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Short communication

Evolution of immune response against *Neisseria meningitidis* B:14:P1.7,16 before and after the outer membrane vesicle vaccine MenBvac

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ABSTRACT

A meningococcal B:14:P1.7,16 outbreak in Normandy (France) was recently controlled using MenBvac, an outer membrane vesicle vaccine previously designed against the B:15:P1.7,16 strain. The further emergence of a new B:14:P1.7,16 outbreak in another district in Normandy led us to explore immunity against B:14:P1.7,16 before and after the MenBvac campaign using a 2 + 1 (day 0, week 6, month 8) schedule.

Children (1–5 years) were sampled before, during and up to one year after vaccination. Serum bactericidal activity against B:14:P1.7,16 was titrated using human complement (hSBA) and immune response was defined by hSBA titer ≥4 as a surrogate for protection.

The percentage of hSBA titer ≥4 was 10.8% before vaccination, raised to 84.1% 6 weeks after the completion of the schedule, but declined to 39.7% one year later. This level is lower than the targeted 60% level and suggests only short-term persistence of response against B:14:P1.7,16 using this schedule.

1. Introduction

In Europe, cases of invasive meningococcal diseases (IMD) are mainly sporadic serogroup B cases [1]. Rare outbreaks are encountered and their emergence is partially linked to low natural immune response against some particular strains [2].

From 2003, several districts in Normandy (in North-Western France) experienced an outbreak of IMD due to a particular clone of serogroup B, serotype 14, serosubtype P1.7,16, and sequence type 32 (B:14:P1.7,16/ST-32). The most affected district was the city of Dieppe and its immediate surroundings (Dieppe area). From 2006, children and teenagers in the area have been vaccinated using MenBvac. MenBvac is an outer membrane vesicle vaccine developed by the Norwegian Institute of Public Health (NIPH) in the late 1980's in response to a B:15:P1.7,16 outbreak, which mainly targets the major outer membrane protein PorA [3]. A 3 + 1 schedule (day 0, week 6, week 12, month 12) was initially planned for all the 1- to 19-year-old subjects of the area, according to the most recent immunological data from NIPH [3]. Because of a shortage of production, a fortune 2 + 1 schedule (day 0, week 6, month 8) was finally applied to most subjects from the Dieppe area. This approach was successful: MenBvac produced a protective antibody response against B:14:P1.7,16, its tolerance was good, and after a two-year follow-up as of today the outbreak has been controlled in the vaccinated area [4]. In the Dieppe area, the natural immunity before the vaccine campaign had not been assessed. Immunogenicity data were obtained from a random sample of 1–5 year old children already enrolled in the program, for which a rather rapid decline of the immune response against PorA was observed after the third dose (given at month 8 after a 2 + 1 schedule as described above): the proportion of children with immune response against B:14:P1.7,16 (see definition below) decreased from 88% 6 weeks after this booster dose to 56% 15 months later [4].

The further emergence of a new B:14:P1.7,16 outbreak in another Norman district (Neufchâtel-en-Bray area) gave us the opportunity to conduct this new immunogenicity study to explore both the natural and vaccine immunities. Its objective was to evaluate the proportion of children with protective antibody level against the B:14:P1.7,16 clone either at baseline (i.e., natural immunity) and at short and long terms after a 2 + 1 MenBvac schedule (i.e., vaccine immunity).

2. Methods

To allow comparison between the two Norman districts, the current study was also restricted to children aged 1–5 years (children

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in this age range were the most affected by IMD). A cohort of 450 subjects was selected by random sampling from the 1335 children aged 1–5 years living in the Neufchâtel-en-Bray area who were eligible to receive MenBvac using the 2 + 1 schedule, with doses given again at day 0, week 6, and month 8. Blood samples were taken before vaccination (D0), 6 weeks after the second dose (M3), immediately before (M8), 6 weeks after (M9.5), and one year after the third dose (M20). This immunogenicity study was approved by the regional ethics committee (Comité de Protection des Personnes Nord-Ouest-1) and written informed consent was obtained from parents or legal guardians of every participant.

Aliquots of sera were sent frozen at −20 °C until analysis at the French National Reference Centre for Meningococci, Invasive Bacterial Infections Unit, Institut Pasteur (Paris). Immunity against B:14:P1.7,16 was assessed by titration of the serum bactericidal activity using a reference strain and human serum as an exogenous complement source (hSBA titer). The titers corresponded to the reciprocal of the final serum dilution causing 50% killing of the inoculum.

Immune response was defined by hSBA titer ≥4 against B:14:P1.7,16 (a surrogate for protection). For subjects with hSBA titer >4 at baseline (i.e., natural immunity) a fourfold rise of hSBA titer was requested to conclude to vaccine response.

For each time point, immunogenicity results were expressed as geometric mean of hSBA titers (GMT) and percentage of individuals with hSBA titer ≥4. The main goal was to achieve a 60% proportion of children with immune response one year after the boost; this goal was assigned by analogy with previous works with OMV vaccine [5].

For computational purposes, hSBA titers lower than 4 were assigned a value of 2.

