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Safety and Immunogenicity of Group Y and Group W135 Meningococcal Capsular Polysaccharide Vaccines in Adults

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Serogroup Y and W135 *Neisseria meningitidis* capsular polysaccharide vaccines were tested as monovalent and divalent preparations in groups of 10 adult human volunteers at a dose of 50 (monovalent) or 100 μg (divalent) injected subcutaneously. Reactogenicity was low for the group Y vaccine and the group Y-W135 combined vaccine; 3 of 10 volunteers developed systemic reactions after group W135 vaccination. All three vaccines induced significant homologous and heterologous binding and bactericidal antibody. Except for group W135 bactericidal antibody, homologous responses exceeded heterologous responses, and divalent and monovalent vaccines induced equivalent homologous responses. Homologous bactericidal antibody responses were maintained for 4 weeks in 85% of group W135 vaccinates and in 100% of group Y vaccinates. Bactericidal antibody was induced in 11 of 11 group Y and 12 of 15 group W135 volunteers without preexisting respective bactericidal activities, regardless of which vaccine they received. For all three vaccines, antibody levels declined only slightly over 6 months. Prevaccination antibody levels positively affected postvaccination binding antibody levels, but not bactericidal levels.

Until the mid-1970s, serogroup Y and W135 strains of *Neisseria meningitidis* were of little epidemiological importance (8). Small waves of group Y disease were occasionally noted in military populations (20, 21, 29), but group W135 strains were rarely a cause of disease (9), and neither serogroup seemed to possess major epidemic potential (20). However, a wave of group W135 disease recently passed through Northern Europe, accounting for 10 to 15% of all cases in England, Scotland, and Belgium at its peak in 1975 (19, 32-34). The incidence of this serogroup as a major cause of disease in this country, first noted in military populations (19), appears to be accelerating (8, 14). In addition, group Y strains have steadily increased as a cause of endemic disease in the absence of discernible outbreaks (8). By 1978, the two groups together were responsible for 16% of all U.S. civilian meningococcal disease (7), one-half of all bacteremic cases in New York City (14), and 30% of all military cases. Among military populations, this trend has continued, with 50% of cases currently due to these two serogroups.

The emergence of group Y and group W135 *N. meningitidis* as real and fairly common causes of disease has emphasized the need to develop their capsular polysaccharides as potential vaccines, either alone or as components of a multivalent vaccine (8, 14). The two capsules are structurally similar, consisting of the identically linked copolymers of sialic acid and hexose, either glucose (group Y) or galactose (group W135) (3).

In the present paper, we report on the safety and immunogenicity of group Y and group W135 capsular polysaccharide vaccines in adult human volunteers.

MATERIALS AND METHODS

Vaccines. The capsular polysaccharides of *N. meningitidis* strains 80-Y and 22-W135, both from the collection of the Walter Reed Army Institute of Research, were prepared from 16-h liquid cultures by the method of Gotschlich et al. (16) and were bottled as individual (monovalent) vaccines and as a divalent combination vaccine containing equal proportions, by weight, of each polysaccharide.

General safety tests in mice and guinea pigs were performed as described in section 610.11 of the *Code of Federal Regulations* (12). The pyrogenicity of the vaccines in rabbits was investigated by testing serial dilutions to determine the largest nonpyrogenic dose. Tests were performed as described in section 610.13 (b) of the *Code of Federal Regulations* (12).

The carbohydrate content of each vaccine preparation was analyzed, quantitatively and qualitatively,

by gas-liquid chromatography (27). The polysaccharides were hydrolyzed with 3% methanolic HCl, *N*-acetylated with acetic anhydride, and derivatized to the trimethylsilyl esters before chromatographic analysis. Mannitol was added as an internal quantitative standard, and peaks were identified by cochromatography with authentic standards.

The protein content of lyophilized material was estimated by the Lowry technique (23), and nucleic acids were estimated by absorbance at 260 and 280 nm (22). Neither estimate was corrected for cation or moisture content. Molecular size was estimated by determination of the partition coefficient, K_d, of each vaccine preparation over Sepharose 4B (Pharmacia Fine Chemicals, Uppsala, Sweden) by the method of Wong et al. (31).

Volunteers. Adult volunteers were solicited from the staff of the Walter Reed Army Institute of Research. Groups of 10 volunteers each were injected with either 50 μg of one of the monovalent vaccines or 100 μg of the divalent vaccine (50 μg of each polysaccharide) subcutaneously in the deltoid region (total of 30 volunteers). Serum samples were obtained from each volunteer at the time of vaccination and at 2, 4, 8, and 26 weeks afterward. Posterior pharyngeal cultures for *N. meningitidis* were obtained at like intervals.

