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Safety and Immunogenicity of 26-Valent Group A *Streptococcus* Vaccine in Healthy Adult Volunteers

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(See the editorial commentary by Madoff on pages 1123–4)

Background. Group A *streptococcus* (GAS) causes illness ranging from uncomplicated pharyngitis to life-threatening necrotizing fasciitis, toxic shock, and rheumatic fever. Attempts to develop an M protein–based vaccine have been hindered by the fact that some M proteins elicit both protective antibodies and antibodies that cross-react with human tissues. New molecular techniques have allowed the previous obstacles to be largely overcome.

Methods. The vaccine is comprised of 4 recombinant proteins adsorbed to aluminum hydroxide that contain N-terminal peptides from streptococcal protective antigen and M proteins of 26 common pharyngitis, invasive, and/or rheumatogenic serotypes. Thirty healthy adult subjects received intramuscular 26-valent GAS vaccine (400 μg) at 0, 1, and 4 months, with clinical and laboratory follow-up for safety and immunogenicity using assays for tissue cross-reactive antibodies, type-specific M antibodies to 27 vaccine antigens, and functional (opsonization) activity of M protein antibodies.

Results. The incidence of local reactogenicity was similar to that for other aluminum hydroxide–adsorbed vaccines in adults. No subject developed evidence of rheumatogenicity or nephritogenicity, and no induction of human tissue–reactive antibodies was detected. Overall, 26 of 27 antigenic peptides evoked a >4-fold increase in the geometric mean antibody titer over baseline. The mean $\log_2$ fold-increase in serum antibody titer ($\pm$ standard error of the mean) for all 27 antigens was 3.67 $\pm$ 0.21. A significant mean $\log_2$ reduction in streptococcal bacterial counts in serum samples obtained after immunization was seen in opsonization assays for all M serotypes.

Conclusions. On the basis of epidemiological data demonstrating that the majority of cases of pharyngitis, necrotizing fasciitis, and other invasive streptococcal infections are caused by a limited number of serotypes, this 26-valent vaccine could have significant impact on the overall burden of streptococcal disease.

Streptococcus pyogenes (group A *streptococcus* [GAS]) is an important human pathogen that causes an estimated 25–35 million infections per year in the United States [1, 2]. Although uncomplicated pharyngitis and skin and soft-tissue infections account for the majority of infections, the incidence of life-threatening illnesses, such as necrotizing fasciitis and toxic shock syndrome, is increasing [3, 4]. Uncomplicated infection can lead to serious sequelae, such as acute rheumatic fever and glomerulonephritis. Acute rheumatic fever continues to be a leading cause of heart disease worldwide, and its incidence has been increasing in North America [4–6].

The burden of illness attributable to GAS worldwide has stimulated vaccine development efforts dating back more than 8 decades [7, 8]. The surface M protein is the major virulence determinant and protective antigen of GAS [9]. In the immune host, M protein antibodies are opsonic and promote ingestion and killing of GAS by phagocytic cells [10]. Development of a GAS vaccine has been hindered by the fact that, although some M protein epitopes elicit type-specific protective antibodies, others can induce antibodies that cross-react with human heart, brain, kidney, or joint cartilage [11–14]. New molecular techniques and a better understanding of the biology of GAS have allowed the development of multivalent M protein–based vaccines that contain

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protective epitopes and exclude potentially harmful tissue cross-reactive epitopes.

The multivalent vaccine used in this study was designed to include protective epitopes from serotypes responsible for 85%–90% of cases of uncomplicated pharyngitis and serious, invasive disease [15, 16]. We present the results of the first phase I study of the safety and immunogenicity of a 26-valent plus streptococcal protective antigen (Spa) M protein–based recombinant vaccine.

PATIENTS, MATERIALS, AND METHODS

Vaccine. StreptAvax (ID Biomedical), a multivalent recombinant vaccine containing amino-terminal M protein fragments from 26 different serotypes of GAS, has been described elsewhere [17]. The vaccine contained 4 recombinant fusion proteins, each containing 6 or 7 N-terminal M peptides linked in tandem. Serotypes were chosen if they were known to be a common cause of uncomplicated pharyngitis, if they were commonly retrieved from normally sterile body sites in the ongoing Active Bacterial Core Surveillance Network, or if they were currently or historically considered "rheumatogenic" [15, 16, 18, 19]. The amino-terminal peptide fragment of Spa, a newly described surface antigen of GAS known to elicit opsonic antibodies, was also included as the 27th antigen [20]. The purified multivalent proteins (figure 1) were combined in equal amounts by weight and adsorbed to aluminum hydroxide to deliver 400 μg of protein and 375 μg of aluminum hydroxide in 0.5 mL.