Pearson's chi-square test was used to compare the proportion of immune responders in the current series with that previously observed in the Dieppe area [3]. Participants and non-participants were compared using Pearson's chi-square test for categorical variables, and Student's *t*-test for quantitative variables. Children with five available samples and the full sets of children with available sample at each point were compared using Pearson's chi-square test for categorical variables, and Student's *t*-test for quantitative variables. Statistical significance was defined as $p < 0.05$. SAS software was used (version 9, SAS Institute, Cary, NC, USA).

3. Results

Overall, 218 children were enrolled in the study (rate of participation: 48.5%). Compared to the 232 non-participants, they were similar in terms of gender and area of residence but slightly older (mean age ± standard deviation: 3.9 ± 1.4 years old versus 3.4 ± 1.4; $p < 0.0005$).

All the participants received the three doses of vaccine but many missed one or two blood collections so that only 90 subjects had the five samples available for analysis. The distribution of hSBA titers against B:14:P1.7,16 at each point is displayed in Fig. 1 for the subset of 90 children with five available samples and in Fig. 2 for the full set of children with available data. For each of the five time points, the percentage of immune responders and the GMT values were similar between the subset of 90 subjects and the corresponding set of children with available samples (data not shown).

For all children with available samples, the percentage of subjects with hSBA titer ≥4 against B:14:P1.7,16 was 10.8% (95% CI: 6.6–15.0%) at baseline, 41.3% (95% CI: 33.9–48.6%) 6 weeks after the second MenBvac dose, and 84.1% (95% CI: 77.7–90.5%) 6 weeks after the third dose, that clearly acted as a booster. However, hSBA titers subsequently declined sharply, with only 39.7% (95% CI: 31.1–48.2%) of subjects with hSBA titer ≥4 one year after the last dose. Because some children had natural immunity, the percentage of vaccine responders was even lower, i.e., 36% one year after the boost (i.e., at M20). Indeed, among the 23 children with hSBA titer ≥4 at baseline, 10 had a fifth sample available among whom only three had a four-fold rise of titer compared to baseline; among the 190 children with hSBA titer <4 at baseline, 115 had a fifth sample available, among whom 42 (37%) had hSBA titer ≥4; hence, 45 out of 125 children overall (36%) were vaccine responders at M20.

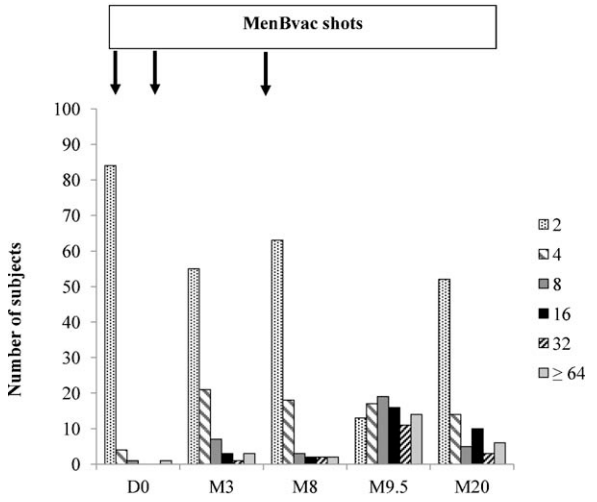

Fig. 1. Distribution of hSBA titers against the B:14:P1.7,16 strain before and during MenBvac vaccination given in a 2 + 1 (D0, W6, M8) schedule; data from the 90 children with five available samples. Blood samples were taken before vaccination (D0), 6 weeks after the second dose (M3), immediately before (M8), 6 weeks after (M9.5) and one year after the third dose (M20) of MenBvac.

4. Discussion

The two main results of this study performed in young children from a Norman area affected by a clonal meningococcal B:14:P1.7,16 outbreak were a rather high (10.8%) natural immunity against the epidemic clone, and an insufficient vaccine immunity, with a percentage of immune response one year after vaccination (using a 2 + 1 MenBvac schedule) lower than expected (39.7% versus a 60% goal).

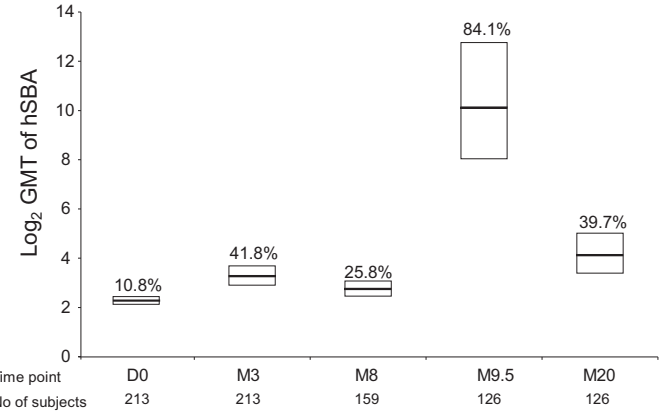

Fig. 2. Geometric means of hSBA titer values (horizontal lines) and 95% CI (boxes) against B:14:P1.7,16 for each time point of sampling (as indicated under each box) in a random sample of 1–5 year old children vaccinated with MenBvac given at a 2 + 1 (D0 W6 M8) schedule. Percentages of subjects with seroprotection (i.e., hSBA ≥ 4) are given for each time point above the corresponding box and the number of subject is indicated under each time point. Data are from of all available children for each time point.