Maternally derived measles immunity in era of vaccine-protected mothers

Measles hemagglutinin-inhibiting and neutralizing antibody titers are lower in women young enough to have been immunized by vaccination than in older women. In the children of both young and older mothers the antibody is concentrated 1.7-fold across the placenta, and the child's initial titer remains proportional to that of its mother. The transferred antibody is diluted by the baby's growth and degraded with a mean half-life of 48 days. By 8½ months of age, 95% of the children of the mothers born since 1963 would have become susceptible to measles and responsive to immunization; the same level of susceptibility is not reached by children of mothers born before 1958 until 11½ months of age. Among the offspring of younger mothers, a small group remains, about 2% of the total, with titers high enough to provide protection for 12 months, and these children would be poorly served if the age for vaccination were reduced for all. However, selective early vaccination of children of young mothers who have low antibody titers would eliminate an important focus of measles susceptibility. (J PEDIATR 1986;108(1):671-676)

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Thirteen percent of all measles cases reported to the Centers for Disease Control in 1984 were in children <15 months of age.[1] These cases are classified by the CDC as "nonpreventable," but they could be prevented by lowering the recommended age for vaccination.[2] The problem is identifying children who need the vaccine and avoiding premature vaccination of other children who might thus be made refractory to reimmunization.[3-6] The determination of 15 months as the optimal age for vaccination was made on the basis of studies carried out 8 or more years ago, when nearly all adult immunity was derived from natural infection.[7-11] Measles vaccine was licensed in 1963, and many recipients were already 6 to 8 years of age when immunized. By 1984, most women <26 years of age derived their immunity from the vaccine. The measles vaccine elicits lower antibody titers than the natural disease.[11] Yeager et al.[6] have noted a progressive decline in the mean titer in cord sera between 1969 and 1980, an effect to be expected with the arrival of vaccinated girls to the age of motherhood. Many of today's infants receive less antibody at birth and become both susceptible to measles and responsive to the vaccine at an earlier age than was the case a decade ago. Our main purpose was to measure this effect.

Not only are titers in younger women lower, but NT titers are more changed than HI titers; this implies a qualitative difference in the vaccine-induced antibody.

HI	Hemagglutination inhibition
NT	Neutralization

Thus, we have also compared other aspects of maternally derived immunity that affect durability of protection in infants: the efficiency of transplacental transport and the rate of antibody degradation in the infant.

METHODS

Specimens. Sera from 20 women born in each year from 1947 to 1967 were contributed by Dorothy M. Horstmann from a set collected in 1982 from persons who had come to the Yale–New Haven Medical Center for rubella antibody

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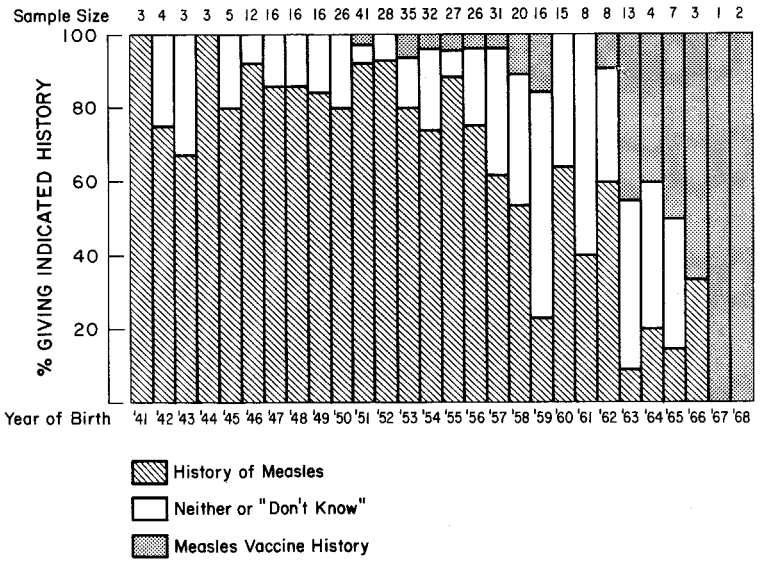

Fig. 1. Distribution of new mothers in this study by measles history and by age.

tests. No individual histories were available for these women.

