

## Control of Meningococcal Meningitis with Meningococcal Vaccines

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The development of effective meningococcal vaccines was based upon the finding that natural immunity to the meningococcus was directly correlated with serum bactericidal antibodies. Purified high molecular weight capsular polysaccharides of serogroups A and C meningococci stimulated the production of humoral antibodies which had group specific bactericidal activity. In controlled field trials in Army recruits, group C polysaccharide vaccines were highly effective in preventing group C disease. Following its use as a routine immunization in recruits in October 1971 group C meningococcal disease has been almost completely eliminated from Army training centers. Group A vaccine has been field tested in Egyptian school children with great success. Group B polysaccharide has failed to induce bactericidal antibodies in humans and, therefore, new research is underway to attempt to develop a cell wall protein antigen as a vaccine against group B disease.

Epidemic meningococcal meningitis has been a serious medical problem during every major military mobilization of the United States in this century. Attempts at control of the disease by nonspecific measures such as environmental manipulation (isolation of infected patients or reducing crowding in barracks) have not met with general success (1). Reduction of person-to-person transmission by means of sulfonamide chemoprophylaxis provided rather spectacular control of epidemics for almost 20 yr until the emergence and spread of sulfonamide resistant strains beginning in 1963 (2). Subsequent intensive research has led to the development and use of meningococcal polysaccharide vaccines which will be summarized in this report.

### BACTERIOLOGY, IMMUNOLOGY, AND PATHOPHYSIOLOGY OF *Neisseria Meningitidis*

*Neisseria meningitidis*, also termed the meningococcus, is a bacterial species of the genus *Neisseria*, which is characterized by its diplococcal morphology, Gram's stain negative reaction, the presence of the enzyme oxidase, and the typical oxidation of both dextrose and maltose. Meningococci are divided into serogroups on the basis of agglutination with antisera. At least nine distinct groups are recognized of which serogroups A, B, C, and Y are the most prevalent. Two distinct patterns of human infection are recognized: (1) the nasopharyngeal carrier state which is almost always asymptomatic and which may persist for weeks to years and (2) systemic infection of which meningitis and/or septicemia are the most frequent manifestations. Two factors are probably involved in determining whether serious disease occurs following acquisition of the organism in the upper respiratory tract. Virulence of the infecting strain is one aspect but cannot be further defined since laboratory and animal models for its study are not available. The other major factor is the state of natural immunity of the host. The studies of Goldschneider, Gotschlich, and Artenstein (3) have clarified to some extent the manner in which human immunity develops. They found that immunity correlated directly with the presence of humoral

bactericidal antibodies against meningococci. These antibodies were present in the blood of newborn infants, fell to a low level by age 6 mo, and were lowest at age 12 mo. After this an increasing prevalence was detected with increasing age reaching peak prevalence in young adults in whom 67–87% had antibodies to the major disease producing serogroups A, B, and C. Disease incidence correlated inversely with the presence of bactericidal antibodies; the peak disease incidence occurring at age 12 mo.

### *Meningococcal Antigens*

Those antigens of greatest interest in terms of vaccines are found in the capsule and cell wall of the meningococcus. The capsules consist of polymers of amino sugars which have been chemically identified as *N*-acetyl-mannosamine-phosphate (group A), *N*-acetyl neuraminic acid (group B), and *N*-acetyl, *O*-acetyl neuraminic acid (group C). Each of these polysaccharides has been extracted in high molecular weight form and has been highly purified (4). Antibodies directed against these capsular antigens are serogroup specific. Cell wall proteins and lipopolysaccharides (LPS) have also been separated and purified (5). The protein antigens show some sharing among the various serogroups but, nevertheless, systems of subtyping of meningococci have been developed which are based upon these antigens (6, 7). LPS, in addition to having antigenic properties (8), is also the endotoxin of the organism and, thus, is responsible for many of the severe clinical features of the disease such as purpura and shock. Of interest, protein and LPS antigens of meningococci crossreact with gonococcal antigens (9).

