Humoral and Cell-Mediated Immune Responses to an Early 2-Dose Measles Vaccination Regimen in the United States

Hayley A. Gans, Linda L. Yasukawa, Amanda Alderson, Mary Rinki, Ross DeHovitz, Judith Beeler, Susette Audet, Yvonne Maldonado, and Ann M. Arvin

1Department of Pediatrics, Stanford University School of Medicine, Stanford, and 2Department of Pediatrics, Palo Alto Medical Foundation, Palo Alto, California; 3Division of Viral Products, Food and Drug Administration, Bethesda, Maryland

Background. Shifts in peak measles incidence to children <12 months old and the associated high mortality support the study of an early 2-dose measles vaccine regimen.

Methods. Fifty-five infants were vaccinated with measles vaccine at age 6 (n = 32) or 9 (n = 23) months, followed by measles-mumps-rubella (MMR)-II vaccine at age 12 months. A control group received MMR-II only at age 12 months. Measles-specific humoral and cell-mediated immunity were evaluated before, 12 weeks after measles immunization, and 24 weeks after MMR-II.

Results. Measles-specific T cell proliferation after both doses of vaccine was equivalent, regardless of age or the presence of passive antibodies. Seroconversion rates, geometric mean titers, and the percentage of infants with antibody titers >120 mIU after the first measles vaccine were lower in infants vaccinated at age 6 months, regardless of the presence of passive antibodies, but measles humoral responses increased after the administration of MMR-II vaccine in children initially vaccinated at age 6 or 9 months.

Conclusion. Measles vaccination elicits T cell responses in infants as young as 6 months old, which may prime the humoral response to the second dose. Initiating measles vaccination as an early 2-dose regimen results in an immunologic response that is likely to have clinical benefits in developed and developing countries.

Achieving protection against measles presents particular challenges. The highest case-fatality rates occur in children <12 months old worldwide [1–5]; recently, epidemics in the United States have shown a shift of peak incidence to infants <12 months old [6–9]. Infants as young as 6 months old are now susceptible to outbreaks of imported measles in the United States as a result of the earlier loss of transplacentally acquired measles antibodies in infants born to mothers with vaccine-induced immunity to measles [10–13]. Most infants in the United States are now born to mothers who have vaccine-induced immunity to measles, which is associated with lower measles antibody titers, compared with titers after natural disease [14, 15]. Therefore, more infants <12 months old are unprotected by maternal measles antibodies and lack active immunity, because routine vaccination is scheduled for age 12–15 months in the United States [16, 17]. These infants are in the highest risk group for life-threatening complications of measles. Maintaining high seroprevalence rates to achieve herd immunity protects young infants, but local epidemics confirm the results of past studies, which have shown that a small population of susceptible persons can sustain a measles outbreak [18]. Therefore, it is important to evaluate whether an early-dose measles vaccine regimen might provide active immunity at a younger age in infants born to vaccinated mothers.

Effective strategies for measles control must include a 2-dose schedule to achieve and sustain adequate levels of measles protection, even in highly vaccinated pop-
ulations [8, 19, 20]. Although a 2-dose measles schedule has been adopted in the United States, with vaccination at age 12–15 months and during later childhood [4, 21, 22], questions remain concerning the optimal age for administering the first vaccination. An early 2-dose regimen, in which the primary dose is given before age 12 months, has the potential to provide earlier protection against measles in a susceptible population that is expected to grow in the United States as more mothers of childbearing age have vaccine-induced measles immunity.

Previous studies that have assessed the measles vaccination of infants <12 months old have revealed poor humoral immunogenicity, which is thought to represent passive antibody interference [23–27]. Additionally, we have identified intrinsic humoral limitations to measles vaccine in infants in the absence of passive antibodies [28, 29]. However, our studies also determined that measles-specific CD4 T cell–mediated immunity was elicited as effectively by primary measles vaccination at age 6 or 9 months as that by vaccination at age 12 months [28–30]. These observations suggest a potential role for these memory CD4 T cells to prime the younger infants for a better humoral response to a second dose of measles vaccine, and the results of previous studies have indicated that an early 2-dose measles vaccination schedule is effective [31]. The objective of the present study was to evaluate the immune responses of infants initially vaccinated at age 6 or 9 months, in the presence or absence of passive antibodies, followed by a subsequent measles dose administered as measles-mumps-rubella (MMR) at age 12 months. Many infants in this population had no passive antibodies; therefore, we were able to evaluate maturational differences in the immune response of younger infants to the early 2-dose measles vaccine regimen, compared with responses of 12-month-old infants who received primary measles vaccination.