Paired specimens from 432 mothers and umbilical cords were collected from consecutive normal-risk maternity cases at the same medical center between October and December 1982. Excluded from this series were infants with birth weight <2500 gm or parturition <36 weeks, infants classified before birth as high risk, and infants who were expected to be put up for adoption. The purposes of the study were explained to the mother after the birth and, if written consent was given, the maternal specimen was collected when routine predischarge specimens were taken. Very few mothers declined participation. At the same time, permission was also sought from mothers in predesignated practices for collection of a specimen from the baby at 6 months of age. The mother's history of measles was solicited from her, and if possible from her own mother, and the baby's weight noted. A recent increase has occurred in the age of mothers giving birth at this hospital. The observed ages were from 14 to 41 years with a mean of 30 and a median of 28.

Oral confirmation of permission to take a specimen from the child was sought at the designated time. Heel-prick specimens were collected from 59 of the same babies 142 to 271 days after birth. The baby's weight was recorded when the sample was collected.

Serologic studies

Hemagglutination-inhibition. Our standard procedure[12] was used. Precipitation of immunoglobulins with one third saturated ammonium sulfate was used instead of kaolin, because this avoids the loss of IgM and permits a lower initial dilution. Test results were scored 1 to 4, and these indices of partial agglutination were retained to estimate the 50% end points to one fourth of a twofold dilution.

Neutralization test. Ten plaque-forming units of recently plaque-passaged virus were used as the challenge dose. Virus and serial serum dilutions were mixed and held at 22° C for 1 hour, and then transferred to duplicate flat-bottom microtiter wells in which Vero green monkey kidney cells had been grown to confluence. After a second hour at 37° C in 5% CO_2, Eagle minimum essential medium growth medium with 5% newborn calf serum was added, and the cultures returned to the incubator. The cultures were examined for cytopathic effects after 5 days. The titer was considered to be the reciprocal of that dilution in which 50% of the wells showed evidence of virus growth.

Variability. It is not at present possible to standardize the HI or NT test to give strictly equivalent results from week to week. Challenge virus may have variable proportions of defective virions or a variable number of hemagglutinating sites per particle, and the tissue culture or erythrocytes may exhibit variable responsiveness. To avoid this problem, all HI comparisons were made between tests carried out on one occasion. Individual serum specimens from different age groups were interspersed with one another in a manner that prevented systematic changes from one end of the test to the other from affecting comparisons. Under these circumstances, the HI variance attributable to serum extraction and titration procedures was 0.26 $\log_2$. The variance from one specimen to another was 1.62 $\log_2$.

Table. Number of sera with low titers

Hemagglutination inhibition	Neutralization titer		
	<1	1-16	>16
<2	10	2	2
2-5	1	4	5
>5	3	10	786

Because the neutralization test is more time-consuming, it was not possible to restrict comparisons to results obtained on a single day. Specimens from the same sets were included in each test, and their mean value adjusted to equivalence. This adjustment was never more than 0.7 $\log_2$. Internal variation within a set of 10 sera repeated with each test was ± 0.39 $\log_2$. Variance between samples was 2.00 $\log_2$.

RESULTS

Antibody titer in women of childbearing age. Women who had come for rubella tests had slightly higher titers than the new mothers. This difference is explicable on the basis of the increase in blood volume during pregnancy.[13] Titers for the sera in the rubella-test group were reduced by 0.4 $\log^2$ to compensate for this effect before pooling with data from new mothers.