Population. Written informed consent was obtained from all participants. The study was approved by the IWK Health Centre Research Ethics Board. Healthy adults aged 18–50 years were eligible for inclusion in the study if they were in good general health, as determined by history, findings of a physical examination, and the results of screening biochemical and hematological tests. Subjects were excluded if they had a history of or echocardiographic findings of valvular heart disease, previous endocarditis, congenital cardiac abnormality, other significant cardiac illness, or signs or symptoms suggestive of rheumatic fever. Exclusion criteria also included a family history of rheumatic fever or a personal history of acute renal failure, poststreptococcal glomerulonephritis, chorea, or intermittent polyarthritis or presence of serum cross-reactive antibodies, as determined by the findings of indirect immunofluorescence assays using frozen sections of human heart, kidney, cartilage, basal ganglia, and cerebral cortex.

Study design and procedures. This was a single-center, open-label, phase I trial. Subjects received an intramuscular deltoid injection of vaccine on study days 0, 30, and 120. Participants were monitored for 30 min after immunization for any immediate adverse events and by self-assessment for solicited vaccine reactions with use of a symptom diary for 14 days after immunization. A study nurse made 2 follow-up telephone calls to each subject at ~24 and ~72 h after immunization to ensure that significant reactions were not missed.

All subjects underwent a complete physical examination (including cardiac auscultation and neurological examination) at baseline and at the final visit 1 year after the first dose and underwent screening neurologic and cardiac examinations at 1, 2, and 4 weeks after each vaccine dose. Transthoracic echocardiogram and electrocardiogram were performed at baseline and 2 months after the third dose was administered and were reviewed by one of the study cardiologists for any abnormalities. Urinalysis was performed before each vaccine dose was administered and at 2 and 4 weeks after each dose was administered.

Blood samples were obtained at baseline, before, and at 2 and 4 weeks after each vaccine dose for measurement of serum biochemical and hematological parameters, cardiac troponin I

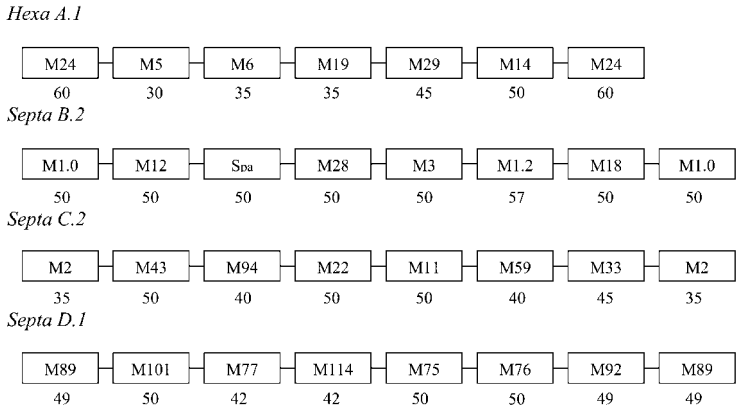

Figure 1. Schematic diagram of the 4 recombinant fusion proteins contained in the 26-valent M protein–based vaccine. The number of amino acids contained in each peptide is indicated below the M type designation.

level, C-reactive protein (CRP) level, and serum complement (C3) level. Screening for cross-reactive antibodies to human heart, kidney, cartilage, basal ganglia, and cerebral cortex samples was performed by immunofluorescence at baseline and at 2 weeks after the second and third vaccine doses were administered [12]. Serum samples were assayed for the presence of IgA, IgM, and IgG by ELISA using recombinant peptides copying each of the 27 components of the vaccine and bactericidal antibodies by indirect bactericidal assay [17, 21]. Results were expressed as the reduction in bacterial population doublings in serum samples obtained after immunization, compared with in serum samples obtained before immunization.

