CLINICAL AND VACCINE IMMUNOLOGY, Oct. 2009, p. 1521–1523 Vol. 16, No. 10
1556-6811/09/$08.00+0 doi:10.1128/CVI.00274-09

NOTES

Absence of *Neisseria meningitidis* Serogroup C-Specific Antibodies during the First Year of Life in The Netherlands: an Age Group at Risk?▽

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Received 3 July 2009/Returned for modification 23 July 2009/Accepted 11 August 2009

In The Netherlands, a single meningococcal serogroup C conjugate (MenCC) vaccination is administered to children at the age of 14 months. Here, we report the levels of MenC polysaccharide-specific antibodies in children at birth and at 3, 11, and 12 months of age and the presence of functional antibodies at 11 months of age, before infants receive their MenCC immunization. We observed a rapid decline in polysaccharide-specific antibodies after birth and no induction of naturally elicited polysaccharide-specific antibodies. Furthermore, at 11 months of age, no bactericidal antibodies are observed. These data indicate that these infants may be at risk in the period prior to MenCC immunization, if *Neisseria meningitidis* serogroup C starts to (re)circulate.

Childhood immunization programs are initiated to prevent infectious diseases in children. Most countries have designed their own national immunization program (NIP), and great variations exist among different countries (7). Immunization of children at 14 months of age with the meningococcal serogroup C conjugate (MenCC) vaccine (NeisVac-C; Baxter, IL) was introduced in The Netherlands in 2002. The choice to administer the vaccine to children at this age was based on programmatic and economical reasons. In The Netherlands, only two immunizations at once are accepted by the public. This fact, taken together with the economical impact, indicated that the best opportunity to include a new vaccine in the NIP was at 14 months of age (10). Furthermore, epidemiological data supported the introduction of the MenC vaccine as a single dose with a catch-up campaign (10). Other countries in Europe adapted the United Kingdom schedule, in which immunization at first was offered at 2, 3, and 4 months of age (14). Currently, the MenCC immunization program in the United Kingdom has been changed to a schedule of administration at 3, 4, and 12 months of age (1).

In addition to the introduction of the MenCC vaccine for children at 14 months of age, a catch-up program in which all children and adolescents up to 19 years of age were offered a single immunization (vaccine coverage of 94%) was carried out in The Netherlands (15). This vaccination strategy led to an almost complete disappearance of MenC disease in children, with only a few cases occurring in unvaccinated individuals, indicating a large herd immunity effect and virtually no circulation of MenC in the community (3). Given this immunization strategy, it is important to monitor the prevalence of antibodies among those age groups who may be at risk because they are not eligible to receive a MenCC vaccination yet. In the Dutch situation, these are mainly children under 14 months of age.

In the present study, we evaluated the prevalence of MenC polysaccharide (PS)-specific antibodies and the serum bactericidal antibody (SBA) activities in populations of infants at various time points during the first year of life. Cord blood samples ($n = 41$) and serum samples from children at the ages of 3 months ($n = 70$) and 12 months ($n = 38$) were obtained from a study that investigated the influence of probiotics on eczema and allergies in 2004 and 2005 (ISRCTN00200954).

TABLE 1. MenC PS-specific IgG concentrations and SBA titers in infants during the first year of life

Sample type or age at sampling	GMC (95% CI) of MenC PS-specific IgG (μg/ml)	MenC-specific SBA titer[a] (95% CI)
Cord blood	0.25 (0.16–0.40)	ND
3 mo	0.10 (0.07–0.14)	ND
12 mo	0.09 (0.07–0.11)	ND
11 mo	0.04 (0.03–0.05)	2 (NA)

[a] Titers were expressed as the reciprocal of the final serum dilution yielding 50% killing at 60 min. For statistical purposes, SBA titers of <4 were assigned a value of 2. ND, not determined (due to insufficient serum volume); NA, not applicable.

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▽ Published ahead of print on 19 August 2009.

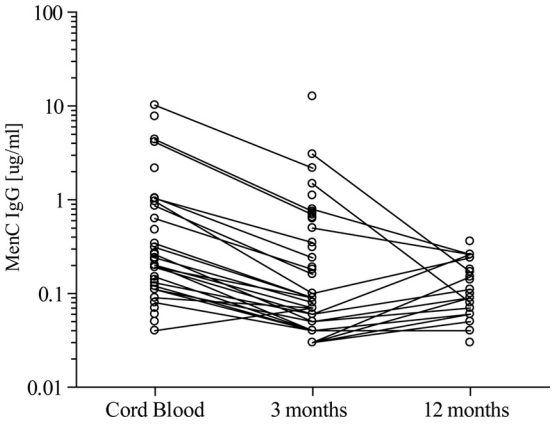

FIG. 1. Concentrations of MenC PS-specific IgG in cord blood samples and in samples from infants at 3 and 12 months of age. Paired cord blood and 3-month samples from 26 infants and paired 3- and 12-month samples from 17 infants were available. Paired samples are indicated by solid lines.