We had histories only for the hospital-based group. In this group, 80% of the women born before 1957 remembered having had measles (Fig. 1). Many of the younger women, and their own mothers, did not remember either measles or measles vaccination. This increase in "don't know" responses coincided with the age when vaccine was first commonly used, and may have been related to a lesser impact on the memory made by the vaccine. Although most of these women may have acquired their immunity through vaccination, we cannot distinguish those who did from the usual 20% who do not remember having measles, when assigning individuals to one category or the other. Titers in women who remembered having had measles were 0.3 $\log_2$ higher than in those who gave negative histories, and 0.8 $\log_2$ higher than in those who remembered vaccination. Because of the small number of definite vaccination histories and the relatively small numbers of young mothers, we have pooled the hospital data with those from the rubella-test series and focused on the relationship of titer with age rather than history. This gave sample sizes between 21 and 61 for each birth-year cohort.

Studies on vaccination of children with low residual levels of maternally derived antibody[14] and revaccination of children with minimal titers derived from too early initial vaccination[5] coincide in showing that an HI titer of 5

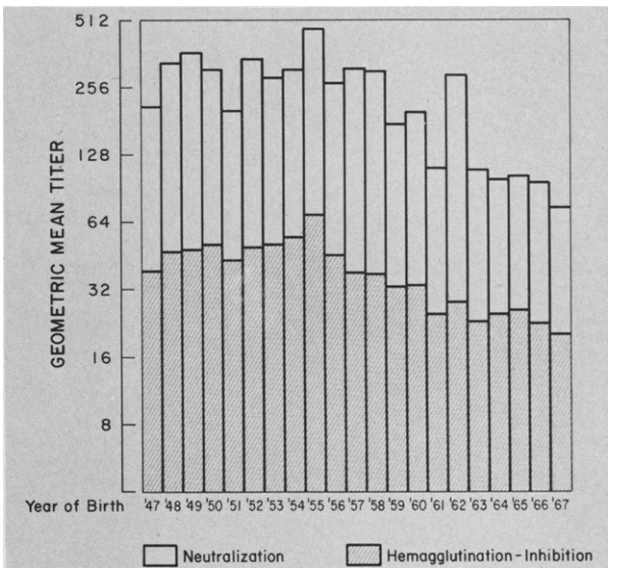

Fig. 2. Mean NT and HI titers for all women tested by year of birth.

or an NT titer of 16, as determined by the methods described above, is the minimal level that will block a vaccine-induced immune response. This seems to be the best available measure of the titer needed to inhibit replication of wild virus and prevent disease. Titers in 17 of 786 women for whom the two test results were available fell below both these standards (Table). The ages of these women who were deficient in measles antibody were distributed across the full span of ages, but these 17 made up 4.6% of the women born since 1959 and only 1.3% of the older subjects ($P < 0.05$ by chi-square test). Some of the 17 may have been immunologically primed by measles virus and able to produce antibody in response to exposure fast enough to protect themselves, but they did not have adequate titers to give protection to their babies.

Among the women with detectable antibody, the average titer by both HI and NT tests declined with decreasing age (Fig. 2). This decline was most pronounced in the cohort born between 1955 and 1961. Geometric mean HI titers in women born since 1959 were 0.6 $\log_2$ lower than in older women, and the NT titers were 1.8 $\log_2$ lower.

Relation between maternal and cord blood titers. The HI and NT titers in serum from the umbilical cord were respectively 0.70 and 0.82 $\log_2$ higher than in the mother's serum. This represents a mean 1.7-fold concentration across the placenta. The degree of concentration was uniform across the entire range of maternal titers (Fig. 3), and was unrelated to maternal age, to baby's weight, or to cesarean (71 observations) vs normal delivery.