The median age of recipients was 33 years (range, 25 to 43 years) for the monovalent group Y vaccine, 36 years (range, 25 to 55 years) for the monovalent group W135 vaccine, and 32 years (range, 22 to 42 years) for the divalent vaccine.

Reactogenicity was evaluated by questioning each recipient 24 h after injection and by noting and measuring erythema or induration or both at the vaccination site. Each recipient's evaluation of the local reaction was given a numerical score according to the following criteria: 0, No noticeable pain or tenderness; 1, slight pain and tenderness, not noticeable at rest and easily ignored; 2, slight to moderate pain and tenderness, intermittently noticeable at rest, without interference with activities, considered a "mild" vaccine (less than influenza or typhoid); 3, moderate pain and tenderness intermittently bothersome at rest and requiring slight adjustment in activity, considered cause for complaining, but acceptable; 4, moderate to severe pain and tenderness which interfered with activities and which was noticeable during sleep or led to taking of analgesics, considered a painful vaccine on a par with typhoid.

Chills without fever and mild malaise or headache were considered evidence of minor systemic reactions. Fever >101°F (38.3°C) (self-measured orally 10 h after vaccination), chills, malaise, coryza, and myalgia with or without headache were considered evidence for a major systemic reaction.

Serology. Responses to the vaccines were assayed both in a radioactive antigen-binding assay (binding antibody) (5) and a standard bactericidal assay (bactericidal antibody) (1). Data for binding antibody are expressed as the antigen-binding capacity in nanograms of 50 μl of undiluted serum and were transformed ($\log_2$) for statistical analysis. For bactericidal antibody, data are expressed as the maximum $\log_2$ dilution of serum capable of lysing ≥50% of 2×10^3 organisms. A 2-$\log_2$ increase in titer was chosen as the minimal criterion for response.

RESULTS

Vaccines. Each of the three vaccines contained ≤1% protein and nucleic acids and was not toxic to mice or guinea pigs. Pyrogenicity data, in rabbits, are shown in Table 1. All three products were within the limits established for meningococcal vaccines (13). The K_d values for each vaccine and their carbohydrate contents are also shown in Table 1. The molar ratios of the individual carbohydrates were very similar to those expected from structural studies (3); all three vaccines were considerably larger than the minimal allowable size for group A or C polysaccharide vaccines (31).

Volunteers. Preimmunization levels of binding and bactericidal antibody were equivalent among each of the three groups of volunteers for both serogroups (P, 0.3 to 0.5; Kruskal-Wallis analysis of variance).

Reactogenicity of the vaccines paralleled pyrogenicity in rabbits (Table 2). Group Y vaccine, the least pyrogenic, produced minimal reactions, whereas group W135 vaccine was not only the most pyrogenic, but also was the most reacto-

TABLE 1. *Characterization of serogroup Y, W135, and Y-W135 combined vaccines*

Vaccine	Pyrogenicity[a] (μg/kg)	Molecular size[b] (%)	Composition of carbohydrate[c] (mol % of total residues detected)		
			Sialic acid	Glucose	Galactose
Y	2.50	68.2	49	51	
W135	0.25	81.1	48.2		52.8
Y-W135	0.50	83.4	46.2	23.6	29.8

[a] Maximum nonpyrogenic dose in micrograms per kilogram of body weight.

[b] Determined over Sepharose 4B, $K_d \leq 0.4$.

[c] Determined by quantitative gas-liquid chromatography.

TABLE 2. *Reactogenicity of serogroup Y, W135, and Y-W135 combined vaccines*

Vaccine	Mean score[a]	No. of vaccinates with:				
		Score of 4	Erythema	Induration	Minor systemic reaction	Major systemic reaction
Y	0.33	0	0	0	0	0
W135	2.0	2	4	4	2[b]	1[b]
Y-W135	2.1	0	4	1	0	0

[a] See the text for criteria of reactogenicity scoring.

[b] Systemic reactions were significantly more common among recipients of W135 vaccine alone than among recipients of the other two vaccines (P, 0.03; Fisher's exact test).

genic (P, 0.03; Fisher's exact test), producing a major systemic reaction consisting of fever to 102.6°F (39.2°C), headache, myalgia, moderately severe malaise, coryza, and chills, lasting 24 h, and two minor systemic reactions (one volunteer with headache alone and one with headache, mild malaise, restlessness during sleep, and chills without fever).

