Early appearance of bactericidal antibodies after polysaccharide challenge of toddlers primed with a group C meningococcal conjugate vaccine: what is its role in the maintenance of protection?

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Abstract

The contribution of memory responses after meningococcal vaccination to protection may depend on the rapidity of the response. Toddlers were challenged with a licensed polysaccharide (PS) vaccine 1 year after vaccination with a single dose of meningococcal group C-CRM(197) conjugate (MCC) vaccine at the age of 12 to 15 months. Bactericidal antibodies and immunoglobulin G (IgG) antibodies detected by an enzyme-linked immunosorbent assay (ELISA) were measured before challenge and 4, 7, 14, or 21 Days later ("Days" refer to treatment groups, "days" to sampling days). Among 281 subjects in the intent-to-treat population, 173 per-protocol (PP) subjects were challenged with 10 microg PS antigen and 103 others with a 50-microg PS vaccinating dose. Capsular PS-specific ELISA IgG titers were negligible in baseline samples and increased only twofold within 4 days of PS administration. In contrast, the proportion of PP subjects with serum bactericidal antibody (SBA) titers of >or=1:8 or >or=1:128 increased, respectively, from 41% and 16% before challenge to 84% and 74% at Day 4 and to 100% and 97% at Day 7. Recipients of 50 microg [...]
Early Appearance of Bactericidal Antibodies after Polysaccharide Challenge of Toddlers Primed with a Group C Meningococcal Conjugate Vaccine: What Is Its Role in the Maintenance of Protection?

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Received 14 February 2006/Returned for modification 28 April 2006/Accepted 23 May 2006

The contribution of memory responses after meningococcal vaccination to protection may depend on the rapidity of the response. Toddlers were challenged with a licensed polysaccharide (PS) vaccine 1 year after vaccination with a single dose of meningococcal group C-CRM197 conjugate (MCC) vaccine at the age of 12 to 15 months. Bactericidal antibodies and immunoglobulin G (IgG) antibodies detected by an enzyme-linked immunosorbent assay (ELISA) were measured before challenge and 4, 7, 14, or 21 Days later (“Days” refer to treatment groups, “days” to sampling days). Among 281 subjects in the intent-to-treat population, 173 per-protoil (PP) subjects were challenged with 10 μg PS antigen and 103 others with a 50-μg PS vaccinating dose. Capsular PS-specific ELISA IgG titers were negligible in baseline samples and increased only twofold within 4 days of PS administration. In contrast, the proportion of PP subjects with serum bactericidal antibody (SBA) titers of ≥1:8 or ≥1:128 increased, respectively, from 41% and 16% before challenge to 84% and 74% at Day 4 and to 100% and 97% at Day 7. Recipients of 50 μg PS responded with similar kinetics but showed a trend toward higher antibody levels. Unexpectedly, 69% of subjects bleed on days 2 to 3 already had achieved SBA titers of ≥1:8. The majority of toddlers previously immunized with MCC and challenged 1 year later with PS antigen mounted protective levels of bactericidal antibody within 2 to 4 days.

In response to an increasing incidence of group C meningococcal disease in the past decade in the United Kingdom, Ireland, and some areas of continental Europe, meningococcal group C polysaccharide-conjugate vaccines (MCC) were developed rapidly and licensed on the basis of serological criteria (37). A three-dose primary infant series and a single dose for toddlers were shown to stimulate levels of serum bactericidal antibody (SBA) believed to correlate with protection (8, 9, 13, 32–34). In addition, the induction of immune memory was demonstrated when infant and toddler vaccinees were challenged 1 or more years after primary vaccination with an immunological probe of plain polysaccharide (PS), in the form of a reduced (10-μg) dose of a licensed polysaccharide vaccine (8, 33, 34). Although prechallenge antibody levels had fallen to low or undetectable levels, high anamnestic SBA responses were triggered by the PS challenge, indirectly demonstrating the existence of immune memory and suggesting that vaccinees might be protected by an accelerated antibody response upon bacterial exposure. Unexpectedly, however, analyses performed 4 years after the introduction of MCC vaccines in the United Kingdom disclosed a significant loss of effectiveness beyond 1 year after primary infant vaccination (41). Vaccine effectiveness in children primed with MCC vaccines between the ages of 1 and 4 years also was reduced 1 year after scheduled vaccination, but to a lesser extent than after primary infant vaccination. A similar pattern also was reported from Spain, calling for a better understanding of the mechanisms that suggest higher sustained vaccine efficacy following toddler than infant immunization (20, 41).

