al. [98] using data from Taiwan, and Halsey et al. [99], using Haitian data, have shown that on an individual basis, the mother's titer correlates with the age at which a child becomes susceptible to measles and responsive to vaccine. However, the differences in mean maternal titer for different populations do not correlate well with the pattern of differences in age at acquisition of responsiveness that are shown in figure 3.

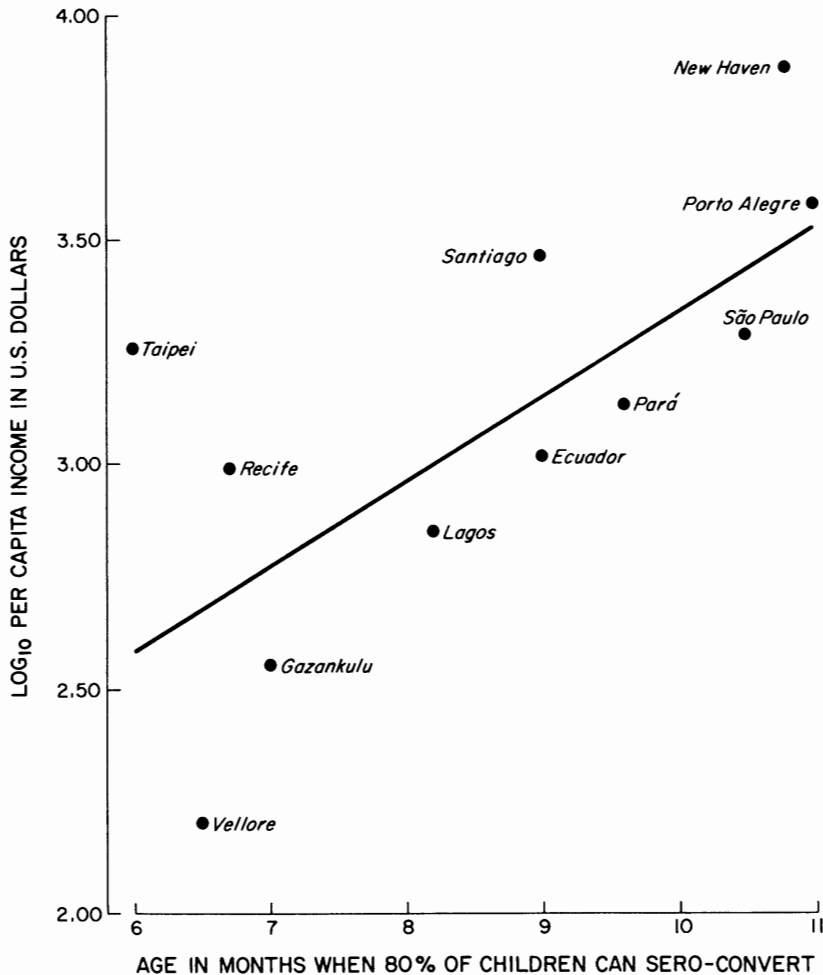


Fig. 3. Relationship between gross per capita product and age at which 80% of children seroconverted after vaccination. See Black et al. [37] for sources of data.

In the US study of mothers of different ages, the differences in mean titer are explicable as due to differences in proportion of the women who were vaccinated [87]. Although we were not able to reconstruct reliable individual vaccination histories for these women, the 1958 birth cohort was probably the last to have been in school at the time of the last New Haven measles epidemic, which occurred in 1964, and hence the last cohort to have been immunized largely by wild virus.