A single volunteer, vaccinated with group Y polysaccharide, was found to be a nasopharyngeal carrier of a group Y meningococcus at the time of vaccination. No other individuals carried group Y *N. meningitidis* at any time during the study, and none carried group W135 *N. meningitidis*. Serological data for the group Y carrier are shown below (see Fig. 1 to 4) but are excluded from statistical analyses.

Response. The ranges and geometric means of binding and bactericidal antibody levels at 0 and 4 weeks for all 30 volunteers are shown in Fig. 1 and 2, respectively. Values for the group Y carrier are boxed. All three vaccines induced significant binding and bactericidal antibody responses both to their homologous serogroup(s) and to the heterologous serogroup. However, only the bactericidal antibody response to group W135 was equivalent among the three vaccines (P, 0.3; one-way analysis of variance); binding antibody responses to both polysaccharides and bactericidal antibody responses to group Y were significantly higher after homologous vaccination than after heterologous vaccination (P, 0.02 to 0.0001; two-sample t-test). Homologous responses were equivalent after monovalent or divalent vaccination (P, 0.16 to 0.29; two-sample t-test).

Homologous lytic antibody responses of ≥ 2 $\log_2$ were maintained in 85% of those vaccinated with W135 polysaccharide, either alone or in combination with Y polysaccharide, and were maintained in 100% of those vaccinated with Y polysaccharide, either alone or in combination, at 4 weeks (Table 3). A heterologous response was induced in 30 to 70% of the volunteers. The sera of 11 of 29 volunteers (38%) were without detectable lytic activity against the standard group Y strain before vaccination (titer of <1 $\log_2$). All 11 volunteers developed bactericidal antibody which persisted for 6 months, regardless of which of the three vaccines they received. For the W135 strain, 15 of 29 volunteers (52%) were without detectable lytic activity before vaccination, and 3 failed to seroconvert after vaccination (1 with W135 polysaccharide and 2 with Y polysaccharide; Table 3).

Persistence of antibody is depicted in Fig. 3. Binding antibody remained constant over 6 months, whereas bactericidal antibody diminished by 1 to 2 $\log_2$ over the same period.

The effect of prevaccination antibody levels on response was opposite for binding and bactericidal antibody (Fig. 4). For group Y binding antibody, a positive correlation was found (P, 8×10^{-5}), with 60% of the increase in binding

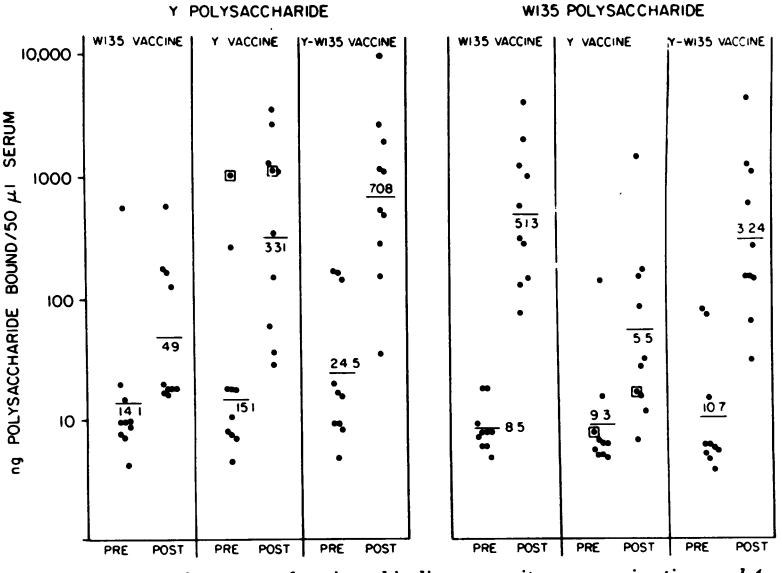

FIG. 1. *Ranges and geometric means of antigen-binding capacity, prevaccination and 4 weeks postvaccination, of sera from all 30 volunteers, arrayed according to vaccine received. Values for the group Y meningococcal carrier are boxed and deleted from calculation of the means. All responses were significant (P, 2×10^{-3} to 6×10^{-7}; paired t-test, one tail).*

