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Research Article

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Antibody Response to Serogroup A and C Meningococcal Polysaccharide Vaccines in Infants Born of Mothers Vaccinated during Pregnancy

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ABSTRACT During the large epidemic of serogroups A and C meningococcal disease in Brazil, we studied the immunologic response to meningococcal polysaccharide vaccine in infants born to women vaccinated during pregnancy. Radioimmunoassay serum levels against serogroups A and C polysaccharide were more than threefold higher in vaccinated than in unvaccinated women at delivery. Cord blood levels were also threefold or higher in infants whose mothers were vaccinated while pregnant compared to infants born of unvaccinated mothers. Within 3 mo, the infants' A and C serum antibody levels declined by ~80%. When vaccinated at about 6 mo of age, infants born of vaccinated mothers had antibody responses to A and C polysaccharide vaccines indistinguishable from those born of unvaccinated mothers. The response did not vary with the trimester of vaccination. We conclude that the vaccination of pregnant women with groups A and C meningococcal polysaccharide vaccine does not produce immune tolerance in the subsequently born infants.

INTRODUCTION

Meningococcal disease continues to occur in epidemic proportions in populations scattered throughout the world (1-4). Large epidemics may be a result of serogroup A (2-4) or C (1), whereas endemic disease and focal outbreaks are more often caused by group B (5-7) or C (5, 8). Milestones in the control of serogroups A and C outbreaks were reached with the licensing of meningococcal serogroups A and C polysaccharide vaccines (9). In field trials, serogroup C vaccines (10, 11),

for persons above 2 yr of age, and serogroup A vaccines (12-14), for persons over 1 yr, have proven safe, immunogenic, and efficacious. Both vaccines are licensed for the control of epidemic disease in the United States, but the guidelines for usage contain an admonition against giving them to pregnant women (9). This admonition is supported by animal studies that show pneumococcal polysaccharide vaccine, given to infant mice, produced immune tolerance (15-17), and by studies of type I pneumococcal polysaccharide in human infants (18).

During the years 1974 and 1975, a large epidemic of serogroups A and C meningococcal disease occurred in Brazil (2, 13). Because of this epidemic, the Brazilian government carried out a countrywide vaccination campaign with serogroups A and C polysaccharide vaccines, which gave us the opportunity to study a mass vaccination program and to observe the immunologic response to meningococcal polysaccharide vaccine (MPV)¹ in infants born to women vaccinated while pregnant.

METHODS

We interviewed a group of women in Amapá, Brazil the day after they were vaccinated, and identified 51 pregnant women that we would be able to follow through delivery. We bled 25 of these women on the day after they were vaccinated, by jet gun, with an intramuscular dose mixture of 50 µg of A and 50 µg of C MPV. The initial vaccine was manufactured by Merieux Co., Lyons, France and was the vaccine used throughout Brazil in the campaign.

We followed these 51 women through delivery, at which time we collected a sample of cord blood. We also collected a cord blood sample from infants of 39 women who had not been vaccinated during the campaign. 39 children of vaccinated mothers were bled at 3 mo, and 31 were bled at 6-8 mo,

This work was initiated while Dr. McCormick and Mr. Gorman were short-term advisors for the Pan American Health Organization.

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¹Abbreviation used in this paper: MPV, meningococcal polysaccharide vaccine.

TABLE I
*Meningococcal Serogroup A Polysaccharide Antibody in Serum of Vaccinated
Gravid Mothers and their Infants in Amapa, Brazil*

Popu- lation	n*	Geometric mean level	95% CI	n*	Mean fold change	95%
$\mu\text{g Ab/ml}$						
G ₁	25	4.98	(3.83–6.48)	25	2.8	(2.2–3.6)
G ₂	51	13.43	(12.03–14.99)	51	0.52	(0.13–0.67)
C	51	7.13	(5.51–9.22)	39	0.20	(0.15–0.25)
I ₃	39	1.33	(1.00–1.77)	31	0.48	(0.36–0.63)
I _{6–8}	31	0.62	(0.50–0.76)	31	2.6	(2.1–3.1)
I _{p-v}	31	1.57	(1.27–1.94)			

Abbreviations used in this table: G₁, gravid bled within 24 h of vaccination; G₂, gravid bled at birth of child; C, cord blood; I₃, infant at 3 mo; I_{6–8}, infant at 6–8 mo of age; I_{p-v}, infant 2–3 wk postvaccination.