More generally, there seems to be a continental pattern of variation. The mean titer for the four African populations, together with that of Jamaica which is largely Africa derived, is 6.90 log₂; that of the New World populations, other than Jamaica, is 5.91; and that of the Asiatic

Table 3. Efficiency of transport across placenta

	Test	Number	Cord titer	Cord minus maternal
1. New Haven, Conn., <1958	NT	326	7.70	+0.86
2. New Haven, Conn., >1959	NT	74	6.76	+0.66
3. Kingston, Jamaica	NT	221	8.72	+0.54
9. Copiapo, Chile	NT	95	6.60	+0.16
11. Accra, Ghana	NT	307	7.32	+0.24
[108] Northwest Tanzania	HI	234		-0.36
14. Northeast Tanzania	NT	119	7.71	+0.38
15. Gazenkulu, S. Africa	HI	98	7.89	+0.29
17. Vellore, India	HI	270	5.06	+0.26
[109] Varanasi, India	HI	165		+0.09
[100] Kuala Lumpur, Malaysia	HI	331		-0.97
18. Yogyakarta, Indonesia	NT	56	6.42	+0.29
20. Taipei, Taiwan	HI	175	3.88	-0.52

Population numbers refer to map locations or, if in brackets, to reference list.

populations is 5.12. Only the low South Asian maternal titers offer some correlation with duration of passive immunity. Their low values serve partially to explain the anomalous position of Taiwan in figure 3. Chen and Lam [100] also report low maternal titers and early age of measles susceptibility in Malaysia, but because their tests were not standardized against the others, comparability is uncertain. The low titers in these women might be due to local virus strain differences, to environmental factors such as diet, or to genetic differences in the host. As yet, we have only minimal data that might help in choosing between these alternatives. Included in the New Haven and Jamaican studies are 12 women with East Asian names; their mean measles antibody titer is nearly $1 \log_2$ below the means of their compatriots.

B. Geographic Differences in Placental Transfer Efficiency

The process of transfer of antibody from mother to child depends on an active transport mechanism that can give significant concentration on the fetal side. The effectiveness of this transport varied between the several populations for which we have data (table 3). It is possible to use data from several laboratories in this comparison, because a difference between two titers is used and the two are presumably equally affected by variations in test sensitivity. The extreme differences between populations are nearly $2 \log_2$. Efficiency of transport was highest in the older US mothers whose children retain passive immunity longest, and lowest in

the Taiwanese and Malaysians. The low position of the Southeast Asian countries on this scale compounds the effect of their already low maternal titers in these populations, to leave the babies of these countries with substantially less passive antibody than children of other areas.

The efficiency of the transport varies between the several IgG subclasses [101]. In US specimens we find the major part (>80%) of the measles antihemagglutinin antibody in the IgG₁ subclass, the one that is most efficiently transported. It remains to be seen if, in Southeast Asia, more of the antibody is in other subclasses.

Although low transport efficiency, together with the low maternal titers, is sufficient to explain the anomalous position of Taiwan in figure 2, most of the populations included in table 3 differ but little from one another and these small differences cannot explain most of the observed differences in age at acquisition of susceptibility.

C. Geographic Differences in Passive Antibody Half-Life

The third hypothesis for the source of differences in duration of passive protection postulates differences in the durability of passive antibody in the infant. This is the most difficult of the three measurements because it requires comparison of paired specimens collected at birth (easy to get from the umbilical cord) and 4–6 months later. The problems of locating the children, securing maternal consent, and actually collecting adequate samples of blood from the screaming babies, have limited the number of studies we have completed. For maximal accuracy, in determining the rate of decline, it is necessary to collect the babies' sample as late as it is possible to measure residual titer, but babies who are tested after the antibody has fallen below the measurable threshold are not informative.

Half-life determinations for four populations have been made at the time of writing. The variation between these values goes a long way toward explaining the observed differences in age when susceptibility appears, and, coupled with the data on cord titers, provides a reasonable estimate of the duration of protection (table 4). The half-lives are all substantially longer than those of 21–23 days for IgG₁ commonly cited in the literature [102]. The commonly cited values are based on old data derived from adults injected with radioiodine-tagged IgG. The adult data may not be applicable to infants, but, more than that, the original studies did not yield constant rates of antibody loss. An early rapid phase, that was averaged to give the 21- to 23-day values, may actually have been due to the accelerated clearance of IgG that had been denatured in the iodination process.

