Vaccine Prevention of Meningococcal Disease: Making Slow Progress

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(See the article by Snape et al. on pages 1387–94)

All is not well in the fight against meningococcal disease. Despite the availability, for decades, of meningococcal vaccines, Neisseria meningitidis remains a leading cause of meningitis, sepsis, and other serious infections in both industrialized nations and the developing world [1]. The meningitis belt in sub-Saharan Africa continues to suffer from devastating epidemics of infection due to serogroup A. Unexpectedly, a serogroup W-135 strain has also recently emerged as a cause of epidemic disease in that region, potentially complicating vaccine development and prevention efforts. There are no vaccines for sporadic serogroup B infection because of immunologic cross-reactivity of B polysaccharide with human neural tissue and other related factors. This is truly a vexing problem, because serogroup B strains account for a substantial proportion of meningococcal disease in Europe, the Americas, and elsewhere, and these strains predominate among infants—the group that has both the highest risk of meningococcal disease and the least immunologic maturity. Although a new tetravalent conjugate vaccine was recently licensed in the United States, initial licensure was limited to individuals aged 11–55 years; no licensed product is yet available for the children who are at the highest risk. Clearly, we have a long way to go in preventing meningococcal disease; progress has been slow [2].

With that somewhat pessimistic backdrop, substantial progress is being made in the development and licensure of new meningococcal vaccines. Work is being done to develop a safe, effective, and affordable serogroup A conjugate vaccine for use in the meningitis belt [3]. Tailor-made serogroup B vaccines have been used to control long-standing epidemics (most recently in New Zealand [4]), which are generally clonal and are, therefore, more amenable to vaccine prevention. In addition, there has been progress made towards identifying novel antigens that could potentially be effective against the very diverse group of strains that cause endemic serogroup B disease [5]. Finally, new conjugate vaccines are becoming available, including a serogroup A/C/W-135/Y conjugate vaccine that was licensed in the United States in 2005 and in Canada in 2006 and is now recommended by the Advisory Committee on Immunization Practices for routine use in adolescents in the United States [6]. This represents the first time that a meningococcal vaccine has been recommended for routine use in the general US population. It is likely that conjugate vaccines will be available for younger children and infants in the United States in the next few years.

The United Kingdom has played a leadership role in both the introduction and evaluation of new conjugate meningococal vaccines. Faced with high rates of serogroup C meningococcal disease, the United Kingdom initiated a mass campaign in late 1999 to immunize children aged <18 years, including infants at 2, 3, and 4 months of age, with serogroup C conjugate vaccine. Monovalent serogroup C conjugate vaccines were considered to be less desirable for the United States where, in addition to serogroup B, a substantial proportion of disease is caused by serogroup Y strains, which rarely occur in the United Kingdom.

Typically, much is unknown about vaccines when they are first introduced for widespread use. Additional studies are generally required to address unanswered questions, such as the need for booster doses. Investigators in the United Kingdom conducted a series of studies that revealed important information about their vaccine program. They revealed evidence of high vaccine effectiveness and no concomitant increase in nonserogroup C me-
ningococcal disease [7, 8]. In addition, there was evidence for a large herd immunity effect from the vaccine, with an observed 66% reduction in nasopharyngeal carriage of serogroup C strains and a decrease of similar magnitude in serogroup C meningococcal disease in the unimmunized population [9, 10].

Previously, it was believed that persistence of protective antibodies was not needed for continued protection from polysaccharide-protein conjugate vaccines because, unlike purified polysaccharide vaccines, they induce immunologic memory. It was assumed that a rapid antibody increase would occur in the face of exposure to the organism, leading to protection from invasive disease. However, evidence has been accumulating that suggests that preexisting antibody levels are required for protection and that immunologic memory in the absence of preexisting levels is insufficient.