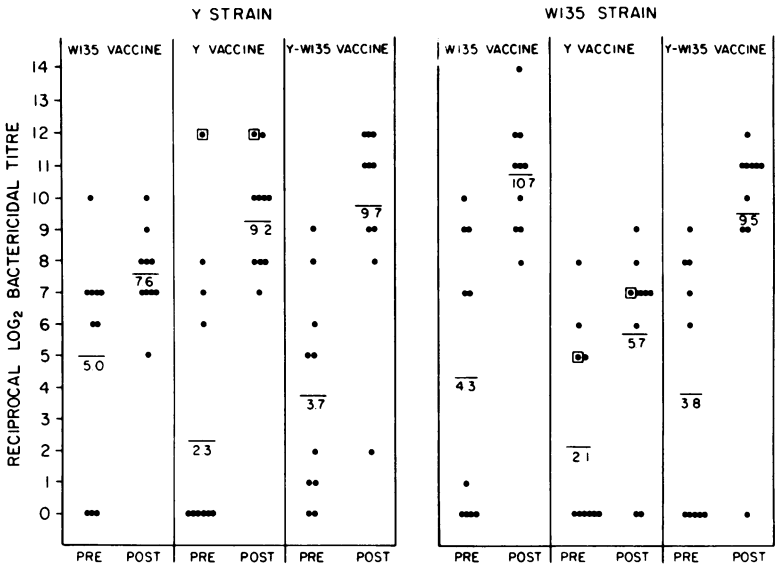

FIG. 2. *Ranges and geometric means of bactericidal antibody values, prevaccination and 4 weeks postvaccination, for all 30 volunteers, arrayed according to vaccine received. Values for the group Y meningococcal carrier are boxed and deleted from calculation of the means. All responses were significant (P, 3×10^{-2} to 4×10^{-5}; paired t-test, one tail).*

TABLE 3. *Immunological responses (bactericidal antibody) of volunteers vaccinated with group Y, group W135, or a combined Y-W135 vaccine*

Antigen	Wk	% Responding[a]			% Seronegative[b]		
		Y (n = 9)	W135 (n = 10)	Y-W135 (n = 10)	Y	W135	Y-W135
Y	0				67	30	20
	4	100	30	100	0	0	0
	26	89	25	90	0	0	0
W135	0				67	40	50
	4	71	90	80	22	0	10
	26	57	80	80	22	0	10

[a] Percentage with a $\geq$2-$\log_2$ increase in serum bactericidal antibody.
[b] Titer of bactericidal activity, <1 $\log_2$.

capacity accounted for by prevaccination levels. The correlation between pre- and postvaccination levels of W135 polysaccharide-binding antibody, although positive, was not significant (P, 0.13). For bactericidal antibody, on the other hand, an inverse correlation was found ($P < 10^{-6}$) with prevaccination titers predicting 75 to 85% of the response. Individuals developed a titer of approximately 10 $\log_2$ regardless of preexisting antibody. The net change in bactericidal titer was, therefore, much less for individuals with high preexisting levels than for those without.

DISCUSSION

The radioactive antigen-binding assay measures total antibody against the capsular polysaccharides themselves, without regard to its ability to initiate immune lysis. The bactericidal assay is a measure of the ability of induced antibody to initiate immune lysis of standard Walter Reed Army Institute of Research strains. As such, it measures immunoglobulin M (IgM) and complement-fixing IgG. The bactericidal assay is not antigen specific; it is assumed, however, that rises in bactericidal activity are a direct result of induced complement-fixing antibody against the capsular polysaccharides.

We conclude that both the group Y and group W135 capsular polysaccharides appear to be safe and are immunogenic for adult humans when administered alone or in combination at a dose of 50 μg; that these structurally similar polysaccharides are cross-immunogenic in humans and