It was to be expected that the values for New Haven and Taiwan would not differ because the difference in age at infection has already

Table 4. Measles passive antibody half-life in infants

	Number in sample	Mean age	Bio- chemical half-life	Biological half-life ± SE	Median age when antibody lost
Taipei, Taiwan	85 ¹	104	53.3	35.7	183
New Haven, Conn., <1958	42	171	48.4	38.1 ± 1.8	301
Kingston, Jamaica	173	187	44.3	33.0 ± 0.5	272
Accra, Ghana	35	146	39.7	31.3 ± 1.3	229

Biological half-life incorporates the diluting effect of infant growth. All times in days.

¹Not paired data. Based on titer difference between 85 babies and 175 cord sera.

²Median titer (\log_2) of the cord sera multiplied by biological half-life.

been accounted for by differences in cord titer. There are no specific data available on the optimal age for vaccination in Jamaica, but because it is a relatively poor country with a significant infant nutrition problem, we had presumed that susceptibility would be acquired early. Only after finding that the passive antibody half-life in Jamaica was only a little shorter than in New Haven or Taiwan did we take note of the facts that Jamaican infant mortality is low, 24/1,000 in 1985 [103], and that the sanitation system is good enough to have protected most Jamaicans from hepatitis A virus [104]. The insular position of the country has facilitated the exclusion of many other diseases. Although the biochemical antibody half-life in Jamaica is not much different from that found in New Haven, there is a greater difference between the biological half-lives. This is because the Jamaican babies were small at birth, but grew more rapidly than the North American standardized curves. There was, therefore, more dilution. A measles vaccination program aimed at children 12 months of age has been remarkably successful [105] and measles has essentially disappeared from the island.

The infant mortality rate in Ghana is relatively high, 97/1,000 in 1983, the latest data available, and sanitation in Accra is poor. The measles antibody half-life in this city is significantly lower than in the other populations studied.

These half-life differences are in the right direction, but their magnitude is not great enough to fully explain the observed differences in age at susceptibility. It may be that at the ages when we tested these children the differences are only beginning to become apparent. The technique we have used is not sensitive to changes with age in rate of antibody catabolism because it measures the average value from birth to age at testing.

Nevertheless, there are some indications that the rate of catabolism accelerates after the first few months. In the largest set, the Jamaicans, the mean half-life for children less than 200 days old is 44.7 days but it is only 41.3 for 30 children who were more than 200 days old when tested. Taken at face value, this would suggest that after 6 months of age the catabolic rate accelerated dramatically. As will be shown, an acceleration is to be expected if enzyme production is substrate dependent.

D. Mechanism of the Effect of Income on Passive Antibody Half-Life

These data permit us to answer the question 'Do differences in antibody half-life affect the durability of measles passive immunity?' in the affirmative, and to begin consideration of the causes of the differences. 'Why do some children have such high IgG levels?' and 'What mechanism(s) relates total levels to passive antibody half-life?'

To better understand the mechanisms involved in the determination of passive antibody half-life, it is necessary to move from consideration of populations to comparisons of individuals. The Jamaican infant serum collection is our largest and the one we have principally used for these comparisons. There was a wide variation in the growth rate of these children and those who doubled their weight in less than 150 days had significantly longer measles antibody half-lives (mean 43.9 days) than those who grew more slowly (40.6 days). Similarly, Rogel, working in our laboratory, found that there was a wide variation in total serum IgG; 9% of the babies he studied had concentrations less than 500 mg/dl although 4.5% had more than 2,000 mg/dl. These total IgG concentrations also correlated inversely with the child's growth rate, but even more strongly with antibody half-life. Children with total IgG levels below 500 mg/dl at 6 months of age had a mean half-life of 51.8 days, whereas those with IgG levels above 1,500 mg/dl had measles antibody half-lives of only 41.0 days. The effect could be sharpened by using an RIA test based on an arithmetic absorbancy scale instead of the geometric scale used in neutralization tests (fig. 4). The ELISA test, as noted earlier, probably measures a broader variety of antibodies than the neutralization test, but because most of these other antibodies are less persistent than anti-H, the passive antibody derived from a mother immunized many years earlier would be predominantly anti-H.