Data analysis and statistical considerations. Adverse events were tabulated by day and by severity; the maximum size and severity reported was used within each time interval. Solicited vaccine reactions were designated as mild (temperature, ⩾37.6°C and <38°C; injection site reaction, <10 mm in diameter; and symptom easily tolerated), moderate (temperature, ⩾38°C and <39°C; injection site reaction, ⩾10 mm and <50 mm in diameter; and symptom caused interference with usual activities), and severe (temperature, ⩾39°C; injection site reaction, ⩾50 mm in diameter; and symptom was incapacitating or required a medical visit). Unsolicited, spontaneous reports of other illnesses or injuries were collected and graded as mild, moderate, or severe. The number and proportion of subjects experiencing an adverse event was tabulated by observation period and severity, and exact 95% CIs were calculated.

Vaccine-induced seroresponse to individual M peptides was defined as a ⩾4-fold increase in antibody titer over the baseline value. Seroconversion was determined by statistical comparison with a healthy adult serum donor distribution. A collection of samples from 121 healthy adult donors were tested with use of the standardized assay format, and the "normal" mean OD value and SD were determined. The calculated cutoff value for seroconversion was greater than the "normal" mean plus 2 SDs. The proportion of subjects achieving seroresponse or seroconversion to each of the M peptides or Spa peptide contained in the vaccine was determined. Geometric mean antibody titers to each M protein type were compared before and after vaccination. For the indirect bactericidal assays, the mean $\log_2$ reduction in viable bacterial doublings was calculated for each M serotype. Because adults are not immunologically naive to these common organisms, some subjects' baseline serum samples demonstrated substantial levels of M serotype–specific inhibition of streptococcal replication even before receipt of the vaccine. When the count of viable bacteria was less than the input inoculum of viable bacteria after a 3-h period of incubation with prevaccination serum samples, the subject was deemed to have levels of preexisting opsonizing antibody that prevented the meaningful quantitation of further vaccine-induced enhancement, and his/her results for the serotype in question were not included in the calculation of means.

RESULTS

Demographic Data

Forty-one subjects were screened, and 30 met eligibility requirements and were enrolled in the study. All enrolled subjects received 3 vaccine doses and completed follow-up. The mean age of the subjects was 34.5 years (range, 19–50 years); 57% were female.

Adverse Events

Clinical adverse events. No adverse events were reported in the 30-min period after immunization. However, local injection-site reactions were reported commonly in the 14-day period after immunization (table 1). The most commonly reported injection-site reactions were tenderness and pain on movement of the arm, each reported by up to 70% of subjects and tending to become more frequent after later doses. The majority of injection-site reactions were mild, occurred within 48 h after injection, and were self-limited (median duration, <3 days). Reports of injection-site erythema, warmth, and tenderness increased in frequency after the second and/or third doses, compared with after the first dose ($P = .028$, $P = .05$, and $P = .011$, respectively). However, the mean severity of these reactions did not increase with increasing dose number.

The most frequent systemic complaints were headache (40%–53% of subjects) and tiredness (17%–23%). Up to 27% of subjects reported either nausea or vomiting following the receipt of 1 or more vaccine doses. Fever was uncommon. Sore joints and muscle aches were mild and uncommon, occurring in only 3%–7% and 13%–17% of subjects, respectively. These complaints were not associated with objective physical findings, and all were self-limited; none was suggestive of acute rheumatic fever. No vaccine-related serious adverse events or other adverse events suggestive of rheumatogenicity or nephritogenicity occurred. A single serious adverse event not related to the vaccine was reported (a 29-year-old subject experienced a traumatic ankle fracture 173 days after the first dose).

Laboratory abnormalities. No significant biochemical or hematological abnormalities were observed. No subject developed clinically significant proteinuria, hematuria, or RBC casts. There were no changes in electrocardiogram or echocardiogram findings that were suggestive of acute rheumatic fever.

Antibody Response

Antibody responses detected by ELISA. Before immunization, subjects were seropositive for a median of 9 (33.3%) of the 27 M peptides in the vaccine. Geometric mean antibody titers against all 26 M protein peptides and Spa increased significantly

Table 1. Adverse reactions among 30 healthy adult subjects in the 14-day period after immunization with 26-valent group A streptococcal vaccine, by dose.

