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Immunogenicity of 2 Serogroup B Outer-Membrane Protein Meningococcal Vaccines

A Randomized Controlled Trial in Chile

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Context Meningococcal disease occurs worldwide, and serogroup B disease accounts for a large proportion of cases. Although persons younger than 4 years are at greatest risk for serogroup B meningococcal disease, vaccine efficacy has not been demonstrated in this age group.

Objective To evaluate serum bactericidal activity (SBA) against homologous vaccine type strains and a heterologous Chilean epidemic strain of *Neisseria meningitidis* as a potential correlate for vaccine efficacy.

Design Double-blind, randomized controlled trial conducted between March 14 and July 20, 1994. All blood samples were taken by December 1994.

Setting Santiago, Chile, where a clonal serogroup B meningococcal disease epidemic began in 1993.

Participants Infants younger than 1 year (n = 187), children aged 2 to 4 years (n = 183), and adults aged 17 to 30 years (n = 173).

Intervention Participants received 3 doses of outer-membrane protein (OMP) meningococcal vaccine developed in either Cuba or Norway or a control vaccine, with each dose given 2 months apart. Blood samples were obtained at baseline, prior to dose 3, and at 4 to 6 weeks after dose 3.

Main Outcome Measure Immune response, defined as a 4-fold or greater rise in SBA titer 4 to 6 weeks after dose 3 compared with prevaccination titer.

Results Children and adult recipients of either meningococcal vaccine were more likely than controls to develop an immune response to the heterologous epidemic strain. After 3 doses of vaccine, 31% to 35% of children responded to the vaccine vs 5% to placebo; 37% to 60% of adults responded to vaccine vs 4% to placebo ($P<.05$ vs control for all). Infants, however, did not respond. In contrast, against homologous vaccine type strains, the response rate was 67% or higher among children and adults and 90% or higher among infants ($P<.001$ vs control for all). Subsequent SBA against 7 isogenic homologous target strains identified class 1 OMP as the immunodominant antigen.

Conclusions These data suggest that neither serogroup B OMP meningococcal vaccine would confer protection during a heterologous epidemic. However, epidemic strain–specific vaccines homologous for class 1 OMP are promising candidates for the control of epidemic serogroup B meningococcal disease.

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MENINGOCOCCAL DISEASE caused predominantly by *Neisseria meningitidis* serogroups A, B, and C occurs predominantly in young children and remains a substantial cause of morbidity and mortality worldwide.[1,2] In addition to causing endemic disease globally, meningococci, unlike other encapsulated bacteria, cause epidemics. Serogroup B epidemics, problematic in Norway and throughout much of Latin America in the 1980s and 1990s,[1] have recently emerged in New Zealand[3] and the United States.[4-6] Response to serogroup B epidemics, unlike serogroup A and C epidemics, is difficult because existing serogroup B vaccines have not been shown to be efficacious on an international scale.[7-10]

Quadrivalent meningococcal polysaccharide vaccine is efficacious against meningococcal disease caused by the A, C, W-135, and Y serogroups.[11-13] Serogroup B polysaccharide antigen, however, is poorly immunogenic in humans,[14,15] and the elicitation of antibodies to serogroup B polysaccharide antigen is of concern because this antigen is present in human neonatal neural tissue.[16,17] Therefore, alternative

See also pp 1493 and 1541 and Patient Page.

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strategies for serogroup B meningococcal vaccine development focusing on outer-membrane protein (OMP) antigens have been pursued.[17-19]

The serum bactericidal activity (SBA) assay has been shown to be the most important serologic correlate for vaccine efficacy.[20-22] Serum bactericidal activity has also become the primary serologic assay used to assess protective immunity stimulated by serogroup B meningococcal vaccine candidates.[10,23-30] Recent evidence suggests that class 1 OMP, encoded by the *porA* gene,[31] plays a major role in the SBA immune response following meningococcal carriage,[32] invasive disease,[33] and immunization with a serogroup B OMP meningococcal vaccine.[27-29]

