Immunologic Memory 5 Years after Meningococcal A/C Conjugate Vaccination in Infancy

Jenny MacLennan,1 Stephen Obaro,4 Jonathan Deeks,2 Derrick Lake,3 Cheryl Elie,4 George Carlone,4 E. Richard Moxon,1 and Brian Greenwood1

Infant vaccination with meningococcal conjugates may provide long-term protection against disease. Antibody levels and immunologic memory were assessed in 5-year-old Gambian children who received meningococcal A/C conjugate vaccination (MenA/C) in infancy. At 2 years, they were randomized to receive a booster of MenA/C (conjugate group), meningococcal A/C polysaccharide (MPS group), or inactivated polio vaccine (IPV group). All groups were revaccinated with 10 μg MPS at 5 years of age, as were 39 previously unvaccinated age-matched control subjects. Before revaccination, titers were higher in the conjugate and MPS groups than in control subjects \( (P < .001) \); titers for the IPV group were similar to those for control subjects. Ten days after revaccination, the conjugate and IPV groups had similar serogroup C serum bactericidal antibody titers (3421 vs. 2790, respectively). These levels were significantly higher than those in the MPS (426) and control (485) groups \( (P < .001) \). Thus, immunologic memory was sustained for ≥5 years; however, MPS challenge at 2 years interfered with a subsequent memory response.

Meningococcal disease is an important cause of morbidity and mortality in children worldwide. In the “meningitis belt” of sub-Saharan Africa, major epidemics of meningococcal meningitis occur every few years. These epidemics are caused mainly by Neisseria meningitidis group A, although group C meningococci are responsible for some smaller outbreaks [1, 2]. The peak incidence of disease occurs among 5–14-year-old children [3]; however, young children may also have high attack rates [4]. In Europe and South America, serogroups B and C predominate. The proportion of cases due to serogroup C has increased in the last few years [5], and this increase is largely due to the emergence of a new virulent clone [6–11]. The case-fatality rate has shown only slight improvement over the last decade and remains >10% in both developed and developing countries [5, 12]. There is a need for effective vaccines capable of conferring long-lasting protection in young children.

Licensed purified meningococcal A/C polysaccharide vaccines (MPS) are characterized by a largely T cell–independent immune response. They result in relatively low and short-lived antibody responses in young children and probably short-lived protection [13–15]. Multiple doses of meningococcal C polysaccharide may result in a reduced response to subsequent vaccination in infants [16, 17], toddlers [18], young children [19], and adults [20–22]. During the last decade, extremely effective protein polysaccharide conjugate vaccines against Haemophilus influenzae type b (Hib) have been developed, and routine infant vaccination has virtually eliminated Hib disease in many countries [23]. These vaccines are associated with T cell–dependent immunity, increased antibody responses in young children, and the induction of immunologic memory [24]. The same technology has been applied to some serogroups of Streptococcus pneumoniae and N. meningitidis.

In 1992, a cohort of Gambian infants was recruited to a randomized controlled trial of a group A plus group C meningococcal polysaccharide–protein conjugate vaccine [25]. The response to primary and booster immunization at age 2 years has been reported [17]. We located these children when they were 5 years old, to determine the persistence of antibody and induction of long-term immunologic memory and to assess the effect of booster vaccination at age 2 years. The response in children randomized to receive 2 doses of MPS in infancy was reported elsewhere [19] and showed that children randomized...
to receive further doses of MPS at 2 and 5 years of age had a lower serum bactericidal antibody (SBA) response at 5 years to both serogroups A and C than did children receiving MPS for the first time. We report here the serologic response to MPS revaccination in children randomized to receive conjugate vaccine in infancy and the responses to MPS vaccination in a previously unvaccinated group. In addition, we consider the implications for routine immunization against N. meningitidis in childhood.

Subjects and Methods

Subjects and trial design. The study subjects consisted of 176 of the 242 5-year-old children who had been recruited to the original trial in 1992 and 39 age-matched control subjects recruited for the purpose of this study. The characteristics of the trial have been described elsewhere [25]. In brief, 59 of 66, 58 of 62, and 109 of 114 children randomized to receive 1, 2, or 3 doses, respectively, of conjugate vaccine by 6 months of age completed their primary immunization schedule (figure 1). The conjugate vaccine (lot 0900991; Biocine) contained 11 μg of each polysaccharide, 49 μg of CRM197, and 1 mg of aluminum hydroxide. Of these 242 children, 176 (76%) received a booster at 18–24 months of age [17] and were allocated randomly to receive either a dose of meningococcal A plus C polysaccharide vaccine (MPS group) containing 50 μg of each polysaccharide (Mengivac A&C; Pasteur Mérieux), conjugate vaccine (conjugate group), or inactivated polio vaccine (IPV group; Pasteur Mérieux).