At the individual level, immune protection is thought to rely on a combination of persisting bactericidal antibodies at the time of exposure and reactivation of PS-specific memory B cells that, upon antigen exposure, are induced to differentiate into antibody-secreting cells. We assessed the early kinetics of SBA and enzyme-linked immunosorbent assay (ELISA) immunoglobulin G (IgG) antibody responses to a PS challenge performed 1 year after toddlers had been immunized with a meningococcal group C-CRM197 conjugate (MenC-CRM197) vaccine.
MATERIALS AND METHODS

This was a prospective, open, randomized, multicenter study conducted in Switzerland from March 2002 to October 2003. The study protocol followed the principles and procedures set out in the Declaration of Helsinki and by the International Conference on Harmonization and was approved by local ethics committees. Informed consent was obtained from the parents or guardians of the subject children. Healthy 12- to 15-month-old toddlers were vaccinated with a single 0.5-ml intramuscular dose of MenC-CRM197 vaccine (Meningitec) and were to be challenged approximately 9 to 12 months later with a low (10-µg) dose of commercial meningococcal A/C PS vaccine to assess the rapidity of their anamnestic antibody responses to group C polysaccharide antigen. The challenge antigen was a single dose of a licensed PS vaccine (Meningokokken-Impfstoff A+C Mérieux or Vaccin meningocoque polyosidique A et C) produced by Pasteur Mérieux Vaccins (France), containing 50 µg of Neisseria meningitidis groups A and C polysaccharide per 0.5-ml dose. The primary endpoint was the proportion of subjects achieving an SBA titer of ≥1:8 (measured using baby rabbit complement [rSBA])—a threshold titer associated with short-term protection, which was measured at each postchallenge interval (Days 4, 7, 10, and 21; group assignments are referenced as “Day” and the actual bleeding occasion as “day”) (1, 6).

Subjects were randomly assigned at each of 60 study sites to one of five groups for a single blood sample to be obtained: just before (Day 0) or 4, 7, 10, or 21 days after PS challenge (groups 1 through 5, respectively). The measles-mumps-rubella (MMR) vaccine could be given concurrently with MenC-CRM197 vaccination, with the PS challenge, or just before the scheduled blood sampling, based on the lack of interference of MMR immunization with B-cell responses to Meningitec; diphtheria-tetanus-acellular pertussis—inactivated polio vaccine—H. influenzae type b (DTaP-IPV-Hib) vaccine was permitted 30 days after MenC-CRM197 administration (33, 34). Serious adverse events and spontaneously reported events were collected from the first study visit to 30 days after PS challenge; spontaneously reported adverse events occurring within 30 min of MenC-CRM197 vaccination were tabulated separately. Solicited adverse events were collected only after PS challenge. Diary cards solicited specific local and systemic adverse events through days 0 to 3 after PS vaccine challenge, and those of grade-3 severity (interfering with normal activity) were analyzed (grade-3 events are defined in Table 1).

Antibody responses were measured by rSBA and also in a binding assay (IgG ELISA) using previously reported methods (15, 25). Briefly, twofold dilutions of heat-inactivated sera were incubated with the C11 strain of group C N. meningitidis and freshly thawed rabbit complement (PelFreez, Brown Deer, WI). The last dilution producing a ≥50% reduction in colonies (killing) compared to control wells, containing complement and bacteria, was taken as the end point rSBA dilution. In the IgG ELISA, twofold dilutions of sera beginning at a 1:50 dilution were added to plates coated with serogroup C N. meningitidis polysaccharide, and after incubation, bound IgG was detected by the addition of a human IgG Fe PAN (1, 2, 3, 4) horseradish peroxidase-conjugated monoclonal anti-beta (Stratech Scientific Ltd.), followed by a 3, 3', 5, 5'-tetramethylylendiamine (Sigma) substrate. Absorbance values were interpreted against a standard curve of the reference CDC 1992 antibody. The lower detection limit of specific IgG in the ELISA is 0.12 µg/ml.