* Number of pairs of specimens.

at which time they were given a mixture of 50 μg of serogroup C vaccine and 25 μg of serogroup A vaccine, by jet gun; the vaccines were manufactured by Merrill National Co., Swiftwater, Pa. (lot Nos. 1228 and 1508, respectively). Both vaccines had been stored at -20°C for a period of 8–12 mo. The children were bled between 2 and 3 wk after vaccination. Control data for children are from a group of comparable age whom we vaccinated in another study, in the same area, using the same vaccine, and whose mothers were not vaccinated during that pregnancy.

Measurement of antibody was done at the Center for Disease Control using a modification of the radioimmunoassay method of Gotschlich (19)². Groups A and C (lots Nos. A3 and C1, respectively) and standardized hyperimmune serum were supplied by Dr. Gotschlich. The same lot of antigen was used throughout the laboratory determinations.

Antibody level was measured as antigen binding capacity of serum compared to a reference standard whose antibody affinity is measured as micrograms of precipitable antibody nitrogen per milliliter of serum. Mean levels are calculated as geometric means. The mean fold change (MFC) in antibody levels is calculated as the geometric mean of the ratios of levels in paired sera. Thus,

$$\text{MFC} = \prod_{k=1}^n \frac{S_{2k}}{S_{1k}} \times \frac{1}{n},$$

where S_{1k} is the antibody measurement of the earlier of the pair of specimens and S_{2k} is the corresponding measurement on the later specimen. The mean fold change is a measure of the relative change in antibody over time. The 95% confidence interval (CI_{95}) is: $\text{CI}_{95} = \text{sample mean} \pm 1.96 (\text{SE})$.

RESULTS

In a group of 25 women from whom serum was collected within 24 h after vaccination, the geometric mean antipolysaccharide A level was 4.98 $\mu\text{g/ml}$, not significantly different from the mean level of 6.37 $\mu\text{g/ml}$ in unvac-

cinated women bled at delivery (Tables I and II). The mean antibody level at delivery for vaccinated women, in contrast, was 13.43 $\mu\text{g/ml}$, significantly higher than that level at the time of vaccination. Results of the serogroup C antibody studies showed the prevaccination levels to be much lower than serogroup A levels, but the rise in antibody after vaccination was relatively higher (Table III).

In both serogroups A and C studies, the cord serum levels averaged about one-half the mothers' levels at delivery, but were significantly higher than controls (7.13 vs. 2.40 $\mu\text{g/ml}$ for A and 2.94 vs. 0.25 $\mu\text{g/ml}$ for serogroup C).

Serogroups A and C serum antibody levels showed 80 and 89% declines, respectively, from birth to 3 mo of age (1.33 $\mu\text{g/ml}$ for A and 0.30 $\mu\text{g/ml}$ for C). At 6–8 mo of age the antibody levels had further declined by significant amounts and were, in fact, equal to levels in children of the same age whose mothers were not vaccinated.

The rise in serogroup A meningococcal antibody after vaccination of infants whose mothers had been vaccinated was 2.6-fold, from 0.62 to 1.57 $\mu\text{g/ml}$ (Table I). This rise was not distinguishable from the 3.1-fold rise (0.57 to 1.78 $\mu\text{g/ml}$) in a group of controls whose mothers had not been vaccinated. The rise in serogroup C meningococcal antibody after vaccination of infants whose mothers had been vaccinated during pregnancy was 6.2-fold (0.16–1.02 $\mu\text{g/ml}$). The mean rise in antibody in 26 infants of the same age born of unvaccinated mothers was 13.3-fold (0.1–1.80 $\mu\text{g/ml}$). There was no statistical difference between cases and controls as to frequency or magnitude of response. More than 90% of children responded to both A and C vaccines with rises in antibody. None had decreases in antibody to either of the antigens after vaccination.

We analyzed the antibody response in children by

² McCormick, J. B., J. C. Feeley, G. Gorman, and P. Wingo. Manuscript in preparation.

TABLE II
Meningococcal Serogroups A and C Polysaccharide Antibody Levels in Serum of Unvaccinated Women at Delivery (G₂) and in Corresponding Cord Serum (C), Amapa, Brazil, 1974-75

	<i>n</i>	Serogroup A geometric mean level*	95% CI	<i>n</i>	Serogroup C geometric mean level†	95% CI
		μg/ml			μg/ml	
G ₂	39	6.37	(5.24-7.75)	39	0.65	(0.44-0.96)
C	39	2.40	(1.64-3.50)	39	0.25	(0.15-0.41)

* Mean fold change, 0.37 (0.29-0.50).