The high IgG levels that were found in Jamaica were unusual relative to published data from more developed countries [101, 102], and we presume that they reflect a high frequency of infection. Such an association would explain the relationship between high IgG levels and failure to grow rapidly. The infections, particularly the diarrheas, may cause accelerated loss of antibody directly, through damage to the gastrointes-

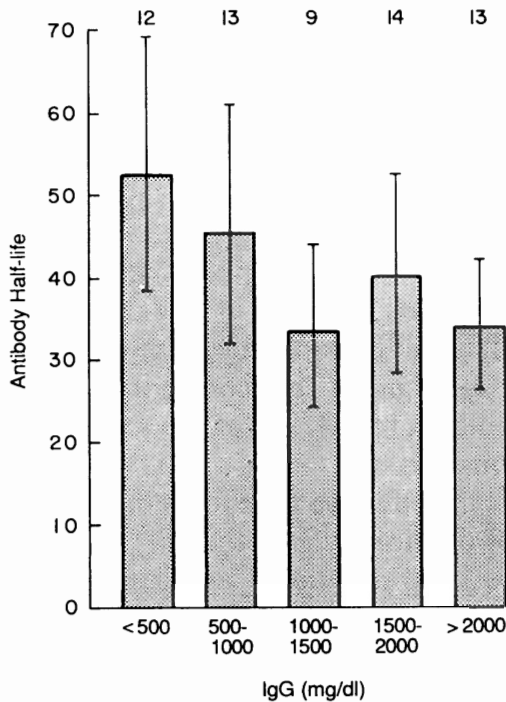


Fig. 4. Half-life of passively acquired measles antibody as measured by ELISA in relation to total IgG concentration at 6 months of age. The numbers above each bar indicate the number of children in the sample.

tinal tract and leakage of serum into the lumen. The passively acquired antibody, lost in this way, would not be replaced.

Alternatively, it may be that the high levels of total IgG stimulate increased catabolism and elimination of passively acquired antibody. In mice, antibody half-life is dependent on the total IgG concentration [102]. This may reflect the common phenomenon of induction of enzyme by substrate. If the same effect is operative in humans, those babies who are stimulated, by frequent infections, to make large amounts of IgG, would accelerate their IgG catabolism. If this is the case, the antibody curves might appear as in figure 5. The curves for actively produced and total IgG in this figure have been modified from those of Gitlin [106] to fit the points that we have determined at birth and at 6 months. The passive antibody is degraded at the same time as the baby is actively making its own IgG, but at a decreasing rate as the level of total IgG declines. A nadir in total IgG is reached, in the USA and in Jamaican children with low rates of IgG synthesis, at about 3 months of age. In children making more IgG, this nadir would be earlier and shallower, as indicated by the 'H' lines in figure 5. From the nadir, the rate of IgG destruction would

start to increase, with acceleration soonest and greatest in the children who make the most IgG. The curves for passively acquired measles antibody in the figure are calculated from the formula:

$$L_k = L_m \times \frac{[IgG_m]}{[IgG_k]}$$

where L_k = half-life for the interval under consideration; L_m = mean half-life for the whole population; $[IgG_m]$ = mean IgG concentration for the population over the total time period, and $[IgG_k]$ = IgG concentration for subpopulation over the interval considered.

The mean half-life used here is the effective time for reduction to half titer and thus includes the effect of dilution by growth.

The successive half-lives have been calculated and summed in the figure to indicate the residual measles titer at different ages, assuming an initial titer of 128. The time at which this antibody would become undetectable by the NT test is reduced 2.5 months from 277 to 188 days. The seventh half-life (the last plotted) is 35 days for the mean IgG group but only half that, 16.6 days, for the high IgG group. If, as with the above formula, direct proportionality is assumed between total IgG and catabolic rate, the successive half-lives become smaller as the total IgG increases. This conforms with our evidence that the half-life is shorter after 5 months of age than it is before. There is, however, no *a priori* reason to assume direct proportionality. Increasing IgG concentrations may have diminishing, or increasing, effects on catabolism and half-lives may change less or more than indicated.

The secondary consequences of increased IgG production in response to more frequent intercurrent infection are thus capable of providing an adequate explanation of the regional differences in age at which children can be successfully vaccinated. This does not mean that increased intestinal leakage does not also play a role.