During the mid-1980s and 1990s, the city of Iquique, Chile, experienced high incidence rates (20-35 per 100 000) of serogroup B meningococcal disease.[10] In 1993, a sharp increase in incidence (5.9 per 100 000) was recognized in metropolitan Santiago, Chile; more than 60% of cases occurred among children younger than 5 years.[34] The predominant serogroup B strain in Santiago was identical to the strain causing endemic disease in Iquique. To control the expanding Chilean epidemic, 2 OMP-based vaccines against serogroup B meningococcal disease, one produced by the Finlay Institute (FI) in Havana, Cuba, and another by the National Institute of Public Health (NIPH) in Oslo, Norway, were considered for widespread vaccination. Vaccine efficacy had been demonstrated among children (age range, 10-16 years) in double-blind, randomized controlled trials using 2-dose regimens of the FI-produced vaccine in Cuba and the NIPH-produced vaccine in Norway (estimated vaccine efficacy, 83% after 16 months and 57% after 29 months, respectively).[7,8] However, vaccine efficacy was not evaluated in younger children in these initial trials. In 1989 and 1990, the FI-produced vaccine was used to control a serogroup B meningococcal epidemic in São Paulo, Brazil; in a 2-dose regimen, vaccine efficacy was not demonstrated among children younger than 4 years.[9]

METHODS

Study Design

We conducted a prospective, double-blind, randomized controlled comparison trial of immunogenicity and reactogenicity elicited by 2 serogroup B OMP meningococcal vaccines among 3 age groups of Santiago residents, including infants (younger than 1 year), children (aged 2-4 years), and adults (aged 17-30 years). Infants and children were recruited from among healthy Consultorio Maipú clinic attendees and adults from San José Hospital staff. Sample sizes were designed to include 165 participants per age group, with one third of the participants in each age group randomized to receive the FI-produced vaccine, the NIPH-produced vaccine, or a control vaccine. In each age group, sequentially enrolled subjects were assigned 1 of 6 unique study group numbers. Two numbers were randomly assigned to each of the 3 possible vaccine groups. With the exception of 1 staff member assigned to draw vaccines, all investigators and study participants were blinded to vaccine study group numbers until completion of the study.

Before enrollment, written informed consent was obtained from parents of participating children and from adult study participants, as approved by the Chilean Ministry of Health and the Human Subjects Protection Institutional Review Board of the Centers for Disease Control and Prevention (CDC).

Vaccines and Clinical Specimens

The FI-produced vaccine consisted of lipooligosaccharide-reduced outer membrane vesicles from an epidemic Cuban strain of *N meningitidis* (CU385, B:4:P1.15); each dose contained 50 µg of OMP and 50 µg of serogroup C meningococcal polysaccharide.[8] The NIPH-produced vaccine consisted of lipooligosaccharide-reduced outer-membrane vesicles from a Norwegian epidemic strain of *N meningitidis* (44/76, B:15:P1.7,16); each dose contained 25 µg of OMP, with no detectable meningococcal polysaccharide.[7,35] Both vaccines present their partially purified OMP as proteoliposome vesicles adsorbed to aluminum hydroxide. Vaccines were provided by their respective manufacturers to the Chilean Ministry of Health and stored at 4°C until the day of vaccination.

Vaccines were administered intramuscularly as a 3-dose regimen, with each dose given 2 months apart. Infant and child control groups received a 3-dose series of a licensed *Haemophilus influenzae* type b (Hib) polyribosylribitol phosphate tetanus conjugate vaccine (Pasteur Merieux, Paris, France); adult controls received 3 doses of aluminum hydroxide adjuvant dissolved in solvent. Following unblinding at the completion of the study, Hib vaccine was offered to all infants and children who had received a serogroup B meningococcal vaccine.

Blood samples were obtained from each study participant prior to vaccination, prior to dose 3, and approximately 4 to 6 weeks following the third dose of vaccine.

Immunogenicity

Serum bactericidal activity assays were conducted by standard methods.[23,30] A vaccine response was defined as a 4-fold or greater rise in SBA antibody titer compared with prevaccination titer; no response was defined as less than a 4-fold rise in titer.

All *N meningitidis* target strains were immunologically classified by serogroup (capsular polysaccharide), serotype (class 2 or 3 OMP), subtype (class 1 OMP), and immunotype (lipooligosaccharide) using standard nomenclature (serogroup, serotype, subtype, and immunotype, respectively, separated by colons).[36] In addition, DNA sequence data for *porA* gene variable regions 1 and 2 are available in the GenBank for the Chilean epidemic strain CH539 (AF051536), FI-produced vaccine type strain CU385 (U92935), and NIPH-produced vaccine type strain 44/76 (X52995). Quality control of target strains was conducted periodically throughout laboratory testing by monoclonal antibody reactivity.[36]