SUBJECTS, MATERIALS, AND METHODS

Populations. Subjects included infants who were receiving well-child care in Palo Alto, California, who received their primary measles vaccination at age 6 (n = 32) or 9 (n = 23) months, followed by a second dose administered as MMR at age 12 months. Blood samples were obtained before vaccination, 12 weeks after they received monovalent measles vaccine, and 24 weeks after they received MMR, to coincide with well-child doctor visits. A control group of 83 12-month-old infants who were receiving primary MMR were enrolled and had blood samples obtained at baseline and 24 weeks later. Not all samples sizes allowed for a full immunologic evaluation. Exclusion criteria were gestation <36 weeks, birth weight <2500 g, and acute or chronic illness. No cases of measles were identified in our area during the study period, 1994–2002.

The study was approved by the Stanford University Committee for the Protection of Human Subjects and the Institutional Review Board of the Palo Alto Medical Foundation; written consent was obtained from parents or guardians. Maternal demographics were collected by questionnaire for participants in the early 2-dose group.

Vaccines. Six- and 9-month-old infants received Measles Virus Vaccine Live (Attenuvax; Merck); these infants received MMR-II vaccine (Merck) at age 12 months. Twelve-month-old infants received 1 dose of MMR-II.

Antibody assay. Serum samples were tested for measles antibodies in parallel with the World Health Organization Measles Reference Serum II by use of a modified plaque-reduction neutralization (PRN) assay [32]. Fourfold serial dilutions of serum (1:4–1:4096) were mixed with low-passage Edmonston measles virus (25–35 pfu). The PRN titer was the dilution that reduced plaques by ≥50%; 1:4 was considered to be a negative result. Seroconversion after the first measles dose was defined as a 4-fold increase in antibody titer; prevaccine levels were corrected for the decay of passively acquired antibodies over 3 half-lives under the assumption of first-order kinetics [33, 34]. Titers after the second measles dose were considered to be positive if they remained the same or increased in comparison with titers after the first measles dose [35]; measles seroprotection was defined as a PRN titer ≥120 mIU [36].

T cell proliferation assay. The T cell proliferation assay was performed as described elsewhere [29]. In brief, purified peripheral blood mononuclear cells (PBMCs) were added to 96-well microtiter plates at 3.0 × 10^5 cells/well in RPMI 1640 medium (Gibco) with 10% heat-inactivated normal human serum (Sigma). Measles antigen was prepared from lysates of Vero cells inoculated with Attenuvax measles vaccine (Merck); Vero cell lysates made in parallel from flasks that had been seeded with the same concentration of cells as the antigen flasks served as controls. Undiluted antigen resulted in <1 pfu/well, and the antigen preparation, which contained 320 μg/mL of cell and viral protein, was equivalent to total protein in uninfected cell lysate.

T cell proliferation was measured by 3[H]-thymidine uptake after the incubation of PBMCs with dilutions of 1:32 and 1:64 antigen and control in triplicate wells for 5 days. The stimulation index (SI) was the ratio of mean counts per minute in antigen divided by the count per minute in control wells (the same dilution of antigen and control was used for each ratio); an SI ≥ 3.0 was considered to be a positive result [29], and the highest SI from either concentration was used for statistical analysis. Phytohemagglutinin, 0.1 mg/mL (Difco), was used as a positive control.

Statistics. Responses were compared by Student’s paired or unpaired t and Fisher’s exact tests. Antibody titers are reported as geometric mean titers (GMTs) with 95% confidence intervals (CIs), and T cell proliferation is reported as SI and SE. The minimum size of the study populations needed for comparisons was based on a statistical projection in which differences in host
response rates of 40% in 1 cohort, as opposed to 5% in another, would be detectable ($\alpha = 0.05; n = 20$).

