Netherlands had always given a booster dose of vaccine, and DTaP-Hib combinations were not introduced until 2005. The number of invasive Hib isolates referred to the national reference laboratory increased from the lowest level in 1999 (15) to 49 by 2004. The number of vaccine failures also increased from an annual number below 5 to between 10 and 15 per year after 2002. It has been suggested that this increase was probably due to waning protection, even in the presence of a booster, possibly exacerbated by reduced natural boosting from lower rates of asymptomatic carriage (90).

MENINGOCOCCAL C VACCINE DEVELOPMENT

Immunology and Development

The pathophysiology and epidemiology of serogroup C meningococcal disease are similar in some respects to that of Hib and present some of the same difficulties for vaccine development. Capsular antigens have been crucial in the development of licensed vaccines against meningococcal C disease (91), and highly purified, high–molecular weight meningococcal capsular polysaccharides were shown to be safe and highly immunogenic in adults and older children in the 1960s. These are the basis of the bivalent A and C and tetravalent A, C, W135, and Y meningococcal polysaccharide vaccines. The highest attack rate for serogroup C meningococcal disease in the developed world occurs in infancy, but, as for Hib, meningococcal capsular polysaccharides are poorly immunogenic in young children. This is because meningococcal capsular polysaccharides usually act as T cell–independent antigens. T-independent responses are age dependent, not generally occurring before 18 months of age, and do not induce immunological memory (92). Consequently, licensed polysaccharide vaccines are ineffective in protecting young children against group C disease and do not provide long-term protection.

The relatively recent development of Hib conjugate vaccine was therefore closely followed by the development of meningococcal conjugate vaccines. The vaccines are made from oligosaccharides derived from purified capsular polysaccharides that are chemically conjugated, using different methods, to tetanus toxoid or diphtheria CRM_{197} carrier proteins to convert them into T-dependent antigens (93).

Correlates of Protection in Meningococcal C Conjugate Vaccines

Serum bactericidal activity (SBA) was established as the natural correlate of protection for meningococcal disease in the 1960s (94,95). Trials with serogroup C plain polysaccharide vaccine confirmed that SBA was also a correlate of vaccine-induced protection, with poor SBA responses in children less than 24 months and increasing SBA response with age (96). A broad correlation between immunogenicity and effectiveness of the group C polysaccharide vaccine with age was shown in separate trials (97–99). These studies established that when SBA activity was present, an individual was protected. Since SBA levels wane after vaccination, it was also known that protection was short lived. Ability to induce SBA subsequently became a WHO-recommended correlate of protection (100), and so serogroup C polysaccharide vaccines were licensed without an efficacy trial.

Vaccine-induced SBA was accepted as a correlate of protection for individuals over 24 months, but MCC vaccines were designed to protect children under two years of age. It, therefore, seemed logical that, if MCC vaccines elicited a SBA response in infants, like plain polysaccharide vaccines did in older age groups, they would protect while SBA levels remained. This assumption was the basis of licensure of MCC vaccines for infants and toddlers in the United Kingdom (101) and was validated by later post-marketing effectiveness data. Clinical trials of MCC vaccines found them to be immunogenic in all age groups with reactogenicity profiles in line with other routine vaccines and no serious adverse events identified (102–106).

MCC vaccines are T cell–dependent antigens shown to induce a booster response up to four years after completion of infant immunization via immune memory (107). It was postulated that they would provide long-term protection as a result of rapid boosting of SBA levels on exposure. This assumption was based on the U.K. experience with Hib conjugate vaccines, which, until the resurgence in 2000, were thought to be providing long-term protection via immune memory despite waning Hib antibody levels (108). It was subsequently realized that the control of Hib disease in the United Kingdom was due to a reduction of carriage and induction of herd immunity and that the direct protection from Hib conjugate vaccine given in the first year of life was short lived (68,109). Had it been known at the time of licensure of MCC vaccines that immune memory induced by Hib conjugate vaccines given in infancy was not generating long-term protection, the assumption that MCC vaccines would protect in the long term despite loss of SBA would not have been made.

IMPACT OF MCC VACCINES IN ENGLAND AND WALES

Introduction of MCC Vaccine in England and Wales

As with many other developed countries, the incidence of all meningococcal infections increased through the 1990s in England and Wales. The incidence rose from 2.8 per 100,000 in the 1990/1991 epidemiological year (running from July to June) to 5.3 per 100,000 in 1998/1999. The rise was in part due to better ascertainment following the wide availability of more sensitive polymerase chain reaction (PCR) methods (110,111), however, there was a true rise in the level of endemic serogroup C infection, which increased proportionately more than other serogroups.

In November 1999, the United Kingdom became the first country in the world to introduce MCC immunization into the routine infant schedule. A phased national MCC immunization catch-up campaign also began in November 1999, targeting all children under 18 years of age (12 million in England and Wales). Recorded MCC vaccine coverage for school children aged 5 to 17 years was 85%, and coverage for children aged 5 months to 4 years of age was 78%. Routine infant immunization rapidly reached levels comparable to other vaccines given in the primary schedule and was 93% in July 2006 (112).

Impact on Disease in England and Wales

Cases of meningococcal B and C infections in all age groups are shown in Figure 2 for England and Wales from the 1998/1999 epidemiological year to 2007/2008. This graph clearly demonstrates that cases of Group B disease continued to occur at levels previously recorded, with natural variation by year, while the level of group C disease was markedly reduced within a year of the MCC campaign. Group C cases decreased by 97% overall between 1998/1999 (955 cases), before MCC vaccine was introduced, and 2007/2008 (29 cases). Deaths also fell strikingly in this period by 99%, from 118 serogroup C deaths in 1998/1999 to only 1 recorded death in 2007/2008.