	Dose 1		Dose 2		Dose 3	
Adverse event	No. of subjects	Percentage of subjects (95% CI)	No. of subjects	Percentage of subjects (95% CI)	No. of subjects	Percentage of subjects (95% CI)
Local reaction						
Redness						
Any	5	16.7 (5.6–34.7)	5	16.7 (5.6–34.7)	11	36.7 (19.9–56.1)
Severe	3	10.0 (2.1–26.5)	2	6.7 (0.8–22.1)	2	6.7 (0.8–22.1)
Swelling						
Any	2	6.7 (0.8–22.1)	3	10.0 (2.1–26.5)	7	23.3 (9.9–42.3)
Severe	1	3.3 (0.1–17.2)	0	0.0 (0.0–11.6)	0	0.0 (0.0–11.6)
Tenderness						
Any	11	36.7 (19.9–56.1)	21	70.0 (50.6–85.3)	20	66.7 (47.2–82.7)
Severe	0	0.0 (0.0–11.6)	1	3.3 (0.1–17.2)	0	0.0 (0.0–11.6)
Pain on movement						
Any	16	53.3 (34.3–71.7)	21	70.0 (50.6–85.3)	20	66.7 (47.2–82.7)
Severe	0	0.0 (0.0–11.6)	1	3.3 (0.1–17.2)	1	3.3 (0.1–17.2)
Elevated injection site temperature						
Any	4	13.3 (3.8–30.7)	8	26.7 (12.3–45.9)	10	33.3 (17.3–52.8)
Severe	0	0.0 (0.0–11.6)	0	0.0 (0.0–11.6)	0	0.0 (0.0–11.6)
All local reactions						
Any	19	63.3 (43.9–80.1	23	76.7 (57.7–90.1)	24	80.0 (61.4–92.3)
Severe	3	10.0 (2.1–26.5)	2	6.7 (0.8–22.1)	2	6.7 (0.8–22.1)
Systemic reaction						
General muscle aches						
Any	4	13.3 (3.8–30.7)	5	16.7 (5.6–34.7)	4	13.3 (3.8–30.7)
Severe	0	0.0 (0.0–11.6)	0	0.0 (0.0–11.6)	0	0.0 (0.0–11.6)
Sore/swollen joints						
Any	2	6.7 (0.8–22.1)	2	6.7 (0.8–22.1)	1	3.3 (0.1–17.2)
Severe	0	0.0 (0.0–11.6)	0	0.0 (0.0–11.6)	0	0.0 (0.0–11.6)
Fever						
Any[a]	3	10.0 (3.8–30.7)	1	3.3 (0.1–17.2)	2	6.7 (0.8–22.1)
Severe[b]	0	0.0 (0.0–11.6)	1	3.3 (0.1–17.2)	0	0.0 (0.0–11.6)
Chills						
Any	2	6.7 (0.8–22.1)	5	16.7 (5.6–34.7)	4	13.3 (3.8–30.7)
Severe	0	0.0 (0.0–11.6)	1	3.3 (0.1–17.2)	1	3.3 (0.1–17.2)
Headache						
Any	16	53.3 (34.3–71.7)	15	50.0 (31.3–68.7)	12	40.0 (22.7–59.4)
Severe	3	10.0 (2.1–26.5)	1	3.3 (0.1–17.2)	0	0.0 (0.0–11.6)
Nausea						
Any	8	26.7 (12.3–45.9)	6	20.0 (7.7–38.6)	4	13.3 (3.8–30.7)
Severe	3	10.0 (2.1–26.5)	1	3.3 (0.1–17.2)	0	0.0 (0.0–11.6)
Vomiting						
Any	2	6.7 (0.8–22.1)	0	0.0 (0.0–11.6)	0	0.0 (0.0–11.6)
Severe	2	6.7 (0.8–22.1)	0	0.0 (0.0–11.6)	0	0.0 (0.0–11.6)
Diarrhea						
Any	5	16.7 (5.6–34.7)	7	23.3 (9.9–42.3)	2	6.7 (0.8–22.1)
Severe	0	0.0 (0.0–11.6)	0	0.0 (0.0–11.6)	0	0.0 (0.0–11.6)
Tiredness						
Any	6	20.0 (7.7–38.6)	7	23.3 (9.9–42.3)	5	16.7 (5.6–34.7)
Severe	0	0.0 (0.0–11.6)	1	3.3 (0.1–17.2)	1	3.3 (0.1–17.2)
All systemic reactions						
Any	20	66.7 (47.2–82.7)	18	60.0 (40.6–77.3)	16	53.3 (34.3–71.7)
Severe	4	13.3 (3.8–30.7)	2	6.7 (0.8–22.1)	2	6.7 (0.8–22.1)

[a] Temperature, ⩾37.6°C.
[b] Temperature, ⩾39°C.