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Three serogroup B *N meningitidis* strains were used in the testing of serum samples prior to the unblinding of study group numbers: the Chilean epidemic strain (CH539, B:15:P1.3:L3,7,9; DNA sequence subtype P1.7^{h},3), the FI-produced vaccine type strain (CU385, B:4:P1.15:L3,7,9; DNA sequence subtype P1.19,15), and the NIPH-produced vaccine type strain (44/76, B:15:P1.7,16:L3,7,9; DNA sequence subtype P1.7,16). These 3 strains are members of a genetically distinct complex (enzyme type 5 [ET-5]) of *N meningitidis* clones.[37-39] Multilocus enzyme electrophoresis testing of these 3 strains gave identical results with a panel of 24 enzymes.[38]

Vaccine type strains were considered homologous during testing of serum samples from participants who were vaccinated with the vaccine based on that strain (eg, CU385 is homologous for a person vaccinated with the FI-produced vaccine). Other comparisons were considered heterologous (eg, CU385 and CH539 are heterologous for a participant vaccinated with the NIPH-produced vaccine; 44/76 and CH539 are heterologous for a participant vaccinated with the FI-produced vaccine). Because neither the FI-produced nor NIPH-produced vaccine is based on a Chilean epidemic strain, the Chilean strain was considered heterologous in all assays performed.

To identify possible immunodominant antigens responsible for homologous SBA, a set of 7 isogenic strains was constructed from the NIPH-produced vaccine type strain (44/76, B:15:P1.7,16); these strains appear to differ only in their OMP compositions.[28,29] Following unblinding of study group numbers, SBA assays were conducted on samples of infant serum obtained from recipients of NIPH-produced vaccine using the following 7 genetically manipulated serogroup B target strains: a class 1 OMP-deficient strain (B:15:-); a class 3 OMP-deficient strain (B:-:P1.7,16); and strains B:15:P1.5,2; B:15:P1.19,15; B:15:P1.7^{h},4; B:15:P1.12,13; and B:15:P1.5^{c},10.

All SBA assays using the Chilean epidemic strain and the 7 isogenic strains as target strains were performed at the CDC. Serum bactericidal activity assays using the vaccine type strains as target strains were performed both at the CDC and NIPH. Human complement lots used at the CDC (lot 1-27-93) and the NIPH (lot HH) were shown to be comparable; both lots lacked SBA against study target strains. Results were highly concordant between the 2 laboratories.

Table 1. Characteristics of Participants by Study Age Group and Vaccine Received*

Characteristics	Vaccine			*P* Value†
	FI-Produced	NIPH-Produced	Control	
	Infants (Aged <1 y)			
	(n = 62)	(n = 62)	(n = 63)	
Age, mean, mo	3.8	4.1	4.3	.33
Sex, female, %	55	57	59	.91
Time from sample 1 to sample 2, mean (range), d‡	110 (95-135)	110 (95-150)	110 (95-141)	>.99
Time from sample 1 to sample 3, mean (range), d‡	143 (88-184)	142 (101-182)	144 (117-174)	.88
	Children (Aged 2-4 y)			
	(n = 60)	(n = 61)	(n = 62)	
Age, mean, y	2.8	2.9	3.1	.71
Sex, female, %	47	40	45	.76
Time from sample 1 to sample 2, mean (range), d‡	113 (104-128)	113 (103-128)	113 (101-126)	.63
Time from sample 1 to sample 3, mean (range), d‡	148 (117-167)	148 (118-167)	146 (119-163)	.68
	Adults (Aged 17-30 y)			
	(n = 59)	(n = 57)	(n = 57)	
Age, mean, y	22.9	23.7	23.2	.48
Sex, female, %	71	65	51	.07
Time from sample 1 to sample 2 mean (range), d‡	109 (103-123)	111 (103-133)	109 (75-120)	.94
Time from sample 1 to sample 3, mean (range), d‡	150 (135-211)	150 (138-186)	149 (135-176)	.49

*FI indicates Finlay Institute; NIPH, National Institute of Public Health. Infant and child controls received *Haemophilus influenzae* type b conjugate vaccine; adult controls received aluminum hydroxide adjuvant dissolved in solvent. All vaccines were administered intramuscularly as a 3-dose regimen, with each dose given 2 months apart.
†Data were calculated using the Kruskal-Wallis test or the χ^2 test.
‡Blood samples were obtained prior to vaccination (sample 1) and approximately 8 weeks following the second (sample 2) and 4 to 6 weeks following the third (sample 3) doses of vaccine.