V. Summary

'The simplest of all virus disease is measles' said Kenneth Maxy 40 years ago in a chapter on epidemiology [107]. I hope that the data set out here provide the reader with a sufficiently complete and clear picture of the factors that determine measles epidemiology, that he or she will agree with Maxy's prescient words. Measles is an antigenically complex virus, but few components of the immune response to this virus are epidemiologically relevant. The relevant components are durable for a lifetime. They can be conveniently

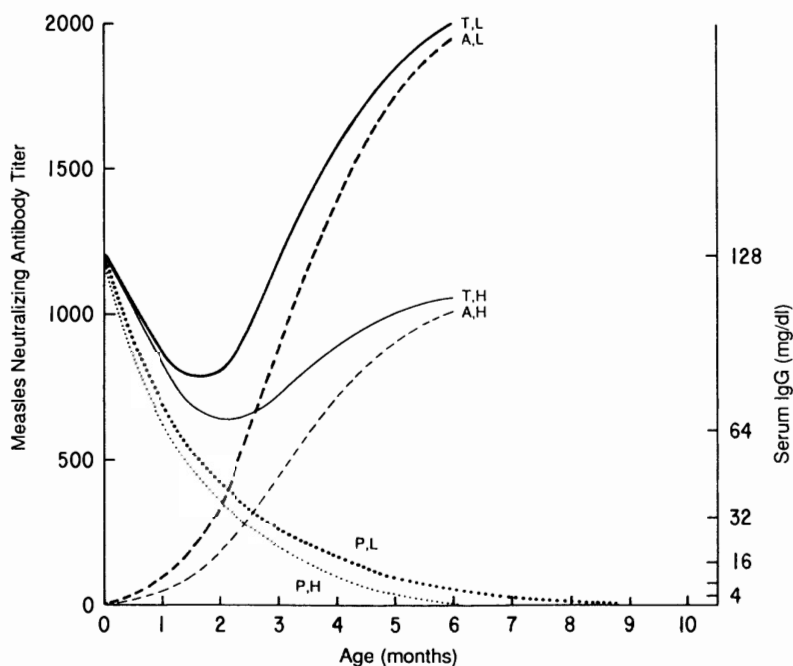


Fig. 5. Curves of total, actively acquired and passive antibody concentration during the first few months of life. See text for method of calculation. L = Children with total IgG concentration near 500–1,500 mg/dl; H = children with total IgG <2,000 mg/dl at 6 months of age; T = total serum IgG: left-hand scale; A = actively acquired IgG: left-hand scale; P = passively acquired measles antibody: right-hand scale.

measured by serological tests, and the results of these tests correlate well with measles immunity. The tests show that measles is an extremely infectious disease, and that very high antibody prevalence rates are needed for herd protection. The currently available measles vaccine is capable of yielding adequate antibody prevalence rates for herd immunity, but to achieve this, immunization procedural flaws and faulty records must be kept to very low levels.

The greatest obstacle to worldwide control of measles is a failure of vaccination programs to produce adequate herd immunity levels in less-developed countries. There, vaccine must be given promptly after passive immunity wanes, because the level of endemicity is so high. It is difficult to determine just what age is optimal, because it varies from one country to another. Premature vaccination not only fails to immunize, but also interferes with subsequent re-immunization. Because we now know this, further direct tests of vaccine effectiveness in very young children are ethically undesirable, and methods that use determination of passively acquired antibody are to be preferred. The levels of antibody that mothers have to pass to their children vary considerably. These differences are important in comparisons of South Asian countries with others, but not elsewhere. Differences in efficiency of transport of antibody across the placenta also play a role, but usually a minor one. Most important seems to be variation in antibody durability in the infant. Where families are poor, the children acquire many infections at an early age, and passively acquired antibody is swept out. These children who are least able to withstand the effects of measles

infection, are hit at the earliest age. To provide protection for them, the vaccine must be given at a carefully determined age, specific for each community. Only when this is done can we hope to reduce measles worldwide to a sufficiently low level that it will be removed as a threat to persons in the United States, or anywhere else.

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