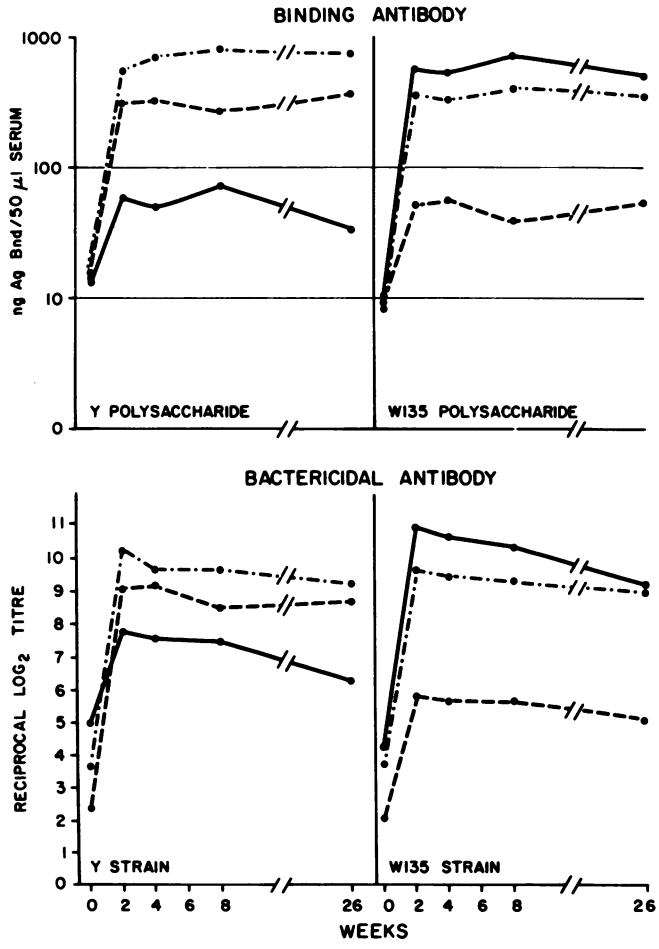

FIG. 3. *Geometric mean binding and bactericidal antibody levels by week after vaccination for each vaccine: group W135 (—); group Y (——); groups Y-W135 combined (——·——). Group Y meningococcal carrier was excluded.*

that combined administration provides the same immunological response as single vaccination; that induced antibody persists for over 6 months; that the levels of bactericidal antibody attained after vaccination are equivalent regardless of the levels of preexisting bactericidal antibody; and, hence, that >90% of seronegative individuals can be converted to seropositivity by a single dose of combined vaccine.

The rather high level of reactogenicity experienced with the group W135 vaccine, although consistent with its pyrogenicity in rabbits, is difficult to explain, since the same lot was less reactogenic when combined with the group Y polysaccharide and administered at the same dose. In contrast, three separate lots of group Y capsular polysaccharide vaccine were reported to be without significant reactogenicity (10); the administration of one of these lots as a component of a trivalent group ACY vaccine was associated with systemic reactions in 40% of recipients (11). Given the vagaries of reactogenicity of these polysaccharides in humans, the current standards for pyrogenicity in rabbits may not provide an adequate margin of safety.

Farquhar and colleagues reported that 80 of 86 (93.0%) and 20 of 23 (87%) adults responded with group Y bactericidal antibody after vaccination with monovalent group Y polysaccharide and trivalent group ACY polysaccharides, respectively (10, 11). Binding antibody data were not reported. The prevalence of seronegative individuals in these studies was higher, and the geometric mean titer achieved was lower than that among our volunteers. This may reflect a lower sensitivity of the assay used, rather than true population or vaccine differences. To our knowledge, data on the human immune response to group W135 polysaccharide vaccination have not been reported.