Safety Monitoring

Reactogenicity was systematically monitored by a study nurse who conducted daily home visits following each dose of vaccine for a minimum of 7 days or until all vaccine-related adverse effects had resolved. Although clinical symptoms were quantified as being absent or present with moderate or severe interference with normal activity, they were analyzed as being either absent or present, regardless of level of normal activity interference.

Statistical Analysis

All data were entered into standardized electronic databases with Epi Info software; analyses were performed with Epi Info and SAS software.[40,41] The Kruskal-Wallis test and the χ^2 test were used to compare distributions of continuous variables and categorical variables, respectively.

RESULTS

Prevaccination blood samples were obtained from 187 infants, 183 children, and 173 adults. At enrollment, the mean ages of infants (4.1 months), children (3.0 years), and adults (23.3 years) were similar for FI-produced, NIPH-produced, and control vaccine recipients (TABLE 1). There was no significant difference in sex distribution or

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time from blood sample 1 to subsequent blood samples by age group among the 3 vaccine recipient groups (Table 1). Seven infants (4%), 18 children (10%), and 18 adults (10%) withdrew from the study (FIGURE). Inadequate volume of serum samples precluded some SBA assays in a small proportion of participants (TABLE 2). There was no significant difference in numbers withdrawn or excluded because of inadequate serum samples by age group among the 3 vaccine recipient groups ($P>.05$ for all).

Immunogenicity

Chilean Epidemic Strain. Among infants, there was no significant difference in SBA response to the heterologous Chilean epidemic target strain (CH539; B:15:P1.7^{h},3) between those vaccinated with either the FI-produced or NIPH-produced vaccine and those vaccinated with the Hib control vaccine (Table 2). Among both children and adults, recipients of either meningococcal vaccine were more likely than recipients of control vaccine to respond ($P<.002$ vs control for all). Only among adults was response between NIPH-produced vaccine recipients (blood sample 3, 60%) and FI-produced vaccine recipients (blood sample 3, 37%) significantly different ($P = .03$).

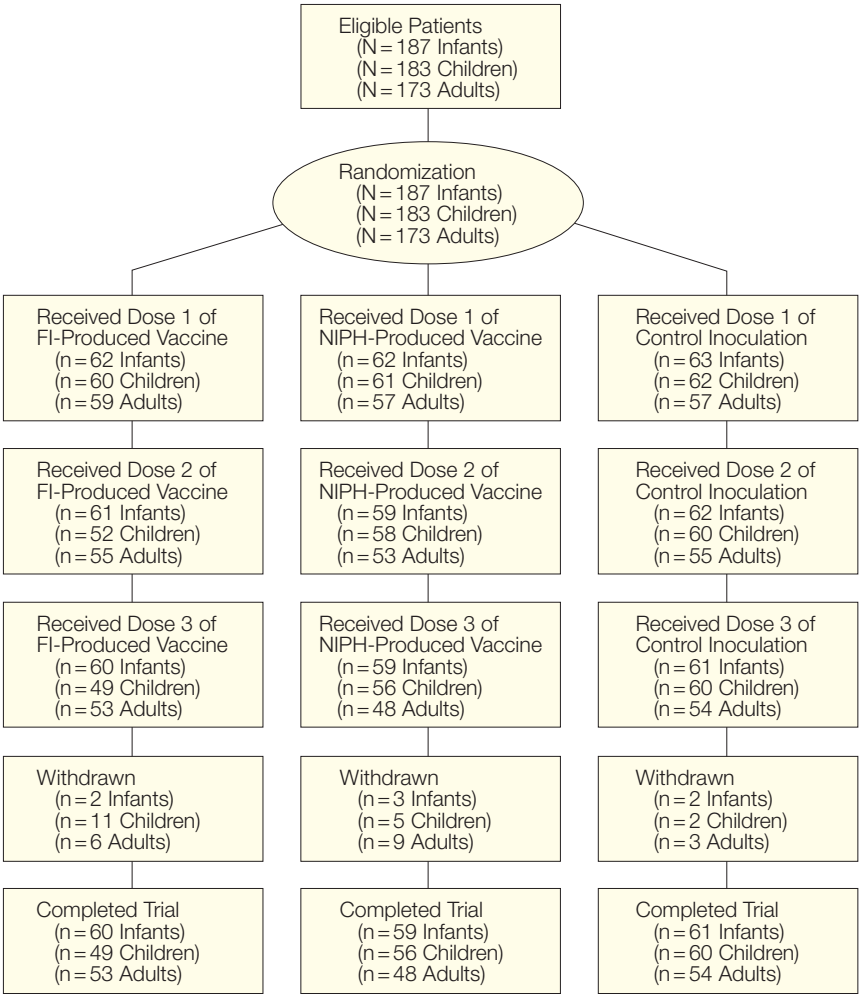
Vaccine Type Strains. For all 3 age groups, recipients of the FI-produced and NIPH-produced vaccines were more likely to mount antibody responses against their respective homologous vaccine type strains than were recipients of control vaccine ($P<.001$ vs control for all) (Table 2). For all 3 age groups, recipients of FI-produced vaccine were more likely than recipients of NIPH-produced vaccine to respond against the FI-produced vaccine type strain (blood sample 3 for infants and children, $P<.001$; blood sample 3 for adults, $P = .05$). For all 3 age groups, recipients of NIPH-produced vaccine were more likely than recipients of FI-produced vaccine to respond against the NIPH-produced vaccine type strain (blood sample 3, $P<.001$ for all).