In the present study, the status of 225 of 226 children who completed primary vaccination with a conjugate vaccine was determined when they were ≥5 years old, and 176 (78%) were recruited into the study. The 176 children included 152 who had received a booster at 2 years of age and 24 who had not been available at the 2-year follow-up. In addition, 39 healthy children who had no history of meningitis and who had never received a meningococcal vaccine (control group) were recruited through field assistants. These children had a known date of birth and vaccination history and were frequency-matched for age (±3 months) and village with the case children.

Revaccination. Before revaccination at 5 years, each child’s identity, recent medical history, and full immunization history were checked, and a 3–5-mL venous blood sample was obtained. Every child was vaccinated with 1 dose of meningococcal A plus C vaccine containing 10 μg of each polysaccharide (Mengivac A&C; Pasteur Mérieux Sérum et Vaccins), given intramuscularly into the right deltoid. The axillary temperature and the presence or absence of redness, swelling, and tenderness at the site of the injection were recorded 1 h and 24 h after vaccination by an experienced field worker. Ten days after vaccination, another 3–5-mL venous blood sample was obtained, the axillary temperature was recorded, and the injection site was examined for redness, swelling, and tenderness.

An epidemic of group A meningococcal disease occurred in the area shortly after the start of the study. No cases occurred among the study children, and no child was vaccinated by a Ministry of Health vaccination team before completion of the study.

Laboratory methods. Blood was centrifuged, and the serum was frozen at −20°C the same day. Serum samples were assayed for antibodies to meningococcal A and C polysaccharides by an IgG ELISA and by a serum bactericidal assay at the Centers for Disease Control and Prevention (CDC), as described elsewhere [26–29]. Postvaccination IgM antibodies to group C polysaccharide were assayed by ELISA in the subgroup of children allocated to receive 3 doses of conjugate in infancy and in the control children. Serum samples were stored in coded vials so that laboratory personnel were unaware of the previous vaccination history. ELISA results are expressed in relation to a standard reference serum that has been ascribed total and class-specific group A and group C meningococcal antibody concentrations. SBA antibody titers are expressed as the reciprocal of the highest serum dilution that gave ≥50% killing of a group A isolate (CDC strain F8238) or group C isolate (strain C-11).

Statistical methods. Geometric mean bactericidal antibody titers and geometric mean IgG ELISA antibody concentrations were calculated for each group before and after vaccination. Bactericidal titers <1:8 were assigned a titer of 4, and antibody concentrations <0.02 μg/mL were assigned a titer of 0.01 μg/mL for analyses. All comparisons between groups were made from log-transformed data, to compensate for the skewed distribution inherent to individual antibody responses. Differences in prevaccination values among conjugate, MPS, IPV, and control groups were analyzed by using one-way analysis of variance, and P values to test for heterogeneity are given. Individual comparisons among groups were analyzed by using t tests adjusted for multiple comparisons and are given where appropriate in the text. The responses to vaccination were analyzed from the paired serum samples, using analysis of covariance to adjust for prevaccination titers (a second analysis ignoring prevaccination titers was also done and gave similar results). Analysis was done using STATA statistical software [30].

Results

The flow of children, including dropouts, through the trial is shown in figure 1. The groups of children recruited to the present study were comparable in respect to age, weight, and interval between booster vaccination and sampling (table 1).

Safety. There were no serious side effects reported and no significant differences in the prevalence of local or systemic side effects among groups of children with different vaccination schedules (data not shown).

Immunogenicity. All results relate to the antibody response to revaccination with 10 μg MPS 5 years after priming with conjugate and 3 years after booster vaccination.

Response to meningococcal serogroup A. Before revaccination, there were significant differences in IgG ELISA geometric mean antibody concentrations between groups (P = .02). The conjugate group had the highest levels, and the control subjects had the lowest (table 2). Prevaccination group A bactericidal antibody titers were high in all groups, including control subjects (table 3), and there was no significant heterogeneity among the groups (P = .7).

