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Seroconversion and duration of immunity after vaccination against group C meningococcal infection in young children ☆

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Abstract

An increase in the incidence of group C meningococcal disease was observed in the Murcia Region (Spain) during 1996–1997. In September 1997, a massive vaccination campaign was implemented among the population aged 18 months to 19 years. The aim of this study was to assess the seroconversion rate of children aged 18–59 months and the persistence of immune response 1 year after vaccination. A total of 296 children were included. Blood samples were obtained before vaccination and 1 month and 1 year after vaccination. Three point seven percent of the children had bactericidal antibody titres of ≥1:8 before vaccination. One month after vaccination seroconversion was 63.7%, with a growing trend related to age at vaccination ($p < 0.0001$). The increase in antibody titres was shown to be quantitatively greater above the age of 36 months ($p < 0.0001$). One year after vaccination only 4.3% of the children who initially seroconverted still had bactericidal activity. Seroconversion in children under 5 increases with age but antibodies decline rapidly in the year following vaccination.

Keywords: Meningococcal vaccine; Post-vaccination seroconversion; Bactericidal antibodies

1. Introduction

The last epidemic cycle of meningococcal disease in Spain reached a peak in 1979, followed by a progressive decline until 1994. In the 1995–96 period, a dramatic increase in incidence occurred in certain areas of the country, to spread almost to the whole of Spain in the following period. This increase was mainly due to serogroup C, particularly to strain C:2b:P1.2,5 whereas in the 1980s, meningococcal disease proved to be linked to the predominance of serogroup B [1].

In the Murcia Region, the same pattern was observed. Since 1995 an increase in the incidence of meningococcal disease has been observed, this increase in the 1996–97 period being 67% over the median for the previous 5-year period. Of the 76 cases of meningococcal disease reported during the 1996–97 period, 45 cases were confirmed microbiologically, 64% of which were serogroup C. The incidence of serogroup C meningococcal disease recorded in the Murcia Region during 1996–97 was 2.7/100,000 inhabitants and 9.0/100,000 persons aged between 18 months and 19 years.

☆ Written informed consent was obtained from the parents or guardians of all study subjects, and the study protocol was reviewed and approved by the Ethical Committee of the General University Hospital, Murcia, Spain, on 18 July 1997.

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The greatest incidence was recorded in the 0–4 and 15–19 year age groups [2].

The Murcia Directorate General of Health decided to implement a vaccination campaign against group C meningococcal disease. The aim of this programme, carried out in September–October 1997, was to vaccinate all the population of the region aged between 18 months and 19 years.

Several studies have been published on the immunogenicity and effectiveness of polysaccharide vaccine against Neisseria meningitidis serogroup C [3–11]. In general, studies performed on the adult population clearly show the effectiveness of the vaccine on the control of the disease, but it is reported that the efficacy in children under 5 years is low and in those under 18 months practically nil [7,10]. However, studies carried out in young children are less frequent and some include only a small number of children, which leads to results being contradictory and difficult to generalise.

Coinciding with the start of the Vaccination Campaign and in view of the poor efficacy of vaccination reported in those aged under 5–6 years, a follow-up immunogenicity study was initiated. The objectives of this study were: (1) to assess the percentage of children aged between 18 and 39 months who seroconverted at 1 month after vaccination and the percentage of those who seroconverted with maintenance of bactericidal activity at one year after vaccination; (2) to evaluate the possible association between seroconversion and age, number of siblings, number of household members and nursery school/school attendance. The aim of this study was to obtain information on the immunogenicity of the vaccine and the duration of immunity in our population, which would be a tool for further decisions on the revaccination of younger children in the event of a persistent high-risk situation.

2. Material and methods

This is a follow-up study including 296 children aged between 18 and 59 months, living in the Murcia Region. The children included in the study were recruited during the 1997 vaccination campaign and selected in four health care centres of different municipalities. The vaccine used throughout the campaign was the polysaccharide meningococcal AC vaccine manufactured by Pasteur–Merieux MSD. Three blood samples were obtained from each participant: immediately before vaccination, and 1 month and 1 year after vaccination. Excluded from the study were children who had been previously vaccinated, those whose parents refused to allow blood samples, those who were seen as unlikely to attend later appointments for follow-up, those who suffered from acute or chronic illnesses of any kind and those who were being treated with antibiotics or had received such treatment five days before blood extraction. Blood samples were centrifuged and frozen at −70°C. Serum samples were sent to the Neisserias Laboratory, National Microbiology Centre of the Carlos III Health Institute, Madrid, Spain, where bactericidal activity of serum was determined using the protocol established by the Centre for Disease Control [12]. Titres greater than or equal to 1:8 in the bactericidal test were considered protective and named as antibody titres with bactericidal activity (BA) [5,7,12–14].