**RESULTS**

**Maternal demographics.** Information was available for 40 (73%) of 55 study participants. Eight percent (3/40) were foreign born, and 15% (6/39) had a history of natural disease, with the remainder reporting measles vaccination. In 6-month-old infants, maternal markers for the presence of passive antibodies were foreign birthplace and a history of natural disease, but these correlations were not observed at age 9 months.

**Humoral responses after 1 dose and 2 doses of measles vaccine.** Transplacentally derived measles antibodies were detected in 52% (15/29) of 6-month-old, 19% (4/21) of 9-month-old, and no 12-month-old (0/83) infants. When all infants were included in the analysis, regardless of their passive antibody status, the GMT (95% CI) after the second measles dose was significantly higher than that after the first dose in the 6-month-old infants ($P < .001$) and showed an increased trend in the 9-month-old infants ($P = .07$) (table 1). The GMT after the first measles dose was lower in the 6-month-old than in the 9-month-old infants ($P < .001$) but not after the second dose (figure 1A). The GMT was significantly lower in the 6-month-old infants after both the first and second measles doses, compared with the 12-month-old infants ($P \leq .02$), and titers after both measles doses in 9-month-old infants were equivalent to those in the 12-month-old infants.

When only the infants who had passive antibodies present at the time of the initial measles vaccination were evaluated, the GMT was determined to be 39 mIU (95% CI, 16–95) and 70 mIU (95% CI, 3–1890) after 1 measles vaccination given at age 6 or 9 months, respectively (table 1). These GMTs were equivalent to each other but were significantly lower than those in infants of the same age who were vaccinated in the absence of detectable antibodies at the time of the initial vaccination. Among these infants, the GMT after the first dose of measles was 516 mIU (95% CI, 209–1274) for 6-month-old infants and 1496 mIU (95% CI, 953–2350) for 9-month-old infants (GMT with vs. without passive antibodies at ages 6 and 9 months; $P < .001$) (figure 1B). The differences in GMT between the groups who had passive antibodies when they received their first measles vaccine dose and those who had lost passive antibodies persisted after the second measles dose in both the 6- and the 9-month-old infants (table 1) (GMT with vs. without passive antibodies at age 9 months, $P = .04$). In infants who were vaccinated in the absence of passive antibodies, the GMT after 1 measles dose was lower in the 6-month-old infants than in the older infants (6 vs. 9 and 12 months, $P \leq .04$), but the GMTs were all equivalent after 2 doses of measles vaccine.

By use of seroconversion as the measure of immunogenicity, only 6-month-old infants who were vaccinated in the presence of passive antibodies had significantly lower rates of seroconversion after the first measles dose, compared with the other groups (table 1). The seropositivity rate was equivalent after the second dose in 6- and 9-month-old infants and in comparison with the rate in 12-month-old infants after 1 measles dose.

When the groups were compared on the basis of the percentage of infants who had PRN titers $\geq 120$ mIU, the rates after the first measles dose were 27% and 79% in 6-month-old infants vaccinated in the presence or absence of passive antibodies and 50% in 9-month-old infants vaccinated in the presence of passive antibodies (table 1). These rates were significantly lower than those in infants vaccinated in the absence of passive antibodies at age 9 or 12 months who had PRN titers $\geq 120$ mIU, which were 100% and 98% after the first measles dose, respectively (all comparisons, $P \leq .02$). After a second measles dose, 80% of 6-

| Table 1. Humoral immune responses to 1 dose and 2 doses of measles vaccine. |
|-----------------------------|------------------------|------------------|------------------------|------------------------|------------------------|
| **Age at time of vaccination, antibodies present** | **GMT (95% CI), mIU** | **SC, no./total (%)** | **SP, no./total (%)** |
| | Before vaccination | After first dose | After second dose | After first dose | After second dose | Before first dose | After first dose | After second dose |
| 6 months | | | | | | | | |
| Total | 8 (4–16) | 130 (58–292) | 702 (344–1457) | 25/29 (86) | 25/29 (86) | 15/29 (52) | 25/29 (86) |
| NPA | NA | 516 (209–1274) | 1231 (511–3105) | 14/14 (100) | 12/14 (86) | 11/14 (79) | 13/14 (93) |
| 9 months | | | | | | | | |
| Total | 2 (2–4) | 835 (317–1882) | 1546 (686–3484) | 20/21 (95) | 19/21 (90) | 19/21 (90) | 19/21 (90) |
| PA | 27 (16–47) | 70 (3–1890) | 258 (27–2463) | 3/4 (75) | 4/4 (100) | 2/4 (50) | 3/4 (75) |
| NPA | NA | 1496 (953–2350) | 2356 (956–5811) | 17/17 (100) | 15/17 (88) | 17/17 (100) | 16/17 (94) |
| 12 months, NPA | NA | 1512 (1156–1984) | 78/80 (98) | NA | 78/80 (96) | NA |