After revaccination, children in all groups showed an increase in mean group A IgG ELISA antibody concentrations (table 2). The conjugate group, previously vaccinated with conjugate
Figure 1. Outcome of children randomized to receive 1, 2, or 3 doses of meningococcal A/C (MenA/C) conjugate vaccine in infancy (primary immunization); boosted with MenA/C conjugate vaccine, MenA/C polysaccharide vaccine, or inactivated polio vaccine (IPV) at 18–24 months of age; and revaccinated with MenA/C polysaccharide vaccine at 5 years of age.
in infancy and at 2 years of age, achieved higher IgG ELISA antibody concentrations than did the control (P < .001), MPS (P = .005), or IPV (P = .05) groups. Postvaccination group A SBA titers were highest in the conjugate group, and those titers were significantly higher than titers in the MPS group (2856 vs. 1351, P < .001). The control group had intermediate titers and MPS groups had higher titers than did the control and IPV groups (67.5 and 35.4 vs. 11.6 and 13.3; P < .001).

After revaccination, all groups showed an increase in geometric mean group C IgG ELISA concentrations, with control subjects achieving a significantly lower concentration than the conjugate (P = .007) and IPV (P = .002) groups. Unexpectedly, after revaccination, the MPS group achieved a geometric mean concentration (GMC) that was no different than that of the control subjects and significantly lower than those for the conjugate group (P < .001), who had received conjugate at 2 years of age, and the IPV group, who had not received a meningococcal booster at 2 years of age (P < .001; table 1). The same pattern was observed for postvaccination SBA titers, and the differences were more marked (table 3). Again, the MPS group achieved a significantly lower titer than both the conjugate (426 vs. 3421; P < .001) and IPV (426 vs. 2790; P < .001) groups, a response that was no different than that of the control subjects (426 vs. 485; P = 1.0). The same pattern was observed regardless of whether 1, 2, or 3 doses of conjugate had been given in infancy. Data for individual groups are shown in figure 2. One dose of conjugate in infancy resulted in significantly higher postvaccination titers than 2 or 3 doses, regardless of the booster given at 2 years of age (analysis of trend, P < .001). One dose of conjugate in infancy without further meningococcal vaccination resulted in the highest response to revaccination with MPS at 5 years of age.

Postvaccination IgM GMCs to group C polysaccharide were low in all subgroups assayed (table 4). The MPS group achieved a significantly lower IgM GMC than did the control (P < .001) and IPV (P = .017) groups.

Discussion

This study has provided 3 important observations. The first is that a single dose of meningococcal group C conjugate vac-

Table 1. The vaccination schedule and demographic details for each study group, according to previous vaccination experience.

<table>
<thead>
<tr>
<th>Booster vaccine groupa (no. with blood samples obtained before/after dose of MPS)</th>
<th>Vaccination schedule and demographic data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugate (52/50)</td>
<td>MPS (48/45)</td>
</tr>
<tr>
<td>Vaccination schedule</td>
<td>Infancy</td>
</tr>
<tr>
<td>2 Years</td>
<td>MenA/C</td>
</tr>
<tr>
<td>5 Years</td>
<td>MPS</td>
</tr>
<tr>
<td>Demographic datab</td>
<td>Age, months</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>15.3 (1.9)</td>
</tr>
<tr>
<td>Interval between 1st and 2d blood sample, days</td>
<td>10.1 (0.4)</td>
</tr>
</tbody>
</table>

NOTE. Children were vaccinated with 1, 2, or 3 doses of group A/C meningococcal (MenA/C) conjugate vaccine in infancy, and all children were revaccinated with 10 μg MenA/C polysaccharide (MPS) at 5 years of age.
a Groups received booster vaccine, as indicated, at 2 years of age: conjugate group, MenA/C; MPS group, MPS; IPV group, inactivated polio vaccine or no vaccine; and control group, never received a meningococcal vaccine.
b Data are mean (SD).

Similar trend was seen for SBA titers (table 3). The conjugate and MPS groups had higher titers than did the control and IPV groups (67.5 and 35.4 vs. 11.6 and 13.3; P < .001).

Table 2. ELISA IgG antibody concentrations to meningococcal serogroup A (MenA) and serogroup C (MenC) polysaccharide before and 10 days after the administration of a single dose of meningococcal A/C polysaccharide vaccine (MPS) at 5 years of age, according to previous vaccination experience.