The sample size was determined in part by clinical considerations. The results of a previous study suggested that, with approximately 40 evaluable subjects per group, the 95% confidence interval (95% CI) on the SBA geometric mean titer (GMT) would be approximately 0.5 times to 2.0 times the estimated GMT for a given interval. Therefore, a total of 250 subjects (50 per group) were to be enrolled to ensure completion by 40 evaluable subjects per group. Immune responses were analyzed using descriptive statistics for subjects who met study criteria (per-protocol [PP] population), for all subjects who had serological results (intent-to-treat [ITT] population), and, in a subanalysis, for subjects who received 50 µg of PS antigen as a challenge dose (see below). Since this was a descriptive study, formal comparisons of antibody responses among the groups were not done. The safety analysis included all subjects who received a PS dose. Exact binomial confidence intervals were computed for proportions; rSBA titers and ELISA IgG concentrations were summarized using geometric means with corresponding 95% confidence intervals. The time courses of rSBA and ELISA antibody responses by day after challenge were described by reverse cumulative distribution curves. Pearson correlation coefficients were calculated for log-transformed rSBA titers and ELISA IgG concentrations by sampling antibody groups by day (4 samples from days 2 to 5) and Days 7 to 21 (samples from days >5). Curves illustrating the relationship of log-transformed rSBA titers and ELISA IgG concentrations were drawn with a smoothing algorithm (SAS procedures guide, version 6, 4th ed., 1990; SAS Institute, Inc., Cary, NC).

RESULTS

A total of 301 subjects were enrolled, and after dropouts were excluded, 281 subjects remained in the ITT group and 173 subjects met criteria for inclusion in the PP population (Fig. 1). Subjects were excluded from the PP population for various reasons, the principal being the inadvertent administration of the entire 50-µg dose of PS vaccine (103 subjects) instead of the reduced 10-µg PS dose. This practice reflected the Swiss recommendation for meningococcal vaccination, which allows for one or more booster doses of PS vaccine after primary MCC vaccination (2, 3). Because the administration of a 50-µg dose of PS vaccine was not anticipated and thus not randomized, these subjects were withdrawn from the PP analysis. The long (ca. 1-year) interval between vaccination and challenge also contributed to a number of subjects dropping out of the trial. A sufficient number of PP subjects remained for each time point (32 to 38 subjects per group) to allow a description of the immune response over time.

Safety and immune response results reported here focused on a comparison of subjects who received 10 µg of PS (the PP population) with those who received 50 µg of PS (a subset of the ITT population). Recipients of 10 µg and 50 µg of PS were similar with respect to demographic characteristics, as were the subsets of 10-µg recipients across blood sampling groups. For all subjects enrolled, the mean age at MenC-CRM197 vaccination was 13.1 months (standard deviation, 1.2 months) and that at PS challenge was 24.1 months (standard deviation, 0.5 months). Among the subjects, 92% were Caucasian, 3.3% Asian, 1.7% African, and 3.0% other, an ethnic distribution similar to that in the Swiss population; 49.5% were female (40).

Safety results. The challenge administration of bivalent plain meningococcal PS vaccine to 24-month-old children who had been vaccinated with MenC-CRM197 1 year previously was
associated with a low frequency of systemic and local adverse reactions meeting grade-3 criteria (i.e., events interfering with usual activities). Compared to the indicated immunizing dose of 50 μg A and C polysaccharides, fewer recipients of the reduced 10-μg dose had local reactions causing a grade-3 level of pain or redness (Table 1). No serious adverse events related to either vaccination were noted. Of note, hypersensitivity reactions that previously had been reported anecdotally after PS vaccine challenge of some MCC-vaccinated subjects were not reported (7, 34).