Table 2. Antibody response to 26 M protein antigens and streptococcal protective antigen (Spa) before immunization and after administration of 3 doses of 26-valent group A streptococcal vaccine in healthy adults.

Peptide	Geometric mean antibody titer (95% CI)		
	Before immunization (study day 0)	After dose 3	
		Study day 134	Study day 360
M24	53.6 (48.3–59.5)	712.7 (449.3–1131)	95.3 (65.7–138.3)
M5	104.7 (60.3–181.9)	552.8 (283.3–1079)	115.4 (62.3–213.7)
M6	95.5 (55.2–165.1)	381.9 (180.3–809)	130.1 (66.3–255.1)
M19	104.7 (81.3–135)	3200 (2233–4585)	293.2 (181.2–474.2)
M29	61.6 (51.3–73.8)	962.4 (524.1–1767)	146.6 (91.6–234.7)
M14	58.8 (44.2–78.2)	381.9 (209.6–696)	68.2 (51.7–90.1)
M1.0	112.2 (69.7–180.7)	1563 (824.9–2963)	266.4 (138.9–511.2)
M12	763.9 (463.7–1258)	7352 (4825–11202)	2018 (1182–3664)
Spa	54.8 (50.1–60)	1637 (1005–2667)	ND
M28	151.6 (89.7–256.2)	4222 (2668–6682)	450.8 (227.6–892.8)
M3	219.4 (133.3–361)	4126 (2706–6290)	429.7 (242.1–762.9)
M1.2	60.2 (48.6–74.5)	696.4 (416.1–1166)	146.6 (87.4–220.5)
M18	107.2 (80.8–142.3)	470.2 (274.5–805.4)	95.3 (69.1–131.6)
M2	79.4 (53–118.9)	800 (396–1616)	181.8 (93.2–354.3)
M43	56.1 (49.8–63.2)	289.5 (182.8–458.4)	66.6 (53.6–82.8)
M94	51.2 (48.8–53.6)	481.2 (302.1–766.6)	65 (53.7–78.8)
M22	459.5 (224.2–941.5)	4740 (2803–8013)	1201 (483.8–2982)
M11	117.6 (84.4–163.6)	1106 (665.6–1836)	118.2 (75.4–185.3)
M59	104.7 (65.4–167.7)	1676 (1047–2683)	177.5 (107.8–292.2)
M33	64.5 (50.7–82)	204.7 (112.5–372.3)	75.1 (49.6–113.6)
M89	91.2 (58.8–141.4)	1796 (1038–3108)	157.5 (96–258.3)
M101	104.7 (80.5–136.2)	1300 (807–2093)	136.4 (92.4–201.5)
M77	60.2 (46.7–77.5)	504 (279.4–909.1)	80.6 (59.8–108.8)
M114	69.1 (51.5–92.7)	1393 (775–2503)	173.3 (100.7–298.2)
M75	155.1 (99.6–241.6)	3592 (2573–5014)	242.1 (137.9–425.3)
M76	74.1 (58.7–93.4)	2851 (1952–4164)	112.7 (75.6–168)
M92	53.6 (48.3–59.5)	3676 (2575–5247)	136.4 (94.2–197.6)

NOTE. ND, not done.

after the third dose of vaccine was administered (table 2). At 1 year after administration of the third dose, geometric mean antibody titer remained significantly greater than at baseline for 15 (57.7%) of 26 M protein peptides. The mean $\log_2$ fold-increase ($\pm$SEM) in serum antibody titer for all 27 antigens was 3.67 $\pm$ 0.21 or 12.6 fold (95% CI, 9.42–16.89) (figure 2). Overall, 26 of the 27 antigenic peptides evoked a >4-fold geometric mean increase over baseline, and the increase was significant for every antigenic peptide ($P < .001$). Subjects experienced a >4-fold geometric mean increase in antibody titer to a median of 22 (81.5%) of 27 antigenic peptides in the vaccine and an increase in antibody titer to >2 SDs above a predefined nonimmune population mean to a median of 26 (96.3%) of 27 peptides (figure 3).