Infants in the United Kingdom were an excellent group in which to address this question. Infants who received serogroup C meningococcal conjugate vaccines at 2, 3, and 4 months of age achieved high serum bactericidal antibody titers 1 month after completing the schedule, but these titers decreased rapidly thereafter [11, 12]. Given the evidence for induction of immunologic memory induced by serogroup C conjugate vaccines in infants [11–15], the presence of immunologic memory after antibody levels had waned was an ideal setting for determining whether memory, in the absence of antibody persistence, is sufficient for protection. Unfortunately, the available evidence suggests that it is not. In a follow-up study performed in the United Kingdom, there was evidence for an absence of clinical protection beyond 1 year in infants despite continued protection in the older age groups that had been immunized [16]. An obvious explanation for the failure of immunologic memory alone is an insufficiently rapid increase in antibody titer following exposure to *N. meningitidis*, but few data are available to address this point.

In this issue of *Clinical Infectious Diseases*, Snape et al. [17] provide laboratory evidence for a mechanism that supports what was observed in the field. The authors studied antibody responses to either a reduced dose of meningococcal C polysaccharide vaccine, which is meant to simulate exposure to *N. meningitidis*, or meningococcal C conjugate vaccine in a total of 260 healthy 13–15-year-olds in the United Kingdom who had been primed with a serogroup C conjugate vaccine 3–4 years previously. The main contribution of this study is the provision of detailed data on the number of days required for antibody levels to increase after boosting with either of the 2 vaccines. Subjects were randomly assigned to 1 of 6 groups, which determined which vaccine was received and the number of days after immunization that blood samples were obtained. The use of 4 serum-sampling schedules for participants who received polysaccharide allowed the authors to finely dissect antibody responses by individual day after exposure.

Serum bactericidal antibody titers of \(\geq 1:4\) using human complement, a level generally felt to provide clinical protection, were observed in 84% of participants at baseline. Although no serogroup C conjugate vaccine-naive controls were included, comparisons using historical data suggested a conjugate vaccine-induced persistence of antibodies for \(\geq 3\) years. Importantly, no substantial increase in antibody titers was observed until after 5 days following administration of either vaccine. Geometric mean titers for the 4 groups that had received polysaccharide were 24.7 on day 0, 37.9 on day 4, and 120.8 on day 5; titers were substantially higher at the 6, 7, and 28 day time points. Because meningococcal disease is known to occur soon after the organism is acquired in the nasopharynx, the lack of an increase in antibodies until day 5 may not be fast enough to prevent invasive disease and provides a plausible mechanism for the lack of protection in infants in the United Kingdom [16]. This would seem to confirm the notion that preexisting antibody levels are required for protection and that immunologic memory in the absence of preexisting levels is not sufficient. The data from this study are consistent with a previous report in which the immune response to low-dose serogroup C polysaccharide was investigated in adults who had been previously immunized with a bivalent A/C glycoconjugate vaccine [18]. However, as pointed out by Snape et al. [17], no immune response data were presented in that study for days 4–6.

The findings by Snape et al. [17] and by other investigators have major implications for vaccine prevention of meningococcal disease. The main message to immunization programs is that sufficient antibody levels must be maintained for sustained protection. The waning effectiveness in infants in the United Kingdom has led to a recent change from the previous schedule to a 2-dose schedule at 3 and 4 months of age, followed by a booster dose at 12 months of age. The goal of this change is to achieve sustained antibody levels and, therefore, sustained clinical protection. For the recently licensed A/C/W-135/Y conjugate vaccine in the United States and for other vaccines that are in the pipeline, optimal immunization schedules will need to be based both on longitudinal studies of antibody persistence and on active, laboratory-based surveillance for invasive meningococcal disease.

If all goes well, in the next few years we could see a dramatic acceleration in progress towards vaccine prevention of meningococcal disease. We could have a conjugate vaccine to prevent serogroup A disease that is affordable for Africa, tetravalent conjugate vaccines that are licensed for infants, and, if we are really lucky, safe and broadly protective serogroup B vaccines.

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References