INFECTIOUS DISEASE

Childhood meningitis may be preventable if we can afford it

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Bacterial meningitis, one of the infections most feared by parents, and on the mind of every pediatrician who evaluates a febrile child, is an important cause of morbidity and mortality in childhood. New vaccines have the potential to prevent the majority of these cases and could transform child health.

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Hemophilus influenzae type b (Hib), *Streptococcus pneumoniae* and *Neisseria meningitidis* (Men) cause almost all cases of bacterial meningitis worldwide. Only one type of Hib exists, but over 93 different types of *S. pneumoniae* and five major disease-causing serogroups of *N. meningitidis* (A, B, C, Y and W135) have been identified (Figure 1). Hib and *S. pneumoniae* are the global leading causes of vaccine-preventable deaths in children under 5 years of age, since they are also the main etiological agents of bacterial pneumonia, which kills more children than any other disease. For this reason, roll-out of vaccines that target these bacteria plays a major part in global efforts to meet Goal 4 of the United Nations Millennium Development program—reduction of the under-five mortality rate by two-thirds between 1990 and 2015[1]—and is set to transform child health in the decade ahead. Vaccines that combine protection against more than one of these pathogens could simplify control of meningitis. Bryant and colleagues have reported excellent immunogenicity for a novel combination vaccine (HibMenCY), a tetanus toxoid conjugate vaccine that targets Hib in addition to *N. meningitidis* serogroups C and Y (MenCY), which, along with MenB, are the most common causes of meningococcal disease in the USA.[2]

In Bryant's study the vaccine was administered to 4,180 infants according to the routine US infant immunization schedule, at the ages of 2 months, 4 months, 6 months and 12–15 months. Serum antibody levels against all three components reached or exceeded the accepted protective threshold in almost all vaccinated infants.[2] Given these favorable immunogenicity results, and the excellent safety data reported by Bryant *et al.*, this vaccine could probably extend protection against meningitis beyond Hib to MenC and MenY, but it is by no means certain that the additional coverage will lead to a recommendation in the USA.

Although the Hib vaccine has been included in the US infant immunization schedule for over 20 years, and despite the launch (in 1999) of a highly effective vaccine for MenC across Europe, Australia and Canada (which has almost eliminated the disease in those regions), routine infant vaccination for meningococcal disease is not used in the USA. This lack of interest reflects the very low rates of childhood meningococcal disease in the USA; in one surveillance area, which included approximately 40 million Americans, on average just seven cases per year occurred in children under 5 years of age,[3] which was considered too few to justify the costs of a vaccination program. This HibMenCY vaccine might be more useful, therefore, in countries other than the USA—those with

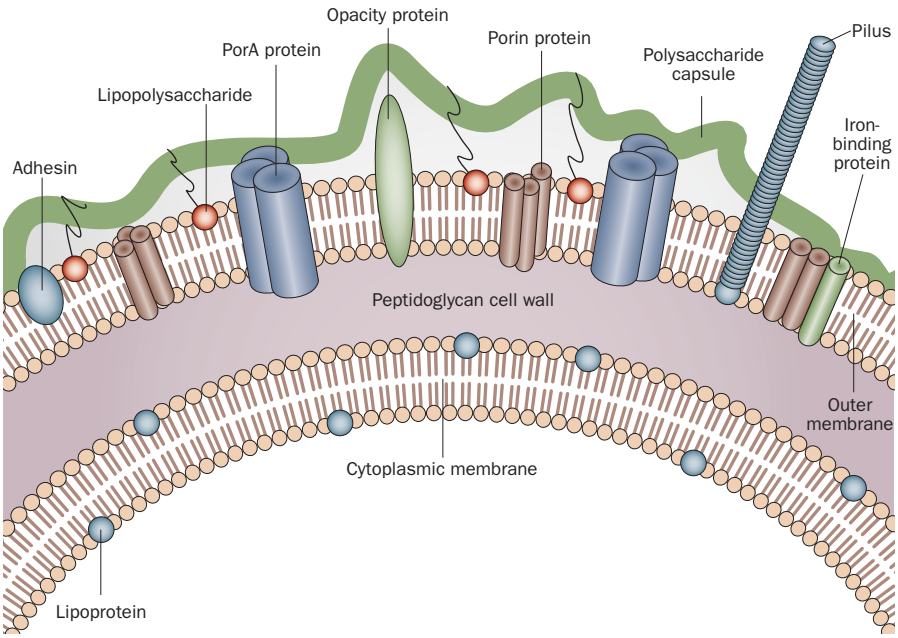

Figure 1 | Surface structures of *Neisseria meningitidis*. The organism is encapsulated in polysaccharide which confers the serogroup (A, B, C, Y or W135). Protein–polysaccharide conjugate vaccines are made by attaching these serogroup antigens to another immunogenic protein. The outer membrane contains a large number of surface-exposed proteins, many of which are highly variable. These proteins are being used to develop meningococcal B vaccines.