### *Development and Use of Meningococcal Vaccines*

Purified, high molecular weight group A and C polysaccharides, although nonimmunogenic in laboratory animals, were highly active in inducing antibody responses in humans (10). A single, parenteral injection of 50  $\mu$ g quantity produced antibody response in 90–100% of subjects without evidence of toxic side effects. Antibodies induced by vaccines were measured by a variety of techniques and, significantly, bactericidal antibodies were formed (10). The bactericidal antibodies were serogroup specific. After a number of preliminary studies which demonstrated safety, optimal dose, and route of injection (11), large-scale field studies were initiated with group C

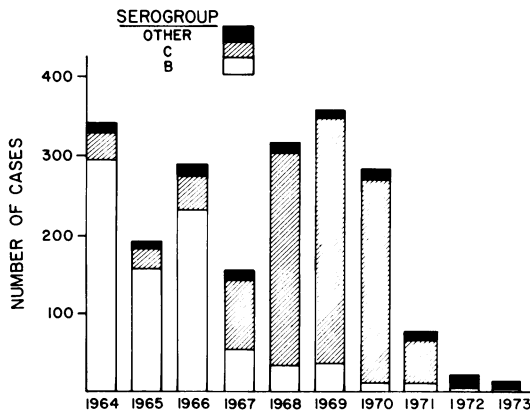


FIG. 1. Meningococcal meningitis. U. S. Army cases by serogroup and year. Data based upon strains submitted to Walter Reed Army Institute of Research for confirmation.

TABLE 1  
Field Trials of Group C Meningococcal Polysaccharide Vaccines<sup>a</sup>

Year	Vaccine group			Control group		
	No. of men	No. of cases and serogroup		No. of men	No. of cases and serogroup	
		B	C		B	C
1969	13,763	4	1	54,309	3	38
1969-1970	14,482	0	1	60,172	0	35
Totals	28,245	4	2	114,481	3	73

<sup>a</sup>Data compiled from references (12) and (13).

vaccine because of the high incidence of group C disease in Army recruit training centers (12,13). The results of these studies are summarized in Table 1. In vaccinated men the attack rate of group C disease was reduced to 89% of that observed in the control group. However, the number of illnesses caused by group B meningococci was greater in men who received C polysaccharide than in nonvaccinated controls. Following the demonstration of the safety and efficacy of this vaccine routine immunization in Army and Navy training centers was instituted in the Fall of 1971 and somewhat later in Air Force trainees. The impact of this immunization has been quite striking in that reported cases of meningococcal disease have fallen and remained at levels less than one-tenth those previously observed (Fig. 1). Although the specificity of the antibody response (10) and the failure of the group C vaccine to prevent illness due to other serogroups (Table 1) were a source of some concern, there has been no evidence of the emergence of group B or group Y disease as an epidemic threat. Nevertheless this possibility still exists and Army meningococcal case rates must be closely watched.

Group A vaccines could not be field tested in the United States since this organism has only rarely been isolated here in the past decade. Trials carried out in Egyptian school children by the World Health Organization with assistance from U. S. Navy research scientists have shown the group A vaccine to be highly effective in preventing group A disease (14).

Recent studies by the Walter Reed Army Institute of Research Laboratory have shown that group C antibodies induced by vaccination persist at nearly the early peak levels for a period of at least 5 yr (15). From these data it is inferred that immunity will also be long-lasting.

Group B polysaccharide vaccines have been prepared and tested in several hundred volunteers but very few subjects showed antibody response (16). The reasons for this lack of immunogenicity are not understood. An alternative approach to a group B vaccine is now under study at Walter Reed; namely, to utilize purified cell wall protein antigens. Should these be effective it might be possible to combine the protein vaccine with polysaccharides to encompass the three major pathogenic serogroups in one vaccine.

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