**NOTE.** The single (or first) dose of measles was administered as Attenuvax at age 6 and 9 months and as measles-mumps-rubella (MMR)-II at age 12 months. The second dose of measles was administered as MMR-II at age 12 months to infants who had been originally vaccinated at age 6 or 9 months. CI, confidence interval; GMT, geometric mean titer; NPA, no passive antibodies present at the time of the initial measles vaccination; PA passive antibodies present at the time of the initial measles vaccination; SC, seroconversion (defined as a 4-fold increase in antibody titer after the first dose of measles and an equivalent or greater antibody titer after the second measles dose); SP, seroprotection (defined as GMT $\geq 120$ mIU).
Figure 1. Humoral immune responses to measles vaccination. Shown are the geometric mean titers, measured by plaque-neutralization assay, before (white bars) and after (striped bars) 1 measles vaccination and 24 weeks after (black bars) a second measles vaccination in the presence (PA; A) and absence (NPA; B) of passive antibodies. Infants were 6, 9, or 12 months old at the time of primary measles vaccination. The inset provides the 95% confidence intervals. A plaque-reduction neutralization titer \( >120 \) mIU is considered to be protective (dotted line). MMR, measles-mumps-rubella.

A significant increase in the mean SI was seen after the first measles vaccination in infants in each age group, and no age-related or passive antibody effects were noted on the acquisition of cell-mediated immunity to measles. Six-month-old infants had a mean SI that was not statistically different from that in 9- and 12-month-old infants, respectively (table 2). The 6-month-old infants showed an increase after the second measles vaccination, with an increase in SI (SE) to 10.9 (1.7), which was equivalent to the SI (SE) of 7.5 (1.4) detected after the second measles vaccination given to 9-month-old infants. The response in the 6-month-old infants was significantly higher than that in 12-month-old infants after 1 dose of MMR \( (P = .03) \) (figure 2A).

When the groups were stratified on the basis of the presence or absence of passive antibodies at the time of initial measles vaccination, the 6-month-old infants with passive antibodies developed a mean SI after the first measles vaccination that was equivalent to that of infants of the same age who did not have passive antibodies (figure 2B). The mean SI in the 6-month-old infants, regardless of the presence of antibodies at the time of initial vaccination, was equivalent to the mean SI in 9-month-old infants with and without passive antibodies, respectively, and in 12-month-old infants who did not have passive antibodies before vaccination. After the second measles vaccination, the mean SIs in infants with and without passive antibodies were all equivalent (table 2).

The percentage of 6-month-old infants who achieved an SI \( \geq 3.0 \) after 1 measles dose, with or without passive antibodies at the initial vaccination, was equivalent to the percentage of 9- and 12-month-old infants who achieved positive measles-specific T cell proliferation responses (table 2). In infants with passive antibodies, 71% and 75% of the 6- and 9-month-old infants, respectively, had an SI \( \geq 3.0 \), compared with 91% and 81% of infants of the same age who had no passive antibodies at the time of vaccination. These percentages were not significantly different and were equivalent to those of 12-month-old infants, of whom 71% had an SI \( \geq 3.0 \). An equivalent number of infants achieved a positive SI after the second measles dose, regardless of age or the presence of passive antibodies at the time of initial vaccination. Among 6-month-old infants, the percentages of infants with an SI \( \geq 3.0 \) after a second measles vaccination were 71% and 85% among those first vaccinated in the presence or absence of passive antibodies; the percentages were 75% and 88% of 9-month-old infants after the second dose.

