Serogroup B Meningococcal Disease
New Outbreaks, New Strategies

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MENINGOCOCCAL DISEASE IS AMONG THE MOST feared infections of children and young adults because of the rapidity of onset, high mortality rate, devastating sequelae, and tendency to spread and cause outbreaks. Two articles in this issue of THE JOURNAL[1,2] highlight the challenge of serogroup B meningococci—the most common cause of meningococcal disease in many countries.

Meningococci are commonly classified based on serologic reactivity of their polysaccharide capsules. At least 13 serogroups have been identified, but serogroups A, B, and C strains are the most common causes of human disease. Serogroup A organisms can cause massive outbreaks, and in some areas, such as the African meningitis belt, countrywide epidemics with attack rates approaching 1 to 2 cases per 100 persons per year strike repeatedly. In other areas, including the Americas and Europe, serogroups B and C cause most meningococcal disease. In North America and Western Europe, multiple small outbreaks of serogroup C disease have recently occurred.[3] Since protective antibody is readily induced in older children and adults following immunization with purified A and C polysaccharides, prevention strategies using effective polysaccharide vaccines are applied widely for these outbreaks.

Serogroup B meningococci differ from serogroup A and C strains both in disease epidemiology and in tools and strategies needed for prevention. In contrast to serogroup A or C epidemics, which usually resolve in 1 to 3 years, serogroup B outbreaks begin slowly, usually reach countrywide rates of 5 to 20 cases per 100 000 population per year and may persist for 5 to 10 years or longer, as seen in Norway[4] and areas of Chile[5] and New Zealand.[6] A higher proportion of serogroup B disease occurs in children younger than 5 years of age. More problematic, however, is that the serogroup B polysaccharide is not immunogenic in humans and, thus far, an effective serogroup B polysaccharide–based vaccine has not been developed. Vaccine research has focused instead on other bacterial components and especially on preparations of outer-membrane proteins (OMPs).

The 2 most thoroughly evaluated serogroup B vaccines were developed by countries as a direct response to national epidemics. Increasing rates of serogroup B disease in Norway in the 1970s led to development of an OMP vaccine using the outbreak strain. Two doses of the vaccine given to schoolchildren showed an efficacy of 57% in a randomized trial.[4] Because of declining rates of disease and moderate efficacy, the vaccine was not immediately used on a national level, but work continues on developing the product. An outbreak in Cuba with a different strain of serogroup B meningococci led to development of a different OMP vaccine. This vaccine had an efficacy of approximately 80% in a randomized trial among adolescents.[7] Both the Norwegian and the Cuban outbreak strains were genetically related (members of the enzyme type 5 [ET-5] complex of strains), but they did not share some OMPs, including the class 1 OMP, which is believed to be an important determinant of OMP-induced immunity. Subsequent outbreaks were identified in many countries in South America, and more than 40 million doses of the Cuban vaccine were used in mass immunization campaigns. Several case-control studies confirmed effectiveness in older children, but results varied in children younger than 4 years of age, ranging from no to moderate effectiveness, and in all studies the vaccine was less effective in younger children. The same pattern was observed in a study of a third OMP-based vaccine prepared with a strain that caused epidemic disease in Chile.[5]

The article by Diermayer and colleagues in this issue of THE JOURNAL[1] documents occurrence of the first large ET-5 serogroup B meningococcal outbreak in the United States. This outbreak has many of the classic features of serogroup B outbreaks previously noted. The onset was gradual, and the outbreak rates of disease have continued for 4 years. An age shift to older children was observed, with rates increasing 7-fold in adolescents. Although the fatality rate remained similar to that in preepidemic years (6% to 8%), it was still substantial. Most meningococci isolated were the same strain and OMP type and members of the ET-5 complex.

A detailed investigation into potentially modifiable risk factors for disease identified exposure to tobacco smoke as a primary risk factor.[8] However, this association accounted for only a portion of all disease, and smoking reduction could not be expected to halt the outbreak. Diermayer et al note an

See also pp 1493 and 1520.

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effective vaccine is needed, but recognize that evaluation of the cost-effectiveness of its use is critical before recommending mass immunization for a disease that occurs at a rate of 2.5 cases per 100 000 population. Other countries have faced similar issues. Norway embarked on its vaccine development program in the face of rates of serogroup B meningococcal disease of 5 to 6 cases per 100 000 total population per year (peak rate nearly 24 per 100 000 population), whereas rates in Cuba were approximately 14 per 100 000 population per year when its vaccine was introduced.[9] Currently, New Zealand is experiencing a group B meningococcal disease outbreak, and rates of disease reached 14 per 100 000 total population in 1996.[6]