Data relating to identification, number of siblings, number of household members and nursery school/school attendance were obtained by means of a structured questionnaire. The information obtained was protected as established by current legislation, in order to guarantee maximum confidentiality [15]. The median and the geometric mean of titres (GMT) were calculated for each age group. The exact Fisher test or the Pearson Chi-squared test for contingency tables with the analysis of residuals was used to assess the relationship between the presence of bactericidal activity or seroconversion and all the other factors. The evolution of seroconversion by age groups was analysed using the Chi-squared test for linear trends of proportions, and the pre- and post-immunisation differences were assessed using the McNemar test. The Kruskal–Wallis test was used to analyse the differences in antibody levels among the different age groups and the Wilcoxon test to compare antibody levels between pre- and post-immunisation.

3. Results

A total of 296 children were included in the study. The second and third blood extractions were done 29.5 $\pm$ 1.2 and 368 $\pm$ 4.7 days after vaccination. The male/female ratio was 1. The distribution by age sub-groups is shown in Table 1. Only 11 (3.7%) children showed bactericidal antibody titres of $\geq$1:8 in the determination made before vaccination. No statistically significant relationship between the presence of antibodies and the factors age, sex, number of siblings, number of household members and nursery school/school attendance was observed.

Two hundred and eighty-three children attended the second extraction (1 month after vaccination), a response rate of 95.6%. Ten of the 11 children who showed pre-vaccination BA attended the second extraction and all showed BA. Of the 285 children who did not show BA in the pre-vaccination determination, 273 came to the second appointment. Eleven sera were rejected because they were qualified as "non-titratable" due to the presence of a serum component

Table 1
Bactericidal activity in serum against *N. meningitidis* C in children aged from 18 to 59 months[a]

	Determination 1 (before vaccination)			Determination 2 (month one)			Determination 3 (year one)		
Age groups (months)	*N*	BA (%)	CI (95%)	N_+	BA (%)	CI(95%)	N_{++}	BA (%)	CI(95%)
18–23	41	2 (4.9)	(0.6–16.5)	34	13 (38.2)	(22.2–56.4)	9	0	(0–33.6)
24–35	81	1 (1.2)	(0.03–6.7)	73	42 (57.5)	(45.5–69)	36	0	(0–9.7)
36–47	64	4 (6.3)	(1.7–15.3)	55	35 (63.6)	(49.5–76.2)	28	3 (10.7%)	(2.3–28.2)
48–59	110	4 (3.6)	(1–9)	100	77 (77)	(67.5–84.9)	67	3 (4.3%)	(0.9–12.5)
Total	296	11 (3.7)	(1.9–6.6)	262	167 (63.7)	(57.7–69.6)	140	6 (4.3%)	(1.6–9.1)

[a] *N*, number of children in the first determination (before vaccination); BA (%), number (percentage) of children with bactericidal activity in serum ≥1:8; CI (95%), 95% confidence interval; N_+, number of children with no bactericidal activity before vaccination and assessed 1 month after vaccination; N_{++}, number of children with no bactericidal activity before vaccination who seroconverted 1 month after vaccination and were assessed 1 year after vaccination.

at the time of extraction, for example the presence of antibiotics, which prevented the determination of BA. One hundred and sixty-seven (63.7%) of the 262 children with serum analysed in the second determination showed titres of ≥1:8, similar results were obtained when the 1:32 or 1:64 cut-offs were used. Significant differences between the percentage of children with BA before and after vaccination were shown ($p < 0.0001$). A statistically significant linear trend ($p < 0.0001$) between seroconversion rate and age at vaccination (38.2% in children aged 18–24 months, 57.5% in those aged 24–35 months, 63.6% in those aged 36–47 months and 77% in those aged 48–59 months) was found. No statistically significantly relationship was found with other variables studied. Children with BA before vaccination showed a significantly higher BA titre in the second determination compared to those who had not shown BA before vaccination ($p = 0.04$): median of 1024 vs 256. Children aged over 36 months showed significantly higher quantitative increases in antibodies than those under this age ($p < 0.0001$) (Fig. 1). No significant differences in the increases in titres were observed between the 18–23 month and 24–35 month groups, or between the 36–47 and 48–59 month groups (Table 2, Fig. 1).

The percentage of children who showed titres of ≥1:8 1 month after vaccination decreased significantly ($p < 0.0001$) 1 year later. One year after vaccination, serum was obtained from 140 of the children who showed seroconversion at 1 month (response rate 85%), and only six (4.3%) showed BA (Table 1). Fifty-eight of the 95 children who had not seroconverted 1 month after vaccination came to the 1-year appointment, and only one showed BA. None of the children aged under 29 months showed BA after 1 year of follow-up.

Table 2
Bactericidal activity in serum against *N. meningitidis* C in children who seroconverted 1 month after vaccination. Median, geometric mean[a]

Age group (months)	*N*	Median	GMT	CI (95%)
18–23	13	128	150.20	(106.00–212.83)
24–35	42	128	187.09	(124.74–280.61)
36–47	35	256	261.45	(184.22–370.11)
48–59	77	256	306.45	(230.31–407.89)
Total	167	256	247.64	(206.15–297.47)

[a] *N*, total number of children with bactericidal antibodies ≥1:8 1 month after vaccination; Median, median of the figures for antibody titres >1:8 1 month after vaccination; GMT, Geometric mean of antibody titres ≥1:8 1 month after vaccination; CI (95%), 95% confidence interval.