Decline in antibody titer during the first months of life. Because of the small volumes available, only HI titrations

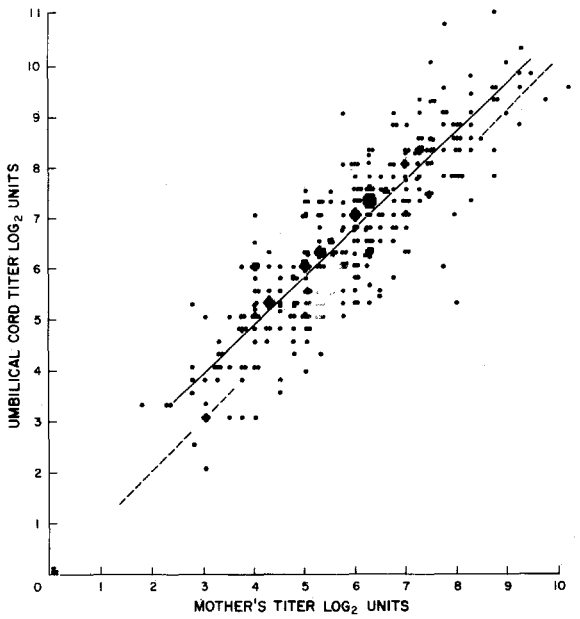

Fig. 3. Relationship between cord and maternal HI titers for individual serum pairs.

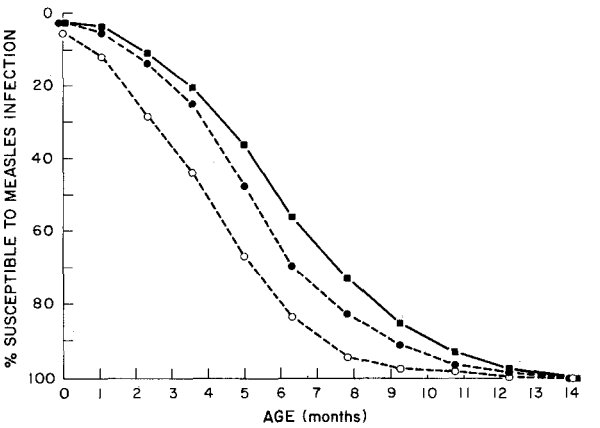

Fig. 4. Proportion of children expected to be suscuptible to measles infection and responsive to vaccine by infant's age and mother's birth-year cohort. ■——■, Children of mothers born 1957 and earlier; ●– – –●, children of mothers born 1958 through 1962; ○– – –○, children of mothers born 1963 and later.

were carried out in infant sera. Antibody titers in 17 specimens had fallen below the measurable threshold, leaving 42 cord-infant pairs in which the rate of titer loss could be examined. The proportional weight change of each baby was calculated, and the presumed effect of antibody dilution by increase in blood volume was subtracted from the overall reduction in titer. The net reduction in titer in $\log_2$ units was divided into the baby's age in days to calculate the half-life of measles HI antibody. The geometric mean half-life was 48.4 days with a SEM range of +3.0 to −2.8 days. Ten of the babies had been entirely formula-fed; the geometric mean antibody half-life in these children was not significantly different from that of the breast-fed group. Most of the children were 140 to 190 days of age when tested. No significant change was found in the half-life over this period. Only three of the mothers gave a history of vaccination; the rate of antibody loss in their babies showed no consistent deviation.

Proportion of babies expected to be susceptible to measles. In evaluating the effect of low measles antibody titers, the mean value is less relevant than the proportion of babies at each age whose titers fall below the critical threshold. This depends primarily on the initial distribution of titers in the mothers. Fig. 4 shows the percent of babies born to mothers from different age cohorts who are expected to be susceptible to measles infection at any age up to 14 months. These curves were calculated from the mother's NT titers on the following assumption: that the mother's antibody was diluted in pregnancy to 1/1.3 of its usual titer, that this antibody was concentrated across the placenta 1.7-fold, that antibody would be diluted by the child's growth at a rate equal to that of the 50th percentile on the Stewart-Meredith scale,[15] that antibody decayed in the infant with a uniform half-life of 48.4 days, and that an NT titer of 16 is the minimal protective level. The curves for children of women born since 1963 indicate that a 95% vaccine-induced seroconversion rate can be attained in this group at 8½ months of age, but that a few children in this cohort remain refractory until their first birthday.