<table>
<thead>
<tr>
<th>Booster vaccine groupa (no. before/after dose of MPS)</th>
<th>Group</th>
<th>Conjugate (52/50)</th>
<th>MPS (48/45)</th>
<th>IPV (76/74)</th>
<th>Control (39/39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MenA IgG</td>
<td>Before</td>
<td>0.83 (0.65, 1.04)</td>
<td>0.80 (0.65, 0.99)</td>
<td>0.59 (0.48, 0.74)</td>
<td>0.52 (0.42, 0.65)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>No. (%) with titer ≥2 μg/mL</td>
<td>7 (13)</td>
<td>4 (8)</td>
<td>5 (7)</td>
<td>1 (3)</td>
<td>.3</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>11.1 (8.30, 14.8)</td>
<td>4.95 (3.66, 6.69)</td>
<td>6.34 (4.92, 8.18)</td>
<td>3.74 (2.53, 5.54)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>No. (%) with titer ≥2 μg/mL</td>
<td>36 (72)</td>
<td>35 (78)</td>
<td>51 (69)</td>
<td>22 (56)</td>
<td>.2</td>
</tr>
<tr>
<td>MenC IgG</td>
<td>Before</td>
<td>0.80 (0.58, 1.09)</td>
<td>0.67 (0.48, 0.93)</td>
<td>0.21 (0.16, 0.27)</td>
<td>0.21 (0.13, 0.36)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>No. (%) with titer ≥2 μg/mL</td>
<td>10 (19)</td>
<td>8 (17)</td>
<td>4 (5)</td>
<td>5 (13)</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>7.62 (5.51, 10.5)</td>
<td>2.79 (2.01, 3.88)</td>
<td>7.79 (5.69, 10.4)</td>
<td>3.15 (2.10, 4.73)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td></td>
<td>No. (%) with titer ≥2 μg/mL</td>
<td>44 (88)</td>
<td>30 (67)</td>
<td>63 (85)</td>
<td>28 (72)</td>
<td>.02</td>
</tr>
</tbody>
</table>

NOTE. Data are geometric mean concentrations (95% confidence limits), unless otherwise stated. Children are grouped by the booster given at 2 years of age.
a Groups received booster vaccine, as indicated, at 2 years of age: conjugate group, MenA/C; MPS group, MPS; IPV group, inactivated polio vaccine; and control group, never received a meningococcal vaccine.
Table 3. Serum bactericidal responses to Neisseria meningitidis serogroup A (MenA) and serogroup C (MenC) before and 10 days after the administration of a single dose of meningococcal A/C polysaccharide vaccine (MPS) at 5 years of age, according to previous vaccination experience.

<table>
<thead>
<tr>
<th>Booster vaccine group* (no. before/after dose of MenA/C)</th>
<th>Conjugate (52/50)</th>
<th>MPS (48/45)</th>
<th>IPV (76/74)</th>
<th>Control (39/39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MenA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>281 (179, 442)</td>
<td>279 (162, 481)</td>
<td>258 (167, 400)</td>
<td>385 (210, 705)</td>
<td>.7</td>
</tr>
<tr>
<td>No. (%) with titer &gt;1:8</td>
<td>51 (98)</td>
<td>43 (90)</td>
<td>69 (91)</td>
<td>38 (97)</td>
<td>.19</td>
</tr>
<tr>
<td>After</td>
<td>2856 (2295, 3555)</td>
<td>1351 (1034, 1766)</td>
<td>1954 (1651, 2314)</td>
<td>2160 (1634, 2857)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. (%) with titer &gt;1:8</td>
<td>50 (100)</td>
<td>45 (100)</td>
<td>74 (100)</td>
<td>39 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>MenC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>67.5 (41.8, 109)</td>
<td>35.4 (20.1, 62.4)</td>
<td>13.3 (9.15, 19.4)</td>
<td>11.6 (6.5, 20.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. (%) with titer &gt;1:8</td>
<td>44 (85)</td>
<td>34 (71)</td>
<td>34 (45)</td>
<td>13 (33)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>After</td>
<td>3421 (2122, 5513)</td>
<td>426 (231, 785)</td>
<td>2790 (1826, 4262)</td>
<td>485 (295, 799)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. (%) with titer &gt;1:8</td>
<td>49 (98)</td>
<td>41 (91)</td>
<td>74 (100)</td>
<td>38 (97)</td>
<td>.03</td>
</tr>
</tbody>
</table>

NOTE. Data are geometric mean serum bactericidal antibody concentrations (95% confidence limits), unless otherwise stated. Children are grouped by the booster given at 2 years of age.