4. Discussion

In this study, antibodies were determined by a "bactericidal test", as it has been reported that they appear to be associated with clinical protection against group C meningococcal disease [16,17]. Protective efficacy has not been demonstrated in children aged under 24 months, suggesting that the production of antibodies against the polysaccharide group C is quantitatively and qualitatively different to the antibodies produced by children aged over 24 months. However, the significance of those in the protection against meningococcal disease is unknown. Several authors propose BA determination as a preferred method in young children, in whom it has been observed that no correlation exists between BA and total antibodies (TAs) [5,7]. We regarded as protective titres values greater than or equal to 1:8, since these are the values established in standardised protocols [12] and because our results can be compared with those of recently published studies [5,7,18].

Three point seven percent of the children showed BA of ≥1:8 before vaccination, these results being similar to those obtained by other authors [5,7,19]. In the present study, a 63.7% seroconversion rate was

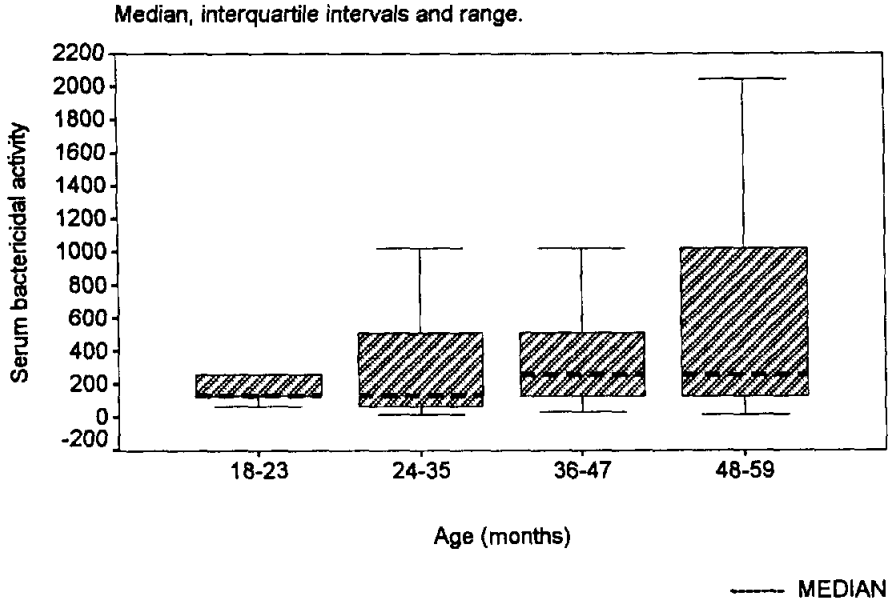

Fig. 1. Box-plot of the distribution of bactericidal activity serogroup C *Neisseira meningitidis* in children with seroconversion.

found, these results being slightly higher than those reported by Mitchell et al. [18] in 1996 (50% in children aged 2–6 years). The seroconversion rate by age group is also higher (Table 1). Maslanka et al. [5] studied the bactericidal activity 7 weeks after vaccination and found that 18% of children aged 1 year showed BA, as well as 35%, 56%, 75% and 68% of children aged 2, 3, 4 and 5 years, respectively. King et al. [7] found BA in more than 30% of children aged 6–23 months, 1 month after vaccination.

Our results match previous findings regarding the trend between age at vaccination and seroconversion rate [3,5,7,18]. Furthermore, we observed that 1 month after vaccination the quantitative increase in the BA titre was greater above the age of 36 months. This aspect has to be taken into account when indicating vaccination in young children, as vaccination must be based on a fully justified risk situation. Only 4.3% of the children that were seropositive 1 month after vaccination still had BA one year after vaccination, a figure lower than that found by Mitchell et al. [18], who determined BA and TAs in children aged between 2–6 years and observed that although 80% of the children still had TAs at one year bactericidal activity had dropped to 20%. However, our results are similar to those obtained in Cantabria, Spain, where BA was determined at 10 months after vaccination [20]. Other authors find that BA levels decline substantially before 1-year post-vaccination in children younger than 5–6 years [3,5,7,18]. Although this rapid fall has also been observed with conjugate vaccines, a significant advance of these vaccines is that they show an anamnestic response after re-vaccination [13,21–24].

In short, a statistically significant trend was found between seroconversion and age at vaccination, with a higher increase being observed in BA after the age of 36 months. The duration of the immune response, measured by BA, in the great majority of children who showed seroconversion 1 month after vaccination, was less than 1 year. However, it has been observed that the effectiveness of the vaccine is greater than that expected by the serology results, as an important decrease in the incidence rate and mortality was observed in some communities where the risk population was massively vaccinated [6,8,11].

In view of the relatively poor immune response of younger children to the polysaccharide vaccine and its short duration as documented in serological studies, we have expectations that the polysaccharide conjugate vaccine, at present in clinical development, may shortly be an alternative to the current vaccine [13,21,22,25,26]. This conjugate vaccine could be used for the control of epidemic outbreaks, but also in massive vaccination programmes in those populations with endemic meningococcal disease.

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