Isogenic Strains. At blood sample 3, 52 (98%) of 53 infants vaccinated with the NIPH-produced vaccine showed a 4-fold or greater rise in antibody titer against the homologous NIPH-produced vaccine type strain devoid of class 3 OMP. There was no SBA response in these same 53 serum samples against the homologous NIPH-produced vaccine type strain devoid of class 1 OMP, except 1 sample that had low titer against several heterologous strains. Serum samples from the 14 recipients of NIPH-produced vaccine who had the highest titers against the homologous NIPH-produced vaccine type strain devoid of class 3 OMP were subsequently tested by SBA against strains expressing B:15:P1.5,2; B:15:P1.19,15; B:15:P1.7^{h},4; B:15:P1.12,13; and B:15:P1.5^{c},10. None of these 14 serum samples showed a response.

Reactogenicity

In general, infants, children, and adults vaccinated with either meningococcal vaccine had more pain, induration, and erythema at the site of injection than did control vaccine recipients (TABLE 3). However, more than 95% of subjects who reported symptoms stated

Figure. Study Profile for the Randomized Controlled Trial



FI indicates Finlay Institute; NIPH, National Institute of Public Health. Control infants and children were inoculated with *Haemophilus influenzae* type b vaccine; control adults were inoculated with aluminum hydroxide adjuvant in solvent.

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that their symptoms did not interfere or only moderately interfered with normal activities. When reported, severe interference with normal activity was more likely to occur among meningococcal vaccine recipients than control vaccine recipients, but interference lasted only 1 to 2 days and was not aggravated by subsequent doses of vaccine. No serious adverse events were attributed to vaccination.

COMMENT

This is, to our knowledge, the first prospective, double-blind, randomized controlled immunogenicity trial comparing proteoliposome OMP vesicle vaccines against serogroup B meningococcal disease among infants and young children. Both vaccines were found to be safe among Chilean infant, children, and adult vaccine recipients; local and systemic reactions were consistent with reactogenicity results from adult trials.[7,8,30]

In the present study, among children and adults who received the FI-produced and NIPH-produced vaccines, there was a significantly higher proportion of SBA responders against the heterologous Chilean target strain than among those who received the control vaccine. In addition, among children and adults, a third dose of either the FI-produced or NIPH-produced vaccine was associated with a higher proportion of SBA responders than 2 doses. However, among infants, there was no evidence of a significant increase in SBA titers in response to vaccination following 2-dose or 3-dose regimens with either vaccine against the Chilean epidemic strain. These data suggest that neither vaccine would confer sufficient protection during a heterologous epidemic.

Children and adult recipients of the FI-produced and NIPH-produced vaccines demonstrated SBA cross-reactivity to their respective heterologous vaccine strains. Surface components responsible for this heterologous bactericidal activity have not been identified but may include shared lipooligosaccharide immunotype (L3,7,9), Opa and Opc proteins, or other age-dependent bactericidal epitopes.[24,26,42]

Infant, children, and adult recipients of the FI-produced and NIPH-produced vaccines showed higher SBA titers against their respective homologous vaccine type strains than against heterologous target strains. Enhanced immunogenicity against homologous vaccine type strains is consistent with findings comparing SBA immunogenicity elicited by the FI-produced and NIPH-produced vaccines among 15- to 20-year-old subjects in Iceland.[30] However, because infants receiving both FI-produced and NIPH-produced vaccine in this study showed exceedingly low response rates to the heterologous Chilean epidemic strain, we were surprised to find that infant recipients of the FI-produced and NIPH-produced vaccines demonstrated such high response rates against their respective homologous vaccine type strains.