Opsonizing antibody responses detected in indirect bactericidal assay. Mean $\log_2$ reduction in bacterial counts in serum samples obtained after immunization, compared with in serum samples obtained before immunization, is illustrated for each M serotype in figure 4. For every M serotype, this mean value is significantly different from a hypothetical value of 0 (no vaccine effect), with $P < .035$ by 1-sample t test. For most M serotypes, 28–30 subjects contributed data to these means. However, in the case of M5, M6, and M12 bacteria (among the 18 most common GAS M types in Canada [22]), 10%–20% of subjects had preexisting antibodies in serum samples obtained at baseline that supported marked reduction (and often complete elimination) of the bacterial test inocula.

Tissue Cross-Reactive Antibody Assays

None of the serum samples obtained at baseline contained antibodies that cross-reacted with any of the human tissue samples tested, and none of the 30 subjects developed such antibodies after 2 or 3 doses of the vaccine.

DISCUSSION

The type-specificity of protective antibodies evoked by GAS, first defined by Rebecca Lancefield in 1919 [7], requires that effective vaccines be relatively complex to ensure broad protection against a large proportion of epidemiologically significant strains. Early attempts at the development of subunit vaccines containing M proteins extracted from viable streptococci were limited by toxicity associated with contamination of the vaccine by streptococcal extracellular toxins [23–25]. This toxicity was largely overcome when it was determined that dilute solutions of pepsin released significant amounts of M protein while leaving the cell wall relatively intact [26, 27]. Unfortunately, early laboratory studies with vaccines containing large peptide fragments of M proteins revealed that these potential vaccine candidates evoked not only opsonizing antibodies but also antibodies that cross-reacted with human tissues [11–14, 28]. This observation led to a series of studies to identify the structures of M proteins that induced protective and tissue–cross-reactive antibodies, in hopes of separating the 2 functional activities so that vaccines could be developed that did not elicit autoreactive immune responses [29–32]. Sequencing of M proteins revealed that the amino-terminal regions were hypervariable and accounted for type-specific immune responses [26, 29, 30, 33–37]. Because most of the tissue–cross-reactive epitopes of the M proteins were localized to repeating amino acid sequences distinct from the type-specific amino-terminal epitopes, it was then possible to construct multivalent, fusion protein vaccines that contained limited amino-terminal sequences derived from multiple M proteins designed to elicit opsonizing antibodies but not tissue–cross-reactive antibodies.

Recombinant technology has been used to construct multivalent vaccines containing 4, 6, and 8 M protein fragments linked in tandem [38–40]. Rabbits immunized with such tetravalent, hexavalent, and octavalent vaccines developed significant antibody levels and opsonic antibodies against all included