Evidence of adaptive immunity after 1 dose and 2 doses of measles vaccine. Only 5% (1/21) of infants vaccinated at age 6 months did not develop either seroconversion or an SI \( \geq 3.0 \) after the first vaccination. All of these infants had 1 or both responses after they received MMR. Seventy-one percent (15/21) of these infants had both seroconversion and an SI \( \geq 3.0 \) after they received MMR, 24% (5/21) had seropositivity only, and 5% (1/21) had only measles-specific cell-mediated immunity after the second measles dose. Among infants first vaccinated at age 9 months, all had either seroconversion or an SI \( \geq 3.0 \) after the first and second measles doses. Seventy-five percent (12/16) of the 9-month-old infants demonstrated both responses; 19% (3/16) had seropositivity only, and 6% (1/16) showed only measles-specific cell-mediated immunity after the second measles dose. Two percent (1/66) of 12-month-old infants lacked both humoral and cell-mediated immunity after vaccination.
MMR, 71% (47/66) had both responses, and 27% (18/66) had only seroconversion.

Kinetics of immune responses after 1 dose and 2 doses of measles vaccine. The patterns of humoral and cellular immunity observed over the first 18 months of life in infants vaccinated at ages 6, 9, and 12 months are illustrated in figure 3. The population of infants first vaccinated at age 6 months in the absence of passive antibodies had GMTs $>120$ mIU (figure 3A) and a mean SI $=3.0$ (figure 3B) by age 9 months, when the first evaluation occurred. The responses of these infants were even higher after the second measles dose. This population would be expected to be protected from measles infection, because the kinetics of their immune responses mimicked those of infants who received their first dose of measles at age 12 months. Thus, our cohort avoided $\geq3$ months of susceptibility to measles. The 9-month-old infants without passive antibodies responded with kinetics equivalent to those of the 12-month-old infants; this group also had higher GMTs and mean SIs after their second measles dose, compared with infants vaccinated at age 12 months (figure 3A and 3B). Thus, this group avoided a period of susceptibility before age 12 months and had more-robust responses than infants who received routine MMR vaccination at age 12 months.

The infant groups that were first vaccinated with measles vaccine at age 6 or 9 months in the presence of passive antibodies had T cell kinetics that mimicked those of the older infants and those in the same age group who did not have passive antibodies. Although these populations did not achieve comparable GMTs after a second measles vaccination (figure 3A and 3B), their rates of seropositivity were equivalent to those of infants vaccinated in the absence of passive antibodies and to those who received MMR at age 12 months only. Although PRN titers in some of these infants before they received MMR may not have conferred protection against measles infection, their cell-mediated immunity paralleled the response of the 12-month-old infants. Thus, the degree of susceptibility of these 6- and 9-month-old infants during this critical period between 6 and 12 months of age is not known but would be expected to be lower than the naive state.

**DISCUSSION**

An early 2-dose measles vaccine schedule has the potential to benefit groups at high risk and is likely to be the necessary schedule for the effective control of measles worldwide. Recent epidemics in the United States have documented a shift in peak measles incidence to children $<12$ months old [37, 38], who account for 24% of cases of measles, despite making up only 2% of the general population [37]. The increasing proportion of infants as young as age 6 months who are susceptible to measles is a result of an earlier loss of transplacentally acquired antibodies in infants who are born to mothers with vaccine-induced immunity to measles [12, 15], which is associated with lower measles antibody titers than natural disease. The percentage of infants in the United States born to vaccinated mothers is expected to grow and, thus, to create a larger population of susceptible infants. The measles attack rate in these unvaccinated infants exposed to measles during the 1990–1991 epidemic was 33%, compared with only 12% for infants born to mothers with naturally induced immunity to measles [13]. This experience underscores the need to consider an early effective vaccine strategy to protect these susceptible infants.