* Groups received booster vaccine, as indicated, at 2 years of age: conjugate group, MenA/C; MPS group, MPS; IPV group, inactivated polio vaccine or no vaccine; and control group, never received a meningococcal vaccine.

cine given in infancy provided immunologic memory that persisted until 5 years of age, regardless of whether a conjugate vaccine booster had been administered to the child as a toddler. Indeed, a single dose of conjugate at 6 months of age gave the best memory response to group C polysaccharide at 5 years of age. This raises the hope that 1 dose of conjugate in infancy might be all that is required to give long-term protection, a most attractive strategy, particularly for sub-Saharan Africa, where only ~50% of infants complete their primary immunization schedule at 9 months of age. However, before revaccination at 5 years of age, group C antibody concentrations were no different in groups who did not receive a meningococcal booster at 2 years of age than in previously unvaccinated control subjects. The only correlate of protection for group C disease was provided by adult military recruits in whom a group C bactericidal titer >1:4, obtained as a result of natural exposure, resulted in a significantly lower risk of group C disease [31]. In this study, 45% of children vaccinated with conjugate in infancy who did not receive a booster at 2 years of age achieved this level; this compares with 33% of control subjects, 85% of those boosted with conjugate, and 71% of those boosted with polysaccharide. It is not known whether a low resting antibody concentration in the presence of immunologic memory is sufficient to confer protection or whether antibody concentrations above a protective level are also required.

The second observation is that the nature of the meningococcal group C geometric mean reciprocal serum bactericidal activity (GMC) and 95% confidence intervals for individual groups 10 days after revaccination with meningococcal A/C (MenA/C) polysaccharide vaccine (P) at 5 years of age. Children were randomized to receive 1, 2, or 3 doses of MenA/C conjugate vaccine (C, CC, and CCC, respectively) in infancy and were randomized to receive booster vaccination with MenA/C conjugate vaccine (C, conjugate group), MenA/C polysaccharide vaccine (P, MPS group), or inactivated polio vaccine (I, IPV group) at 18–24 months of age before revaccination with P at 5 years of age.
Hyporesponsiveness after booster doses of group C polysaccharide given at 18–24 months of age is important in determining the subsequent response to revaccination. Challenge with meningococcal polysaccharide or conjugate at 2 years of age augmented antibody responses in these children, indicating that immunologic memory had been induced [17]. The unexpected finding in this study is that former challenge with polysaccharide was associated with an inability to show similar memory on subsequent challenge with polysaccharide at 5 years of age. Because the children who had not received a meningococcal booster at 2 years of age retained immunologic memory at 5 years of age, we conclude that the polysaccharide vaccination at 2 years of age interfered with the immune response to subsequent polysaccharide vaccination. This interference is demonstrated by reduced total IgG, IgM, and bactericidal antibody responses and is also reflected in the percentage of children with postvaccination titers above a putative protective level, although, interestingly, the IgG:IgM ratio is higher than that in control subjects.

Evidence that B cell memory can be elicited by polysaccharide challenge comes from a study in which the reactivation of B memory clones identified by idiotypic was demonstrated in children immunized with Hib conjugate and challenged with Hib polysaccharide [32]. It has been accepted practice, and even a requirement for licensure, to show evidence of the induction of immunologic memory after conjugate vaccination by demonstrating an augmented response to a purified polysaccharide booster. Previous studies of Hib, pneumococcal, or meningococcal conjugate vaccines have not challenged twice with polysaccharide. The data from this study suggest that, although a first challenge with polysaccharide after priming with conjugate elicits memory, it may frustrate responses on subsequent exposure to polysaccharide.

Hyporesponsiveness after booster doses of group C polysaccharide has been demonstrated in several studies in adults, toddlers, and infants [16, 18, 20–22], including a subgroup from this cohort of children [17, 19]. In these studies, lower antibody responses were seen after booster vaccination than after primary vaccination. The mechanism for this is unknown, although murine data suggest that suppressor T cells may be involved in the induction of tolerance [33, 34]. The data presented here have some similarities to these findings in that they show hyporesponsiveness after a second dose of MPS. However, the critical difference is that the second MPS vaccine was administered to children whose primary meningococcal vaccination was conjugate vaccine and in whom the induction of immunologic memory had already been demonstrated. That a second MPS vaccination can no longer demonstrate similar memory in the same children at 5 years of age is an important and unique finding. It goes further than previous observations and suggests that polysaccharide vaccination can interfere not only with T cell–independent responses but also with immune memory responses.