**Immunogenicity results.** One year after MenC-CRM197 vaccination, capsular PS-specific ELISA IgG levels were negligible in baseline samples, with a geometric mean concentration (GMC) of 1.1 μg/ml. Four days after challenge with an "immunological probe" of a 10-μg dose of PS vaccine (one-fifth of the normal immunizing dose), specific IgG levels increased just twofold to 1.4 μg/ml, reflecting a slow rise of ELISA binding IgG antibodies early after PS administration (Table 2; Fig. 2). A greater increase in total IgG levels was seen later, with a ≥10-fold further rise in GMC from Day 4 to Day 7, followed by a relative plateau by Day 10. Kinetics were similar for children who received a booster PS vaccination of 50 μg instead of the reduced 10-μg challenge dose, although significantly higher peak (Day-10) IgG ELISA levels were reached.

Paralleling the ELISA results, the baseline rSBA GMT was just 9 (95% CI, 5 to 18), and only 40.6% of subjects had an rSBA titer of ≥1:8 (Table 3). At Day 4 after challenge with a 10-μg dose of PS vaccine (all subjects in group 2), however, 84.2% (95% CI, 68.7 to 94.0%) responded with putative protective levels of bactericidal antibody (≥1:8). The Day-4 response was robust, with the GMT reaching 330 (95% CI, 139 to 787). Indeed, at Day 4, 73.7% (95% CI, 56.9 to 86.6%) of the children had already reached an rSBA titer of ≥1:128, so that even by this conservative criterion of a protective rSBA titer threshold, three-quarters of the subjects had circulating antibodies considered protective against illness by this point.

The protocol-specified analysis of children assigned for a blood sample on Day 4 included children who actually were bled over an interval from 2 to 5 days after PS challenge. A posthoc day-by-day subanalysis of subjects within this nominal Day-4 group showed, unexpectedly, that a ≥1:8 rSBA titer was reached by 69% of children at days 2 to 3, by 82% at day 4, and by 100% at day 5 after the 10-μg PS challenge (Table 3). The point estimate GMT increased from 42 on days 2 to 3, to 424 on day 4 and 1,855 on day 5, and confidence intervals for the GMTs on days 2 to 3 and day 5 did not overlap. Only 2 of 25 subjects sampled on day 4 or 5 failed to achieve an rSBA titer of ≥1:128. Thus, the rise in rSBA antibodies after PS administration was earlier and sharper than the overall rise in ELISA PS-specific IgG antibodies, which increased only twofold between Day 0 and Day 4. The evolution of rSBA and IgG antibodies reaching various threshold levels is shown in Fig. 2a.

**TABLE 2. ELISA IgG GMCs at intervals after PS challenge, by study population**

<table>
<thead>
<tr>
<th>Group</th>
<th>Value for the population receiving the following dose (μg) of PS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10&lt;sup&gt;th&lt;/sup&gt; No. of recipients tested</td>
</tr>
<tr>
<td></td>
<td>33</td>
</tr>
<tr>
<td>1 (Day 0)</td>
<td>38</td>
</tr>
<tr>
<td>2 (Day 4)</td>
<td>32</td>
</tr>
<tr>
<td>3 (Day 7)</td>
<td>35</td>
</tr>
<tr>
<td>4 (Day 10)</td>
<td>35</td>
</tr>
</tbody>
</table>

<sup>a</sup> Per-protocol population.  
<sup>b</sup> Subgroup of ITT population receiving 50 μg polysaccharide at challenge.
and b, respectively; for example, on days 2 to 3, no subject had achieved an IgG concentration of ≥2 µg/ml while 69% had reached an rSBA titer of ≥1:32.

The secondary rSBA response appeared to have reached a plateau by Day 10 (actual bleeding days were ±1 day for the Day 10 and Day 21 groups), when the GMT reached 7,719 (95% CI, 4,197 to 14,199). Children receiving a full 50-µg dose of PS vaccine responded with similar kinetics but
showed a trend toward higher rSBA responses at each interval.

The discordant rise in rSBA and ELISA IgG responses was further analyzed by examining their correlation by day after PS challenge (log-transformed data) (Fig. 3). A linear relationship of the transformed data was seen among samples taken after day 5 (Day-7, -14, and -21 groups) ($R = 0.73; P < 0.001$). Samples from the Day-4 group (sample days 2 to 5) exhibited a nonlinear relationship, with an $R$ of 0.48 ($P < 0.01$). The test for model improvement with the addition of a quadratic term was highly significant for the day-2 to -5 group ($P = 0.003$) and was not significant for the Day-0 (not shown) and >Day-5 groups.