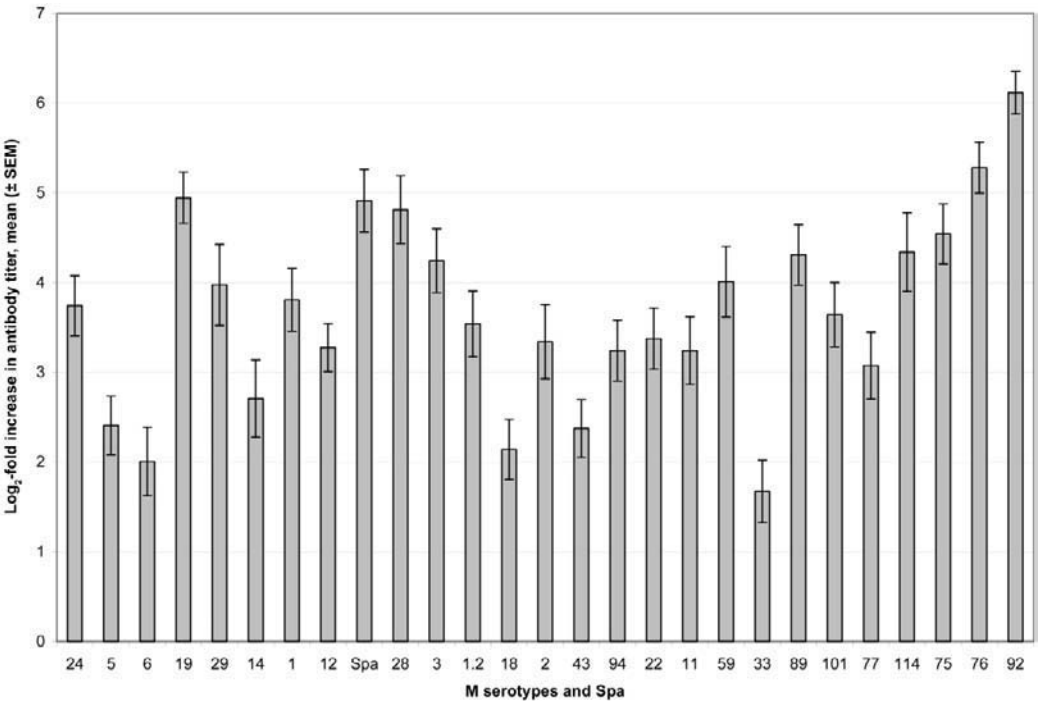

Figure 2. Mean (± SEM) $\log_2$-fold increase in M serotype–specific antibodies detected by ELISA after 3 doses of 26-valent group A streptococcal vaccine in healthy adults. Error bars indicate SEM. Spa, streptococcal protective antigen.

serotypes [38–40]. None of the animals developed human tissue–cross-reactive antibodies [38–40]. Recently, the hexavalent vaccine has been shown to be well tolerated and highly immunogenic in healthy adults [41].

These studies demonstrated the feasibility of evoking broadly protective immune responses against multiple serotypes of GAS using complex hybrid M protein fragments. On the basis of these observations, a 26-valent vaccine was constructed that was composed of 4 recombinant fusion proteins, each containing 6 or 7 type-specific M protein peptide antigens linked end-to-end in a tandem fashion. This vaccine was highly immunogenic in rabbits, eliciting a ⩾4-fold increase in antibody levels against 25 of the 26 vaccine serotypes [17]. Immune rabbit serum samples were broadly opsonic and were bacteri-

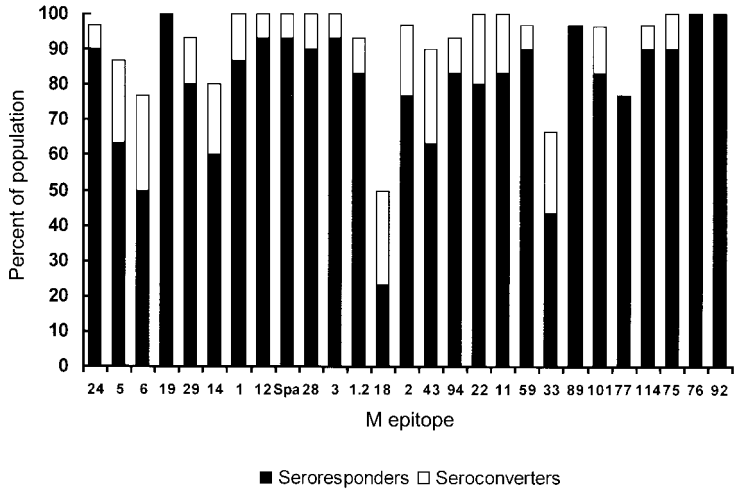

Figure 3. Percentage of subjects demonstrating seroconversion (seroconverters) or seroresponse (seroresponders) to each vaccine antigenic peptide. Seroresponse was defined as a ⩾4-fold increase in antibody titer over baseline. Seroconversion was defined as an increase in antibody titer to >2 SDs above the mean for a nonimmune population. Spa, streptococcal protective antigen.