In the present study, 95% of the infants who were 6 months old at the time of primary vaccination had parameters of vaccine immunogenicity measured as either positive T cell proliferation and/or seroconversion in response to their first measles vaccination, and all infants showed a response to the second measles dose. In addition, 6-month-old infants showed no ob-

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**Table 2. Cell-mediated immune responses to 1 dose and 2 doses of measles vaccine.**

<table>
<thead>
<tr>
<th>Age at time of vaccination, antibodies present</th>
<th>Mean SI (SE)</th>
<th>SIs $&gt;3$, no./total (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before vaccination</td>
<td>After first dose</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2.0 (0.2)</td>
<td>6.8 (1.7)</td>
</tr>
<tr>
<td>PA</td>
<td>2.2 (0.3)</td>
<td>4.5 (0.9)</td>
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<tr>
<td>NPA</td>
<td>1.7 (0.2)</td>
<td>8.5 (3.7)</td>
</tr>
<tr>
<td>9 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.6 (0.2)</td>
<td>8.4 (2.1)</td>
</tr>
<tr>
<td>PA</td>
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<td>3.3 (1.6)</td>
</tr>
<tr>
<td>NPA</td>
<td>1.8 (0.3)</td>
<td>9.7 (2.5)</td>
</tr>
<tr>
<td>12 months, NPA</td>
<td>1.5 (0.1)</td>
<td>7.0 (0.9)</td>
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**NOTE.** The single (or first) dose of measles was administered as Attenuvax at age 6 and 9 months and as measles-mumps-rubella (MMR)-II at age 12 months. The second dose of measles was administered as MMR-III at age 12 months to infants who had been originally vaccinated at age 6 or 9 months. NPA, no passive antibodies present at the time of initial measles vaccination; PA passive antibodies present at the time of initial measles vaccination; SI, stimulation index.
Figure 2. Cell-mediated immune responses to measles vaccination. Shown is the mean stimulation index, calculated as the mean counts per minute in antigen-stimulated wells, divided by the mean counts per minute in control wells, before (white bars) and 12 weeks after (striped bars) 1 measles vaccination and 24 weeks after (black bars) a second measles vaccination in infants who were 6, 9, or 12 months old at the time of primary vaccination in the presence (PA; A) and absence (NPA; B) of passive antibodies. SEs are reported in the inset. A positive stimulation index is defined as >3 (dotted line). MMR, measles-mumps-rubella.

Figure 3. Kinetics of the humoral and cell-mediated immune response to 1 dose and 2 doses of measles vaccination. Shown are the geometric mean titers, measured by plaque-neutralization (PRN) assay (A), and the mean stimulation index (SI), calculated as the mean counts per minute in antigen-stimulated wells divided by the mean counts per minute in control wells (B) in infants originally vaccinated with measles at age 6 months, in the presence (PA) and absence (NPA) of passive antibodies, who also received a second measles dose at age 12 months and infants originally vaccinated with measles at age 9 months, in the PA and NPA of passive antibodies, who received a second measles dose at age 12 months and infants who received a single measles vaccination at age 12 months. Samples were obtained before vaccination, 12 weeks after the first measles vaccination, and 24 weeks after the second measles vaccination. Dotted lines indicate a protective PRN titer >120 mIU and positive T cell response (SI) >3. MMR, measles-mumps-rubella.

The relative protective role of humoral, compared with cellular, immunity alone against viral disease is not understood for measles. In support of a protective role for cellular immunity alone, children with agammaglobulinemia are not susceptible to repeated measles infection [39]. Additionally, in the macaque model, the development of measles-specific T cell immunity alone was protective against measles challenge, despite poor humoral responses in these animals [40]. Furthermore, Ruckdeschel et al. [41] showed that pediatrics residents who had positive lymphocyte responses to measles but who did not have measurable measles antibodies were clinically protected against measles, despite routine exposure.

We have shown that the youngest infants developed T cell responses that were equivalent to those of older infants and that their responses were not affected by the presence of passive antibodies or a functionally immature immune system that limited humoral responses. Although the T cell responses resulting after primary measles vaccination were not boosted by the administration of a second measles dose, 6-month-old infants demonstrated significantly higher SIs after 2 measles doses, compared with 12-month-old infants given MMR only. Furthermore, increases were observed in GMTs, seropositivity, and the percentage of infants with PRNs >120 mIU in the 6- and 9-month-old infants after a second measles dose, even if the initial humoral responses were limited by passive antibodies or immaturity of the immune system. Experiments in infant animals have also demonstrated the capacity of the developing immune system to achieve “prime-boost” responses [42].