DISCUSSION

The age-associated differences considered in this study are, for the most part, less than twofold. Such differences would not be significant in comparisons of individual sera, in view of the limits of reproducibility of replicate tests. When populations are considered, however, the reproducibility is dependent on the SEM; with 100 or more tests, these differences attain high statistical significance. From the biologic point of view, a twofold difference in maternal antibody will make a difference of a month and a half in the age at which a child becomes susceptible to measles, and hence has practical significance.

Measles vaccine was first licensed in 1963, but its use did not become general in Connecticut until the further-attenuated strain was introduced and mass campaigns were begun in 1967. The last major measles epidemic in New Haven County occurred in 1964 and 1965. The highest attack rates in epidemics in New Haven occurred in the 5- to 9-year age group.[16] It is probable, therefore, that very few persons born before 1958 were immunized by

vaccination, but that the great majority of those born after 1963 gained their antibody in this way. Thus, the decline in measles antibody titers coincides with the age at which vaccination became an important factor. The dichotomy between HI and NT titers in extent of decline was unexpected. In most ways the response to vaccination is analogous to a very mild case of measles,[17] and qualitative differences in the effects of the two immunizing agents are rare.

The extent of antibody concentration across the placenta varies with the antibody being measured.[18, 19] The data we present for measles agree well with previously published estimates from London[18] and Birmingham, Alabama.[19] In contrast to published data on influenza antibodies,[20, 21] the measles antibody cord/maternal ratios did not depend on maternal titer. The influenza studies probably included persons who had recently been immunologically stimulated, and the women with higher titers may have had greater amount of IgM and IgA.

The half-life estimate from our data is longer than that usually given for passively acquired antibody.[21,22] The largest published set of titers from which measles antibody half-life in babies might be calculated, the World Health Organization Kenya study,[23] was not originally analyzed for this purpose. Our analysis of these data, in which we assumed a growth rate equal to the U.S. norm, indicates that the half-life in the Kenyan children was 46.8 days. The commonly used estimate of 20 to 30 days seems to be based on studies of ^{131}I-tagged 7S immunoglobulin injected into adults.[24, 25] Cohen and Freeman[24] state that the rate of ^{131}I clearance was highest during the first 2 weeks, as if a damaged fraction of immunoglobulin was being cleared at an accelerated rate. Animal studies show that the rate of degradation depends on the total IgG concentration.[22] Because IgG levels in infants show a nadir at 3 to 6 months, the rate of degradation would be expected to change as the baby grows. Such variations would not be revealed by our data. The 48-day half-life estimate fits well with other available data to predict a vaccine-induced seroconversion rate that corresponds well with experience[4, 5, 7-10]; a 30-day half-life would not.

Since vaccination has become general in the United States, attention has commonly focused on the increased percentage of adolescents among the continuing cases.[6] An increased percentage of very young children is a relatively new phenomenon, but it is likely to increase without remedial action. The reduction of measles antibody titer in younger maternal cohorts means that progressively more children <15 months of age are becoming susceptible. To make a general modification in the current policy for vaccination at 15 months of age would shift the problem onto that group whose mothers continue to have high antibody titers. Even to do this selectively for children of young mothers might mean premature vaccination of 2% of this group, a proportion sufficient to weaken herd immunity.[26] It might seem that these children could be protected by a second dose given at school entry, but we do not advocate such a plan because children who have been vaccinated too early may produce only transient or very low titer antibody after revaccination.[3-6] As an alternative, identification of mothers with low titers and selective early vaccination of their children is a feasible policy in terms of the time available to complete and act on the test. Titration of measles antibody is not difficult, but to obtain standardized results the test should ideally be done in a few centralized laboratories. Our data indicate that the 336 cases of measles reported in 1984 in young babies were probably concentrated in about 1 million children of young mothers. If so, antibodies in 3000 women would have to be titrated to permit the prevention of one case of measles. The cost of such a program would be difficult to justify in terms of children directly protected, but if we hold to the broader goal of eliminating measles from the United States, earlier immunization of young susceptible children may be essential.

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