high rates of MenC and MenY and/or an established vaccine program for MenC —where this vaccine could extend the existing protection (to include MenY) for marginal additional cost.

N. meningitidis is the leading infectious cause of death in childhood in some developed countries, including the UK. High-profile outbreaks of serogroup C meningococcal disease among adolescents and young children led to the launch of protein–polysaccharide conjugate vaccines for MenC, administered in infancy, a decade ago. *N. meningitidis* is also responsible for explosive epidemics of MenA disease across the 'meningitis belt' of sub-Saharan Africa, which led to the launch (in December 2010) of the MenAfriVac vaccine against MenA.[4] MenC has a second peak in adolescence and MenY is somewhat more common in older adults. The persistence of vaccine-induced antibody after childhood immunization is, therefore, important for calculating both the potential duration of vaccine effectiveness and the timing of booster doses of vaccine. In the UK, titers of bactericidal antibodies to MenC fall rapidly after primary immunization with two or three vaccine doses given in infancy,[5] and this decline is associated with a rapid fall in vaccine effectiveness. A booster dose at 12 months of age increases antibody titers, but levels in 3-year-old children who received the booster were no higher than those in children who did not receive it.[5] For this reason, authorities in countries that have already introduced MenC vaccination are now considering schedules that include boosters during adolescence to sustain protection through the second decade of life and beyond.[6]

By contrast, in the USA, a vaccine covering meningococcal serogroups A, C, Y and W135 (MenACYW) has been used since 2005 for immunization of adolescents at 11–12 years of age.[7] Development of the MenACYW vaccine was triggered by college outbreaks of meningococcal disease, and recent data suggest that this vaccine is effective in 80–85% of recipients.[8] Data on waning of serum antibody levels led to a decision in October 2010 by the American Committee on Immunization Practices for a booster dose to be administered at 16 years of age;[9] however, little information has been collected on the persistence of antibody titers after this booster dose.

The bacteria associated with meningitis are commonly found 'carried' in the nasopharynx of healthy individuals. Accordingly, vaccines that prevent acquisition of carriage of these organisms will protect the individual and induce herd immunity by preventing transmission to meningitis-susceptible members of the population. Acquisition of Hib nasal carriage probably occurs in the first few years of life, and Hib vaccines given in infancy provide population protection by blocking transmission of these bacteria over the next few years, in addition to the individual benefits of immunization. The situation differs for MenC vaccines, as very low carriage rates of this organism occur in the first decade of life and, therefore, vaccine programs targeting adolescents and young adults (who have the highest carriage rates) are most likely to produce the added benefits of herd immunity. The age at which vaccination against MenY would induce herd immunity throughout the population is currently unknown.

> "*N. meningitidis* is the leading infectious cause of death in childhood in some developed countries..."

In most developed countries, especially those that have an established MenC immunization program, MenB is now the main cause of meningococcal disease and deaths, especially in childhood. MenB presents a major challenge for vaccine development, as the polysaccharide capsule that surrounds these bacteria shares antigens with human self-epitopes and is, therefore, not immunogenic. Vaccine development has focused on antigens beneath the capsule in the bacterial outer membrane, but these proteins are rather variable, making vaccine design difficult (Figure 1). Two MenB vaccines are advancing through clinical development, and one of these was submitted for regulatory approval at the end of 2010 in Europe.[10]

The multitargeted conjugate vaccines (MenACYW and HibMenCY) provide expanding potential for control of bacterial meningitis. If MenB vaccines are effective, and if policy-makers can justify the cost of using them in conjunction with existing vaccine programs, bacterial meningitis could become a clinical problem of the past. However, if the value of meningitis vaccines continues to be framed in the same terms as that of other health interventions, children and young people will continue to be affected by this devastating, but uncommon, disease.

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Competing interests
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