The decision to use an available vaccine must be preceded by having a vaccine that is effective. One key issue with the available OMP vaccines is whether a vaccine prepared with 1 serogroup B strain (such as the Norwegian or Cuban vaccine) will protect against other serogroup B strains that do not share the same critical OMPs (such as strains causing the outbreak in Chile). Assessing efficacy in a field trial is complex, time-consuming, and costly. However, experience with serogroup A and C vaccines demonstrated that serum bactericidal activity (SBA) was correlated with protection. Studies evaluating SBA and field efficacy estimates in Brazil and Chile provide additional support for the use of SBA.[5,10] In these studies, age groups with substantial SBA after immunization had higher efficacy than those with lower, or absent, SBA. Although these studies did not define a "protective level" and it is possible that clinical efficacy of a vaccine may be better than indicated by SBA measurements, development of SBA following immunization was correlated with clinical protection.

The study by Tappero and colleagues,[2] also in this issue of THE JOURNAL, addresses the issue of appropriate serogroup B meningococcal OMP vaccines for use in control of an epidemic in Chile.[2] Their study compares the immunologic response (ie, the SBA) with the Cuban and Norwegian vaccines, which feature 2 different class 1 OMPs. Subjects received one of the vaccines or a control preparation, and SBA was measured against the 2 strains from which the vaccines were prepared and against the strain causing the outbreak, which has a different class 1 OMP from either of the 2 candidate vaccines. In addition, the SBA of a subset of sera was tested against genetically modified strains derived from the Norwegian vaccine strain, which contained different class 1 OMPs.

Among older children and adults who received either vaccine, there was excellent activity against the strain from which the vaccine was derived (the "homologous" strain), but only moderate activity against the epidemic strain and the strain from which the other vaccine was derived ("heterologous" strains). Among infants, there was excellent activity against the homologous strain only, and activity against the heterologous strains, including the epidemic strain, was not different from controls. Some activity was present against heterologous strains in older subjects, which was most likely due to antibodies induced against other membrane components, but the class 1 OMP was the primary functional target of the immune response. The studies using the altered Norwegian strains confirmed that SBA induced by the OMP vaccine was mediated primarily through the specific class 1 OMP.

The results of the study by Tappero et al[2] indicate that vaccines prepared from strains sharing class 1 OMPs with epidemic strains will be more effective than vaccines prepared from other strains. This suggests that "designer" vaccines should be prepared to fit different epidemic strains as they occur. Although this strategy is more complicated than control of group A and C disease with polysaccharide vaccines, there are parallels in the vaccine world, including creation of new influenza vaccines to address the new strains that circulate every year. The epidemiology of serogroup B disease allows for this approach, since it takes several years for most epidemics to develop, and elevated rates then may persist for 10 to 20 years. Thus, the bulk of disease could be addressed with a vaccine developed during the initial phases of the outbreak.

For maximum benefit, however, this approach requires rapid completion of a number of coordinated activities. Surveillance for meningococcal disease must be conducted continuously. If increased rates are noted and are consistent with an epidemic, epidemic strains must be fully identified, including sequencing of the class 1 OMPs. On identification of a substantial outbreak and the offending organism, vaccine development, testing, licensing, and production must be facilitated. Doing so may require international coordination between manufacturers and the countries involved, in which the World Health Organization and other international organizations can play a major role. The cost of development and production of these vaccines may be substantial and may be a major obstacle for less wealthy countries. The political will to proceed is critical to the process of development and production of appropriate vaccines. Moreover, mass immunization programs must be planned and coordinated at national and local levels. Successful completion of this series of activities will be difficult but has been done, most notably in the development and use of the Cuban vaccine. However, the complexity of this strategy highlights the importance of development of serogroup B meningococcal vaccines with wider applicability. Research groups are now studying a variety of approaches to create vaccines that can protect against a wider range of serogroup B organisms, including multivalent (ie, multiple class 1 protein) vaccine preparations or serogroup B polysaccharide-protein conjugate vaccines.[11,12]

Serogroup B meningococci continue to cause epidemics for reasons that cannot be defined clearly. Although factors associated with disease can be identified, many of these factors are not modifiable, and prevention will require use of vaccines. Although preparing vaccines specifically for an epidemic strain requires coordination and commitment on the part of public health personnel, government, and industry to be fully successful, it is the best hope until vaccines that are effective against all serogroup B strains are developed.

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Letters: A Forum for Scientific Discourse

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SCIENTIFIC DISCOURSE OCCURS IN MANY FORMS: AMONG colleagues, at scientific meetings, during peer review, and after publication. Such discourse is essential to interpreting studies and guiding future research. However, most forms of discourse become part of the scientific record only indirectly, such as through revision of a manuscript in response to peer review or through the influence of colleagues' comments on the author. Only 1 form of discourse—letters—becomes part of the permanent biomedical record, linked with the scientific article through its citation in databases such as MEDLINE.

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