Of note, the magnitude of homologous SBA response was similar across all

Table 2. Percentage of SBA Responders by Target Strain, Number of Vaccine Doses Received, Vaccine Group, and Age Group*

No. of Vaccine Doses Received†	SBA Responders (Control Responders), %‡					
	FI-Produced Vaccine Group			NIPH-Produced Vaccine Group		
	Infants	Children	Adults	Infants	Children	Adults
			CH539			
	n = 52 (n = 55)	n = 49 (n = 57)	n = 52 (n = 52)	n = 52 (n = 55)	n = 55 (n = 57)	n = 51 (n = 52)
2	2 (2)	14 (2)§	27 (2)‖	6 (2)	22 (2)§	49 (2)‖
3	10 (6)	31 (5)§	37 (4)‖	12 (6)	35 (5)‖	60 (4)‖
			CU385			
	n = 50 (n = 52)	n = 46 (n = 55)	n = 53 (n = 53)	n = 50 (n = 52)	n = 51 (n = 55)	n = 48 (n = 53)
2	56 (0)‖	38 (2)‖	53 (6)‖	2 (0)	12 (2)	44 (6)‖
3	90 (0)‖	78 (2)‖	67 (8)‖	2 (0)	24 (2)§	46 (8)‖
			44/76-SL			
	n = 51 (n = 52)	n = 46 (n = 55)	n = 53 (n = 53)	n = 50 (n = 52)	n = 51 (n = 55)	n = 50 (n = 53)
2	16 (14)	22 (8)	42 (4)‖	96 (14)‖	75 (7)‖	88 (4)‖
3	31 (26)	41 (6)‖	56 (10)‖	98 (26)‖	98 (5)‖	96 (9)‖
			44/76-SL Without Class 3 OMP, n = 53			
3	. . .	. . .	. . .	98	. . .	. . .
			44/76-SL Without Class 1 OMP, n = 53			
3	. . .	. . .	. . .	0	. . .	. . .

*SBA indicates serum bactericidal activity; FI, Finlay Institute; NIPH, National Institute of Public Health; CH539, 1993 Chilean epidemic strain; CU385, FI-produced vaccine type strain; 44/76-SL, NIPH-produced vaccine type strain; OMP, outer-membrane protein; and ellipses, data not applicable.
†All vaccines were administered as a 3-dose regimen, with each dose given 2 months apart; blood samples were obtained prior to dose 1 and approximately 8 weeks following the second dose and 4 to 6 weeks following the third dose of vaccine.
‡A responder was defined as a person with a 4-fold or greater rise in antibody titer compared with prevaccination titer. Infant and child controls received *Haemophilus influenzae* type b conjugate vaccine; adult controls received aluminum hydroxide adjuvant dissolved in solvent.
§$P<.05$ vs control using the Yates corrected χ^2 test.
‖$P<.001$ vs control using the Yates corrected χ^2 test.

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3 age groups. The prevaccination geometric mean titers were essentially 2 or less across all 3 age groups in both homologous assays. Among FI-produced vaccine recipients, 67.9% of infants, 67.4% of children, and 67.3% of adults had a geometric mean SBA titer of 1:8 or greater following the third dose of vaccine (2-tailed Fisher exact test, $P>.99$). Similarly, among NIPH-produced vaccine recipients, 96.4% of infants, 100% of children, and 96.0% of adults had a geometric mean SBA titer of 1:8 or greater following the third dose of vaccine (2-tailed Fisher exact test, $P=.47$) (data available from the authors on request). Although SBA may be a less sensitive measure of protection than clinical vaccine efficacy, SBA is likely to be an acceptable serologic correlate for estimating the protective potential of OMP serogroup B meningococcal vaccines.[9,10,25,30]

In 1989 and 1990, the FI-produced vaccine was used during a homologous serogroup B meningococcal epidemic in São Paulo.[9] Age-dependent differences in vaccine efficacy among children aged 3 months to 6 years were observed. Vaccine efficacy was not demonstrated among children younger than 4 years following a 2-dose regimen, suggesting that the FI-produced vaccine did not confer protection against disease caused by the São Paulo strain in young children.[9] In our study, infant recipients of the FI-produced vaccine had nearly a doubling in their homologous SBA response rate following a third dose of vaccine suggesting that a 3-dose regimen may have had a positive effect on vaccine efficacy among chil-