**DISCUSSION**

The introduction of MCC vaccines into routine infant and catch-up immunization programs in the United Kingdom significantly reduced reported cases in the targeted populations, with short-term effectiveness ranging from 87 to 92% (4, 30). Because circulating levels of bactericidal antibodies decline to subprotective levels in a substantial proportion of vaccinees
within 1 year after primary vaccination, sustained protection likely has been provided by a combination of herd protection and immune memory (24, 31, 41). A clear understanding of vaccine-induced memory required for sustained individual protection is of crucial importance for countries, like Switzerland, that currently do not face epidemiological circumstances requiring routine MCC vaccination and thus are unlikely to benefit from significant herd effects.

The mechanisms of protection against invasive group C meningococcus infection have not been fully defined but likely include a combination of preexisting serum antibodies and the secondary elaboration of bactericidal antibodies, which are considered the cornerstone of immunity to meningococci (6, 16). The induction of immune memory has been formally demonstrated following priming with MCC vaccines (8, 22, 33, 34). However, recent reports of secondary vaccine failures occurring 1 to 4 years after infant priming have tempered the view that anamnestic responses are sufficient for protection and support concerns that rapidly invading bacteria such as meningococci may challenge the rapidity with which the immune system can generate anamnestic responses. In contrast to preexisting serum antibodies that may immediately neutralize invading bacteria, anamnestic responses require the reactivation of memory B cells and their differentiation into antibody-producing cells. This process is not instantaneous, and its kinetics are of particular interest for meningococcal infections, in which invasion and disease may follow just days after bacterial exposure and admission to intensive care, and death frequently follows within 24 h of onset (11, 12, 14).

One year after primary vaccination, only 41% of the study subjects primed at the age of 12 to 15 months maintained bactericidal antibody titers at the ≥1:8 level considered to be protective, with a group GMT of 9. This proportion is similar to that reported for young children 2 years after single-dose primary vaccination and lower than that found in another study, in which 57% to 86% of toddlers retained a protective primary vaccination and lower than that found in another study, which previously was correlated with an rSBA titer of ≥1:128 (1, 6, 16). In the race between the host immune response and the typically rapid invasion of meningococci, the speed required of a protective response is unclear; however, this study suggests that anamnestic SBA responses in vaccinated toddlers may develop within a relevant time frame to provide protective levels of bactericidal antibodies after infection.

The elaboration of anti-capsular IgG, as detected by this ELISA procedure, appeared to lag behind the rSBA response, with a small incremental difference between baseline and Day-4 GMCs, while SBA titers rose more sharply (Table 3; Fig. 2). This did not reflect differences in timing of MMR administration or methodological issues, because (i) ELISA is more sensitive than SBA in detecting even a minute increase in antibody concentrations and (ii) SBA titers could have increased to much higher levels than those observed here. Previous reports showing good correlations between rSBA and ELISA results did not compare the dynamic response of rSBA and total IgG at early points after administration of antigen (10, 15, 25). Our study also found a strong linear relationship between rSBA titers and IgG concentrations among samples taken at the plateau of the antibody response. However, earlier samples, taken at days 2 to 5 after PS challenge, exhibited a more complex, nonlinear relationship (Fig. 3). Discordance of the respective responses has been noted previously in varying SBA/ELISA ratios over time after vaccination, likely reflecting differences between the composition of high-avidity functional antibodies contributing to bactericidal activity and total binding antibodies measured in the ELISA (38). Bactericidal antibody levels have been shown to correlate more closely with high-avidity IgG species, while the ELISA used in this study measures total anti-PS IgG (18, 42). Small quantities of IgM also could have contributed to SBA activity, and the induction of IgM antibodies to epitopes on plain PS that were not presented previously in the conjugated PS cannot be excluded. Spleen marginal zone B cells and B-1 cells are indeed capable of rapid activation and IgM secretion in response to T-independent antigens (5, 19). The contribution of these “natural immunity B cells” to the early increase in SBA titers after PS exposure is a possibility. It would result in the coexistence, early after PS exposure, of antibodies derived from these preimmune marginal zone B cells and from vaccine-induced B cells. This would explain the poor correlation between SBA and ELISA until day 5, when most vaccine-induced memory B cells have differentiated into plasma cells and predominate in the response. Binding of PS to circulating antibody immediately after its administration also could have contributed to an acute reduction of total antibody levels, possibly reflected to a greater extent in the ELISA (23). It has also been hypothesized that repeat polysaccharide epitopes could cross-link T-cell an-
tigen receptors and thus stimulate memory B cells to increase their antibody production with a certain delay (26). Last, the earlier rise in rSBA titers may reflect the reactivation of vaccine-induced memory B cells with hypermutated Ig genes producing antibodies with higher avidity and greater functional activity; these antibodies may have comprised a smaller proportion of those measured in a conventional ELISA assessing anti-capsular IgG.