These analyses of measles vaccine immunogenicity support
a role for cellular immunity as a mechanism to account for the clinical benefit of vaccinating infants in developing countries against measles at ages when humoral responses would be subject to age-related deficiencies or to passive antibody interference. Many of these vaccinated infants were protected from measles or severe disease [43, 44]. Furthermore, infants given measles vaccination at young ages were protected against measles during epidemics in the United States and Canada, and the results of other studies have revealed that the efficacy of early 2-dose regimens exceeded that predicted on the basis of antibody titers alone [31, 45, 46].

In the present study, the infants vaccinated at 6 and 9 months of age who had passive antibody present at the time of the initial vaccination continued to have lower overall antibody titers after the second measles vaccination, compared with the older infants. Of importance, an equivalent percentage of these infants tested seropositive, which is the traditional marker for vaccine efficacy, in response to a second measles dose, compared with infants of the same age who had no passive antibodies initially and with older infants. Significantly fewer 6-month-old infants in this cohort had PRNs >120 mIU, compared with those vaccinated at age 12 months, but percentages were similar to those of the 9-month-old vaccinees. It is not known whether a PRN titer >120 mIU is a requirement for measles protection, because this threshold was based on the results of a study of 80 adult subjects in which 8 cases of measles developed in 9 subjects who had PRN titers <120 mIU [20]. Furthermore, that study did not evaluate T cells or the contribution of cell-mediated immunity on an individual’s susceptibility to measles. Thus, whether the lower GMT in the presence of T cell immunity in the 6- and 9-month-old infants, who had passive antibodies at the time of vaccination, has clinical relevance is not clear.

The number of infants with passive antibodies in our study was small. This group is expected to shrink further as the number of infants born to mothers with vaccine-induced measles immunity grows, as was seen in 85% of the mothers in the present study. This suggests the need for further study of early measles vaccination in larger cohorts. Although our sample sizes were small overall, it is clear that 6- and 9-month-old infants without passive antibodies at the time of the initial vaccination benefited with both humoral and cell-mediated immunity and avoided a period of measles susceptibility. It is reasonable to expect that the infants vaccinated in the presence of passive antibodies also avoided a period of susceptibility to measles disease, at least in its severe form.

Historical concerns that administering measles vaccination during early infancy produces immunotolerance [26, 47, 48] were based solely on serologic measurements done when the majority of infants would have been vaccinated in the presence of passive antibodies. Recent studies have shown the efficacy of vaccination of young infants during a measles epidemic [31, 45] and of early 2-dose measles vaccination schedules in young infants in developed countries [31, 46]. In addition, despite a lower GMT in infants who received 2 measles vaccinations at ages 6–11 and 12–15 months, compared with GMTs of infants who received a single dose at age 12 months, Hutchins et al. [31] showed the clinical efficacy of this early 2-dose schedule. It is important to note that the lower humoral responses observed in the present study, in the 6-month-old infants who did not have passive antibodies initially, were not associated with a persistent limitation in their ability to respond to a second dose of measles vaccine, compared with the older infants, which likely indicates that they will have similarly brisk memory B cell responses if challenged by wild-type measles virus.

Our observations about the immunogenicity of measles vaccine during the first year of life have practical implications. Two-dose regimens, with the initial dose given at age 6 or 9 months and a second dose at age 12–15 months, may improve the protective efficacy of live attenuated measles vaccine and could compensate for the early loss of passive antibodies in infants of vaccinated mothers. Even if neutralizing antibody titers are lower in the youngest infants and passive antibodies interfere with humoral immunity in some 6- and 9-month-old infants, the initial measles vaccine dose could prime adaptive immunity by sensitizing helper T cells. We have shown that the live attenuated measles vaccine elicits robust cell-mediated immunity even in very young infants and may support boosting of the humoral response on a second exposure to measles antigen. Thus, an early 2-dose schedule with the currently licensed measles vaccine is immunogenic when it is administered to the majority of young infants in a developed country, even in the presence of passive antibodies and the potential immaturity of humoral immune responses.

References