Table 3. Frequency of Local and Systemic Reactions Among Participants by Study Age Group and Vaccine Group*

Symptoms and Signs	Dose 1 (Control Group), %			Dose 2 (Control Group), %			Dose 3 (Control Group), %		
	FI (Hib)	NIPH (Hib)	FI (NIPH)	FI (Hib)	NIPH (Hib)	FI (NIPH)	FI (Hib)	NIPH (Hib)	FI (NIPH)
Infants									
	n = 62 (n = 63)	n = 62 (n = 63)	n = 62 (n = 62)	n = 61 (n = 62)	n = 59 (n = 62)	n = 61 (n = 59)	n = 60 (n = 61)	n = 59 (n = 61)	n = 60 (n = 59)
Temperature ≥38°C	21 (13)	21 (13)	21 (21)	28 (23)	31 (23)	28 (31)	40 (26)	25 (26)	40 (25)
Vomiting	13 (11)	8 (11)	13 (8)	7 (10)	8 (10)	7 (8)	20 (3)†	8 (3)	20 (8)
Poor appetite	18 (11)	15 (11)	18 (15)	20 (18)	22 (18)	20 (22)	23 (8)†	24 (8)†	23 (24)
Irritability	56 (51)	58 (51)	56 (58)	44 (44)	47 (44)	44 (47)	55 (39)	46 (39)	55 (46)
Pain	26 (13)	15 (13)	26 (15)	18 (11)	22 (11)	18 (22)	23 (13)	7 (13)	23 (7)†
Induration	53 (11)‡	45 (11)‡	53 (45)	33 (11)†	34 (11)†	33 (34)	38 (3)‡	41 (3)‡	38 (41)
Erythema	40 (13)†	34 (13)†	40 (34)	33 (15)†	27 (15)	33 (27)	30 (10)†	32 (10)†	30 (32)
Children									
	FI (Hib) n = 60 (n = 62)	NIPH (Hib) n = 61 (n = 62)	FI (NIPH) n = 60 (n = 61)	FI (Hib) n = 52 (n = 60)	NIPH (Hib) n = 58 (n = 60)	FI (NIPH) n = 52 (n = 58)	FI (Hib) n = 49 (n = 60)	NIPH (Hib) n = 56 (n = 60)	FI (NIPH) n = 49 (n = 56)
Temperature ≥38°C	23 (19)	20 (19)	23 (20)	12 (20)	19 (20)	12 (19)	10 (27)	13 (27)	10 (13)
Vomiting	5 (3)	10 (3)	5 (10)	2 (7)	0 (7)	2 (0)	8 (3)	9 (3)	8 (9)
Poor appetite	28 (19)	21 (19)	28 (21)	19 (7)	10 (7)	19 (10)	12 (20)	14 (20)	12 (14)
Irritability	45 (39)	26 (39)	45 (26)†	48 (25)†	26 (25)	48 (26)†	35 (28)	32 (28)	35 (32)
Pain	45 (27)	20 (27)	45 (20)†	60 (42)	47 (42)	60 (47)	55 (25)†	46 (25)†	55 (46)
Induration	46 (21)†	36 (21)	46 (36)	40 (22)	43 (22)†	40 (43)	51 (15)‡	21 (15)	51 (21)†
Erythema	40 (19)†	33 (19)	40 (33)	23 (13)	26 (13)	23 (26)	35 (10)†	34 (10)†	35 (34)
Adults									
	FI (AlOH) n = 59 (n = 57)	NIPH (AlOH) n = 57 (n = 57)	FI (NIPH) n = 59 (n = 57)	FI (AlOH) n = 55 (n = 55)	NIPH (AlOH) n = 53 (n = 55)	FI (AlOH) n = 55 (n = 53)	FI (AlOH) n = 53 (n = 54)	NIPH (AlOH) n = 48 (n = 54)	FI (AlOH) n = 53 (n = 48)
Temperature ≥38°C	8 (4)	2 (4)	8 (2)	5 (4)	6 (4)	5 (6)	4 (6)	6 (6)	4 (6)
Headache	40 (37)	51 (37)	40 (51)	38 (31)	40 (31)	38 (40)	49 (26)†	35 (26)	49 (35)
Nausea	8 (11)	11 (11)	8 (11)	7 (7)	13 (7)	7 (13)	8 (13)	4 (13)	8 (4)
Myalgia	36 (26)	33 (26)	36 (33)	38 (31)	40 (31)	38 (40)	40 (17)†	38 (17)†	40 (38)
Pain	81 (44)‡	51 (44)	81 (51)†	76 (35)‡	68 (35)†	76 (68)	81 (31)‡	65 (31)†	81 (65)
Induration	49 (11)‡	32 (11)†	49 (32)	25 (18)	34 (18)	25 (34)	34 (7)†	35 (7)†	34 (35)
Erythema	22 (5)†	26 (5)†	22 (26)	27 (7)†	26 (7)†	27 (26)	23 (9)	19 (9)	23 (19)