Serum samples from infants at the age of 11 months ($n = 103$) were obtained from a study which investigated the serological responses following the replacement of a whole-cell pertussis vaccine by different acellular pertussis vaccines in the period from 2004 to 2007 (ISRCTN97785537). For all participating children, informed consent to use serum samples for further research was obtained from the parents.

MenC PS-specific immunoglobulin G (IgG) antibodies are quantified using a fluorescent-bead-based multiplex immunoassay (4). Standardized reference serum CDC 1992 (National Institute for Biological Standards and Control, Potters Bar, United Kingdom) was used in this assay. The lower limit of quantitation for MenC antibodies is assigned at 0.01 μg/ml. The levels of MenC-specific functional antibodies in 103 serum samples from the 11-month-old age cohort were determined by an SBA assay using baby rabbit complement (Pel-Freeze Incorporated, Rodgerson, AZ) (12). The target strain for the assay was C11 (phenotype C:16:P1.7-1,1). SBA titers are expressed as the reciprocal of the final serum dilution yielding 50% killing at 60 min. For statistical purposes, SBA titers of <4 were assigned a value of 2. Antibody concentrations in serum samples were calculated as geometric mean concentrations (GMC) or geometric mean titers, with 95% confidence intervals (95% CI).

Overall, cord blood samples showed a MenC PS-specific IgG GMC of 0.25 μg/ml. Antibodies declined to levels of 0.10 and 0.09 μg/ml at 3 and 12 months of age, respectively (Table 1). Paired cord blood and 3-month samples from 26 infants and paired 3- and 12-month samples from 17 infants were available (Fig. 1). The data indicate that, during the first year of life, MenC PS-specific IgG antibodies are not elicited by natural contact.

To determine if, in contrast to PS-specific antibodies, functional antibodies to other surface components of MenC are elicited during the first year of life, we examined serum samples from the 11-month-old age cohort for the presence of SBA titers. In none of the tested serum samples was an SBA titer equal to or above the putative protective value of 8 found. The GMC of MenC PS-specific IgG in this 11-month-old age cohort was 0.04 μg/ml (Table 1).

The level of MenC PS-specific antibodies detected in the present study is very similar to the concentration of 0.23 μg/ml that we found previously in cord blood samples in another study from the same period (5). The findings of the present study support the idea that antibodies in children decline rapidly after birth and that transferred maternal antibodies do not protect children during their entire first year of life. Furthermore, at 11 months of age, when maternally derived antibodies have declined (16), no protective concentrations of MenC PS-specific antibodies or protective SBA titers are observed. This lack of functional protection at 11 months of age further indicates that no natural immunity is elicited after birth.

Under the present conditions in The Netherlands, we do not observe any protective SBA titers before immunization; this finding may indicate that the Dutch vaccine strategy leads to a reduction in naturally induced immunity in infants compared to levels of protection observed in several pre-immunization era studies. These preimmunization studies revealed that approximately 20% of infants under 6 months of age and 15% of infants between 6 and 11 months of age were protected from MenC disease based on naturally derived antibodies before the introduction of the MenCC vaccine (2, 8, 18). Fortunately, the vaccination strategy used in The Netherlands led to a large herd immunity effect due to high-level vaccine efficacy against carriage in older age groups (11) and therefore offered protection to the very young. However, since several studies suggest that a single immunization during infancy does not provide sufficient protection until adolescence (13, 17), this herd effect may eventually wane, and therefore, we place our neonates and infants at possible risk in the future. Other European countries such as Belgium and Luxembourg have also implemented a single immunization in combination with a catch-up campaign in the second year of life, and Germany implemented a single immunization without a catch-up campaign in the NIP (9, 20). Therefore, close clinical and serological surveillance of MenC is required to prevent the resurgence of MenC disease in the very young. In the United Kingdom, NIP vaccinations against MenC are offered during the first year of life and these induce short-term protection in approximately 90% of infants (19). Hence, a thorough exploration of different immunization schedules may be necessary to provide serological protection during the first year of life in the future (17a, 19) and to preserve a high level of herd immunity and thus maintain a low prevalence of MenC disease in The Netherlands in the long term (6).

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