† Mean fold change, 0.38 (0.29-0.53).

trimester of the mothers' vaccination. Although there were some differences in the responses, all had greater than twofold rises, none of the differences by trimester were statistically significant, however, with the small number of subjects very large differences would be required to see a statistical significance.

We also looked at antibody levels in the mothers and infants at birth by trimester of vaccination, and although there were differences, they were not statistically significant.

No obvious physical abnormalities at birth were noted in our study population.

DISCUSSION

Mechanisms have been described for immune tolerance to assorted polysaccharide antigens (15-17). These are more descriptive of events than explanations of processes. Studies have also demonstrated that mice respond poorly to optimal immunizing doses of type III pneumococcal polysaccharide after a low dose of antigen given 2-25 d before (17). Furthermore, inadvertent vaccination of humans with trace amounts of serogroup C MPV has resulted in a very poor response to subsequent optimal immunizing doses of serogroup C anti-

gen (20). All of this experience has justifiably resulted in extreme caution regarding recommendations for giving these vaccines to pregnant women.

Our study shows that children born to mothers vaccinated during gestation, regardless of the trimester of vaccination, were not immunotolerant to group A and C vaccine at 6 mo of age. Whether this reflects the inability of the polysaccharide to reach the fetus, rather than inability of the polysaccharide to induce immune tolerance, is a matter of speculation.

More than 90% of the children in this study responded to vaccinations with a mixture of 50 μg of serogroup C and 25 μg of serogroup A MPV. The proportion of children responding and the magnitude of their response are consistent with other studies of these vaccines in infants (14, 21, 22). In addition, the response to the vaccine was the same in the study populations as in the controls.

Previous studies have shown that antimeningococcal immunoglobulin (G) bactericidal antibody is present in >50% of newborns, usually equal to the level found in maternal serum (23). Additionally, the antibody levels decline during the first year, to minimum levels between 6 and 12 mo of age (23).

A recent study of serogroup A MPV in Finland (14)

TABLE III
Meningococcal Serogroup C Polysaccharide Antibody Levels in Serum of Gravid Mothers and their Infants in Amapa, Brazil, 1974-75

Popu- lation	<i>n</i>	Geometric mean level	95% CI	<i>n</i>	Mean fold change	95% CI
		μg Ab/ml				
G ₁	22	0.48	(0.29-0.79)	22	11.0	(6.23-19.5)
G ₂	47	5.66	(4.05-7.92)	47	0.53	(0.43-0.67)
C	47	2.94	(1.92-4.49)	36	0.11	(0.08-0.16)
I ₃	36	0.30	(0.21-0.42)	27	0.54	(0.37-0.73)
I ₆₋₈	27	0.16	(0.12-0.21)	27	6.2	(4.6-8.4)
I _{pv}	27	1.02	(0.82-1.26)			

See Table I for abbreviations.

concluded that (a) the vaccine protects children 3 mo or more of age from illness caused by group A meningococcus (though specific efficacy was not measured); (b) perhaps as little as 2 $\mu\text{g}/\text{ml}$ may be protective; and (c) children aged 3 mo and older can attain this level after primary vaccination with a booster in the younger infants. Other studies suggest that vaccination before 6 mo of age with serogroup A MPV does not elicit a response, probably because of maternal IgG (22).

In our study, the antibody levels at age 3 mo in children whose mothers were vaccinated during pregnancy were of the same magnitude as the levels attained after vaccination at age 6–8 mo, despite the fact that antibody levels declined >50% from 3 to 6 mo of age. Vaccination of pregnant women, therefore, gives a high antibody level in the newborn that is sustained at levels which may be protective up to and perhaps beyond 3 mo of age. Further, such levels can be reattained and probably sustained throughout most of the first year of life by vaccination at 6 mo of age.

In the face of a meningococcal epidemic it is very desirable to be able to vaccinate the entire population. Indeed, as in Brazil, it is not possible to avoid vaccination of women in early pregnancy. Our study leads us to conclude that precautions against vaccination of pregnant women with licensed meningococcal polysaccharide vaccines during an epidemic should be lifted.

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