*FI indicates Finlay Institute; NIPH, National Institute of Public Health. Infant and child age group controls received *Haemophilus influenzae* type b conjugate vaccine (Hib); adult controls received aluminum hydroxide adjuvant dissolved in solvent (AlOH).
†$P<.05$ vs control using the Yates corrected χ^2 test.
‡$P<.001$ vs control using the Yates corrected χ^2 test.

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dren vaccinated in São Paulo. Age-dependent vaccine efficacy was also shown for a serogroup B meningococcal vaccine produced by the Walter Reed Army Institute of Research, Washington, DC, and evaluated in Iquique in 1992.[10] This OMP vaccine based on a Chilean outbreak strain was not efficacious among children younger than 5 years. However, the Walter Reed Army Institute vaccine trial was administered as a 2-dose regimen, the vaccine did not present its OMPs as proteoliposome vesicles, and the vaccine contained only 0.1% lipopolysaccharide,[10] factors that may have contributed to vaccine failure in young children. Of note, in both the São Paulo and Iquique vaccine efficacy studies, poor SBA responses were associated with vaccine failure among children younger than 4 and 5 years, respectively, whereas higher SBA responses were associated with protection.[10,25]

In the current study, infant recipients of the NIPH-produced vaccine demonstrated a nearly uniform response (98%) against the isogenic, class 3 OMP–deficient, NIPH-produced vaccine type strain, strongly suggesting that class 1 OMP was the immunodominant antigen responsible for the elicited bactericidal immunogenicity. This finding, in conjunction with established serogroup B OMP vaccine efficacy estimates for older children and adults,[7-10] has profound implications for serogroup B vaccine development in response to epidemics. Although serogroup B epidemics are seasonal, they generally persist in the affected population for several years to decades.[3,5,7-10,43] This persistence, however unfortunate, provides OMP vaccine producers ample time to develop and rapidly produce an epidemic strain-specific vaccine following the careful selection of a vaccine type strain. This strategy is being actively pursued in New Zealand in response to a highly clonal epidemic.

Class 1 OMP is conventionally classified by using serosubtyping methods that characterize the *porA* OMP variable region epitopes with monoclonal antibodies.[44] DNA sequence data suggest that the current panel of serosubtype-defining monoclonal antibodies underestimates *porA* variable region variability.[32,45-49] Because minor changes in the variable region can dramatically alter immune recognition,[50] DNA sequencing of a representative sample of epidemic serogroup B strains is imperative for the selection of an epidemic vaccine type strain. Although a recent study found the *porA* gene to be stable for up to 30 weeks in persons with prolonged nasopharyngeal carriage,[32] some evidence suggests that the *porA* gene may not be stable over a period of decades.[48] Therefore, DNA sequencing of a representative sample of epidemic strains throughout the epidemic period may also be important.

Endemic meningococcal disease occurs worldwide.[2] Serogroup B accounts for nearly half of the 2600 endemic cases that occur annually in the United States[51] and two thirds of the 1800 endemic cases of meningoccal disease reported in England and Wales.[52] Laboratory-based surveillance for *N meningitidis* is a reliable method of identifying and monitoring class 1 OMP antigens (and the stability of the *porA* gene) of circulating strains over time.[51-53] In the United States, a limited number of class 1 proteins represent more than three fourths of class 1 proteins expressed by endemic serogroup B isolates, suggesting that an efficacious, multivalent class 1 OMP vaccine could prevent endemic meningococcal disease. However, DNA sequencing of these strains will be necessary to evaluate *porA* variable region variability.[54] A hexavalent, serogroup B class 1 OMP meningococcal vaccine has been developed[28,29] and is being tested in immunogenicity trials in the United Kingdom.[55] Further research and development of multivalent serogroup B meningococcal vaccines based on highly endemic and epidemic strain-specific class 1 OMP antigens is warranted.

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