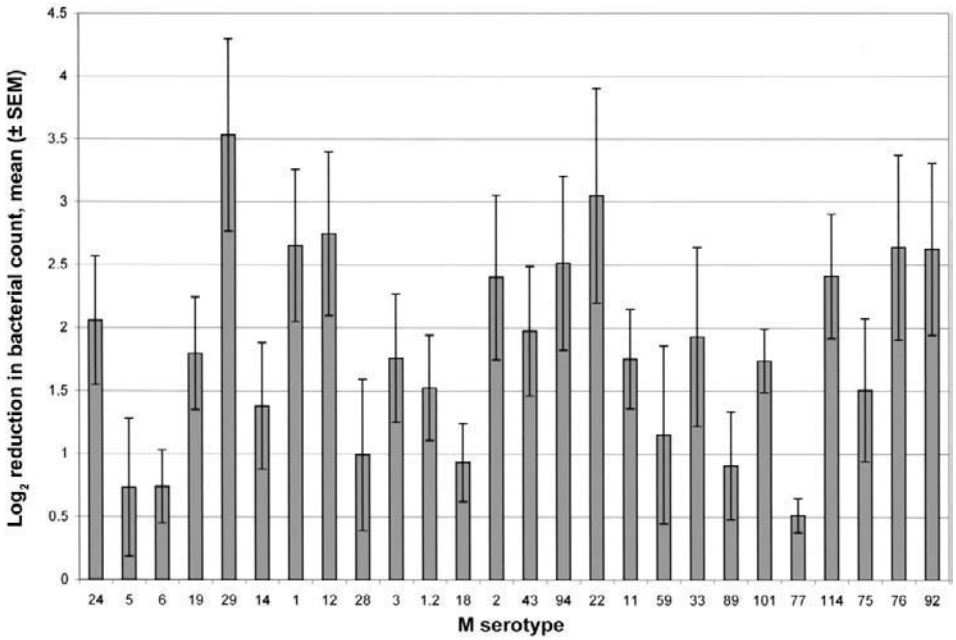

Figure 4. Mean $\log_2$ reduction in bacterial counts in serum samples obtained after immunization, compared with serum samples obtained before immunization, for each vaccine M serotype after incubation of each M serotype of group A *streptococcus* (GAS) for 3 h in the presence of serum samples obtained from subjects either before or after immunization. Streptococcal protective antigen (Spa), which is not an M serotyping GAS surface antigen but is, rather, an antigen common to several M serotypes, was excluded from the Lancefield indirect bactericidal assays. Error bars indicate SEM.

cidal against the majority of the 26 serotypes [17]. Development of tissue–cross-reactive antibodies was not detected [17].

The results of this phase I trial indicate that the 26-valent M protein–based recombinant vaccine was well tolerated and immunogenic. Adverse events were relatively common, but they tended to be mild and self-limited and were generally similar in character and frequency to those observed in our center (Clinical Trials Research Center, Dalhousie University; Halifax, Nova Scotia, Canada)for other aluminum-adjuvant adsorbed vaccines administered to adults [42, 43]. This trial utilized neither a placebo nor a comparator product, and a clear definition of the reaction spectrum attributable to the 26-valent vaccine must await such a controlled trial. Because the formation of antibodies that are cross-reactive with human tissues (and resultant acute rheumatic fever or other poststreptococcal syndromes) is the most significant potential adverse reaction to this vaccine, subjects underwent careful clinical and laboratory screening to detect these complications. No subject developed echocardiographic or electrocardiographic abnormalities suggestive of acute rheumatic fever. Serial urinalysis did not demonstrate the development of significant proteinuria, hematuria, or casts suggestive of glomerulonephritis. No subject manifested any clinical evidence of a poststreptococcal syndrome, and the development of antibodies cross-reactive with human tissues was not observed in any subject.

The vaccine was highly immunogenic, eliciting a 4-fold seroresponse to a median of 81.5% of antigenic peptides in individual subjects and statistically significant increases in antibody titer to every antigenic peptide on a population basis. There is not yet an established level of M antibody that correlates with protection against infection. However, on the basis of recently published epidemiologic data, immunization with this 26-valent M protein–based vaccine elicits seroresponse to 84.5% of isolates causing pharyngitis, 92.5% of isolates associated with rheumatic fever, and 87.6% of invasive disease isolates, including virtually 100% of strains associated with necrotizing fasciitis in the United States [15, 16, 18, 19].

Results of this phase I study support the ongoing evaluation of this recombinant, 26-valent M protein–based vaccine in human subjects. Although the vaccine appears to be well-tolerated, without clinical or laboratory evidence of the development of immunological complications, the study involved only 30 subjects. Safety data should be extended to ensure that the vaccine does not elicit tissue–cross-reactive antibodies that could lead to the development of rheumatic fever or glomerulonephritis before testing of this vaccine in children. Additional trials should include a control group to allow better assessment of injection site reactions. Phase II trials in adults are ongoing to increase the amount of safety data available before initiating trials in children.

On the basis of epidemiological data demonstrating that the majority of cases of pharyngitis, necrotizing fasciitis, and other

invasive streptococcal infections are caused by a limited number of serotypes, we believe that this 26-valent vaccine could have a significant impact on the overall burden of streptococcal disease. Ultimately, this vaccine may prove to be safe and effective and could potentially be administered to preschool-aged children to prevent the majority of cases of GAS pharyngitis and its complications, as well as invasive, life-threatening disease. If broadly implemented, the vaccine also has the potential to significantly decrease the incidence of acute rheumatic fever, the leading cause of heart disease worldwide.

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