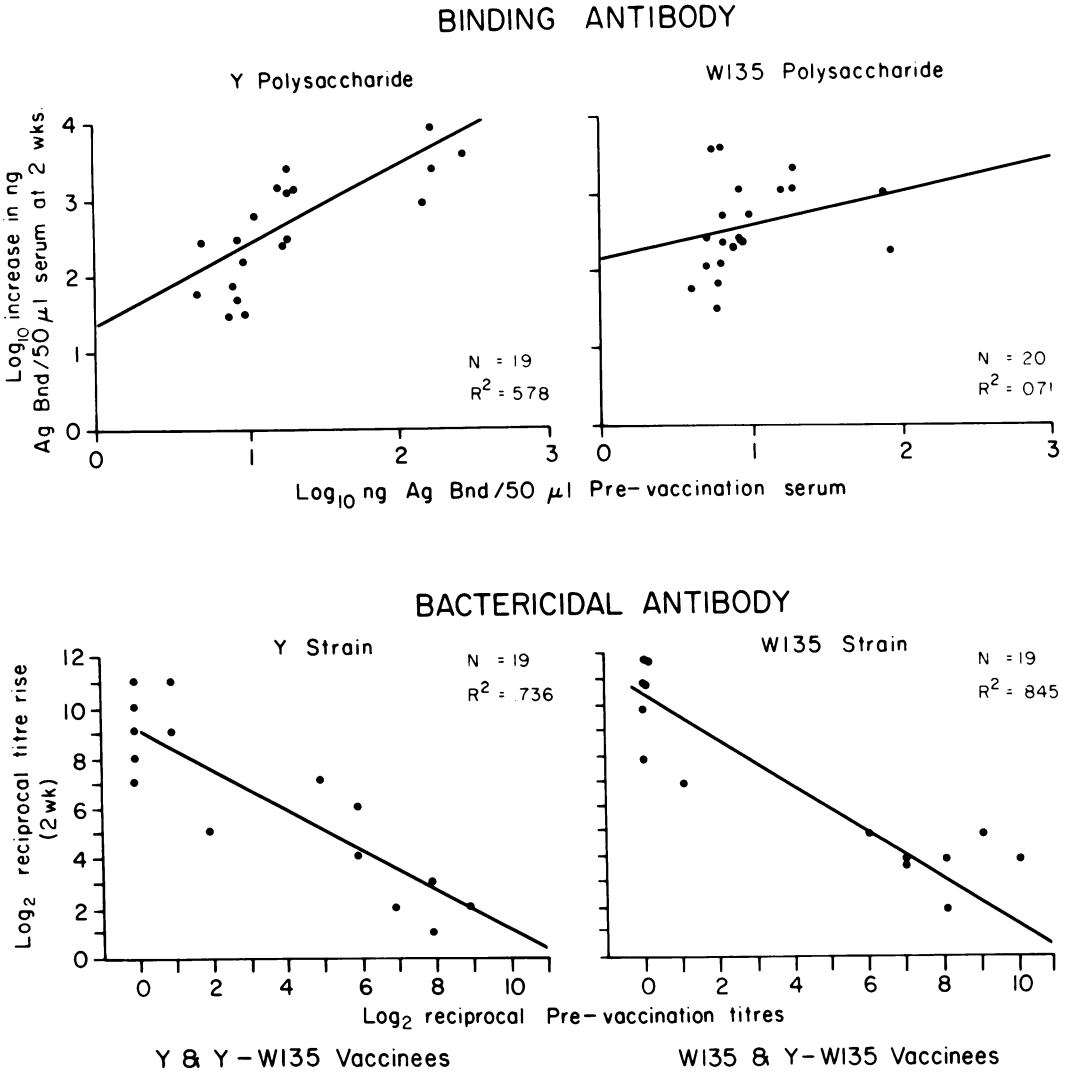

FIG. 4. *Effect of prevaccination antibody levels on binding and bactericidal antibody responses. For each assay, values for each of the 20 volunteers receiving group Y or group W135 polysaccharides, alone or in combination, were combined. Values for the group Y meningococcal carrier were deleted.*

Group A and C meningococcal capsular polysaccharide vaccines also induce both binding antibody and bactericidal antibody in adults (4, 6, 15). Group C antibody persists for 5 or more years as measured by both assays, with little, if any, decline in bactericidal antibody levels and a gradual decline in binding antibody after 1 year (6). Both vaccines effectively prevent disease in children and young adults, including military recruits (2, 24, 25, 30). The protection afforded by the group C vaccine is thought to persist for years, but its exact duration is not known (4). The protection provided by the group A vaccine is restricted to 1 year after the vaccination, although antibody levels persist beyond this time (30). Neither vaccine is optimally immunogenic in infants, although group A is marginally so, and may provide some protection to infants as young as 3 months (26). The minimal protective level of binding antibody has not been established for either polysaccharide (4); the presence of bactericidal antibody is thought to confer protection (18).

Based on the data reported here, the immunogenicity of the group Y and group W135 capsular polysaccharides appears similar to that of group A and C polysaccharides and distinctly different from that of the group B capsular pol-

ysaccharide, which, alone, is not immunogenic (35). Whether these polysaccharides will be immunogenic in infants or effective in preventing disease in any population must await further study.

Although the binding antibody response to these two polysaccharides appears open ended, there is an apparent ceiling to the bactericidal antibody response such that post-immunization levels of approximately 10 $\log_2$ are not exceeded. Since individuals whose preimmunization levels are at or near the ceiling level do not respond with an increase in bactericidal antibody, but do respond with a proportional increase in binding antibody, the incremental binding antibody must not participate in immune lysis. This discrepancy may reflect functional differences among immunoglobulin isotypes. IgA does not initiate immune lysis (17), and those IgG isotypes which activate complement poorly (IgG2 and IgG4) would be expected to initiate immune lysis poorly, if at all. Preferential induction of IgG2 has been suggested for other bacterial polysaccharide vaccines (28). Similarly, a switch from IgM, which is twice as effective as IgG in initiating immune lysis of group C *N. meningitidis* (18), to IgG, over time, may explain the early and slight decline in bactericidal antibody levels despite constant levels of binding antibody.

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