How might these findings be explained? The underlying immune mechanism is not known and is likely to be complex. One possible explanation includes the concept that memory cells were formed after conjugate vaccination in infancy. At 2 years of age, the T cell–independent stimulation of memory cells by polysaccharide may have resulted in the terminal differentiation of these cells, a relatively short-lived antibody response, and depletion of the memory pool. In the absence of T cell help, germinal center formation and regeneration of the memory pool was impossible, so subsequent vaccination with polysaccharide at 5 years stimulated a depleted pool of memory cells, resulting in a reduced antibody response. In contrast to the effects of giving polysaccharide as the second injection, conjugate vaccine challenge recruited T cell help, providing the necessary accessory signals to maintain and augment the memory pool. An alternative explanation to consider is that polysaccharide vaccination at 2 years of age resulted in a more global suppression of B cell responsiveness to further polysaccharide. These explanations are speculative, and further work is required to determine the exact nature of the hyporesponsiveness, which may involve multiple immune mechanisms.

The third observation is that memory to the group A component was only evident at 5 years of age in children who received a booster of conjugate at 2 years of age and not when given in infancy alone. This is consistent with the findings in this cohort at 2 years of age [17] and with results from American toddlers in whom immunologic memory to the group A component was induced by the same vaccine [35], but the observation is in contrast with results from British infants in whom immunologic memory was also demonstrated after vaccination in infancy [36]. It is possible that the group A component of the particular conjugate formulation used in The Gambia was...
unstable or that any benefit of the conjugate was masked in an area with high endemicity for group A meningococcal disease. Group A antibody concentrations before revaccination were high in all groups, and the SBA response at 10 days in the previously unvaccinated control subjects was impressive, perhaps reflecting high levels of natural exposure to the group A meningococcus. We do not know why the differences between groups were more marked for IgG antibodies measured by ELISA than those measured by serum bactericidal assay. Contributions to SBA activity may have been made by IgM anti-polysaccharide antibodies or antibodies to outer membrane proteins and/or lipopolysaccharide, which are not measured by the IgG ELISA assay. We do not feel that immunologic memory to the group A component of this particular vaccine has been conclusively proven. However, it is interesting to note that the pattern of the response to a booster of MPS at 5 years of age, after a booster of conjugate, polysaccharide, or IPV at 2 years of age, was similar to that observed for the group C component.

What might account for the observation that 1 dose of conjugate gave a better postvaccination group C antibody response than 2 or 3 doses [17]? There are several possibilities. First, the age at first vaccination may have had an effect. Children who received 1 dose were older at the time of the first vaccination (6 vs. 2 months) and so may have had a slightly more mature immune system. Second, small amounts of free oligosaccharide in the vaccine may have interfered with the immune response in the same way as a polysaccharide challenge. Last, lower prevaccination antibody titers might allow a greater rate of nasopharyngeal carriage and result in natural boosting.

When comparing the antibody titers achieved in this study with those in other studies, it should be remembered that postbooster vaccination blood samples were obtained 10 days after vaccination rather than at the more usually reported 28–42 days. We chose this early time point, to investigate the persistence of B cell memory [37], because we expected a secondary antibody response to occur sooner and with a higher magnitude than a primary antibody response. Our results may, therefore, not reflect a maximum antibody response, especially in the control group. In addition, a 10-μg dose of polysaccharide (one-fifth of the standard dose) was chosen as the booster dose. In contrast, the vaccination boost at 2 years of age contained 50% of the standard dose) was chosen as the booster dose. In

Several group C conjugate vaccines induce a good antibody response in infants, and immunologic memory in the second year of life has also been demonstrated [36, 38, 39, 41]. This study demonstrates that a single dose of serogroup C conjugate vaccine can induce immunologic memory that lasts for ≥5 years. These vaccines, therefore, have the potential to provide long-term protection when incorporated into an infant vaccination program, a step that has already been taken in the United Kingdom [42]. Good surveillance of the UK national vaccination program will provide evidence of the efficacy of this approach. Progress on the development of effective group A conjugate vaccines has been slower. These vaccines are urgently needed at affordable prices for use in routine immunization programs in sub-Saharan Africa for the prevention of endemic and epidemic group A disease. These data raise further questions about the nature of the immune response to polysaccharide vaccination and revaccination. Further work is needed to guide public health decisions on appropriate meningococcal vaccination schedules now that both conjugate and polysaccharide group C meningococcal vaccines are licensed.

Acknowledgments

We thank the children and their families who participated in the study and the Medical Research Council field staff involved in the project. We also thank Lorna Pais, who died 14 August 1999, for performing ELISA testing.

References