The relative roles of circulating antibodies and protective anamnestic responses in children vaccinated against encapsulated bacteria were first discussed in the context of Hib vaccine failures (21, 29). In one study assessing secondary responses to a polyribosylribitol phosphate (PRP) challenge in a small group of toddlers previously immunized with Hib-conjugate vaccines in infancy, PRP-specific IgG remained at the baseline level at Day 3 and significantly increased only between Days 4 and 5 to Day 7 (29). This pattern suggested that the time required for the reactivation of memory B cells into plasma cells was at least 4 days. Few studies have measured responses occurring earlier than 1 week after PS challenge after MCC vaccination. In a study assessing anamnestic responses 4 years after vaccination with bivalent AC-CRM197 vaccine, 18 adults were probed with 1 μg of PS vaccine, and neither hSBA nor IgG rises from baseline were detected in serum samples obtained 3 days after challenge (17). Both hSBA and IgG levels had risen significantly at Day 7, and all subjects had achieved a ≥1:8 hSBA titer, with a GMT of 136 (95% CI, 69 to 268). The failure to detect a secondary response on the third post-challenge day may have resulted from use of less sensitive immunological assays or, possibly, the smaller probe dose of 1 μg PS. We indeed observed a trend toward higher secondary antibody responses to a 50-μg dose than with a 10-μg dose of PS antigen, although with similar kinetics. The kinetics of secondary responses to Streptococcus pneumoniae PS in children previously primed with conjugate vaccines have not yet been characterized. However, there was no rise in antibody concentrations 4 days after a fourth (booster) dose of an 11-valent pneumococcal polysaccharide-protein D conjugate vaccine for children previously primed as infants (27).

This study, the largest study of secondary antibody kinetics to a bacterial PS antigen administered to young children, disclosed bactericidal antibody responses within 2 to 4 days after a parenteral PS challenge. The observations are consistent with the existence of a large pool of memory B cells in toddlers after a single dose of MCC vaccine—hypothetically, a pool larger than that after three closely spaced doses in infants. The time required for serum bactericidal antibodies to reach protective thresholds is expected to reflect cumulatively the number of memory B cells that have been primed by the initial stimulus, that have hypermutated their Ig genes, and that are capable of rapid differentiation into cells secreting antibodies with a high avidity for the initial antigen.

Although infant immunization induces immunological memory, age-related factors that limit primary antibody responses also may result in a smaller pool of memory B cells following closely spaced infant vaccinations, thus requiring a few additional days for antibody production to reach protective thresholds (35). Attaining such levels just 1 or 2 days earlier after exposure could, indeed, translate into major differences in protection against encapsulated bacteria that so rapidly produce invasive disease. We suggest that the more sustained efficacy of single-dose MCC immunization of toddlers, compared to administration of three closely spaced vaccine doses to infants, may be provided in part by the induction of a larger pool of memory B cells and thus a more rapid induction of protective SBA titers. This warrants the reevaluation of vaccination schedules relying on infant immunization without booster doses in the second year of life.

Acknowledgments

This work was supported by Wyeth Research. We are grateful to the individual physicians, their staff, and patients among the network of Swiss investigators who implemented this study. We thank Betsy Abraham, Carolyn Cimino, and Jay Graepel for assistance in organizing the study and Five Office Ltd., Barbara Safko, Lisa Kriebel, and Sharon Gray for their roles in implementing the study and preparing the study report.

References

Meningococcal Vaccine Anamnestic Antibody Response


39. Reference deleted.


