the United Kingdom (Ref. 19, see chap. 45). MenC CVs have also been licensed in other countries around Europe (20) and in Canada (21). Combination A-C CVs have been proven immunogenic in clinical trials performed in infants and children (22) but these bivalent vaccines were not pursued to licensure.

A quadrivalent diphtheria toxoid–conjugated meningococcal ACYW CV (*Menactra*™, Sanofi Pasteur) was licensed for use in 11- to 55-year-olds in January 2005 in the United States and in 2- to 10-year-olds in May 2006 in Canada. Data concerning one other A, C, Y, and W135 protein-PS CV (conjugated to CRM197) has also been reported (23,24).

In infants, there was a poor immune response to the diphtheria-conjugated ACYW CV after a three-dose (2, 4, and 6 months) schedule with protective levels of bactericidal antibody reached against MenC in 54.2%, MenY in 66.7%, MenW-135 in 62.5%, and MenA 91.7% (25). However, priming was demonstrated by a response to all serogroups after a PS booster in the second year of life. By contrast, higher seroconversion rates were achieved with the CRM197 CV with protective titers reached against MenC in 84%, Y in 92%, and W-135 in 96% after immunization at two, three, and four months (26). In several studies of toddlers with two doses of the diphtheria-conjugated ACYW vaccine, protective titers of bactericidal antibody were achieved in over 90% of the participants (25,27). A study in children from 2 to 10 years with the diphtheria CV showed that protective titers of serum antibody were elicited in a comparable proportion of subjects as children given the previously licensed plain PS vaccine (28), though protective titers waned over the next few years in most participants (29), as has been described for other CVs. Similarly in adolescents, both the diphtheria CV and plain PS vaccine were immunogenic in a comparative trial, but antibody persistence was better in those receiving the CV (30).

Various other ACY and W135 combination vaccines are also in development (other ACYW CVs, Hib-MenCY, and Hib-MenAC-DTPw-HB) and a Hib-MenC CV has been used in the United Kingdom since 2006 as booster vaccine at 12 months. A monovalent serogroup A CV is under development by the Meningitis Vaccine Project (a partnership between PATH and WHO) to provide a low-cost solution for serogroup A disease in the meningitis belt of Africa (31). These developments provide the potential for global disease control of ACY and W135 meningococcal disease.

Progress toward the global control of disease caused by A, C, Y, and W135 must be tempered in view of the current failure to find a solution to the problem of MenB disease. The highest attack rate of meningococcal disease is in children younger than five years and, at this age, 50% of disease is caused by MenB in the United States (199–1996) (7), 39% in Canada (1985–2000) (8), and more than 90% in the United Kingdom (2004) (6).

As for serogroups ACY and W135 described above, the PS capsule of MenB is attractive as a vaccine antigen because, by definition, it is shared across this group of meningococci. However, the PS capsule of the serogroup B meningococcus is a homopolymer of sialic acid, chemically identical to PSs found in human tissues, especially fetal brain during development (32). Hence, the Group B capsule is seen by the immune system as a self-antigen, and this may explain in part its poor immunogenicity even after its conjugation to a protein carrier (33). Since this approach proved so successful for other capsular PSs, Jennings et al. pioneered an innovation in which chemical modification of the PS (N-propionylation) retains immunogenic epitopes. This approach has resulted in the development of a protein-PS CV that elicits functional (bactericidal) antibody in both mice and nonhuman primates (34,35). Some of the antibodies elicited have activity against polysialic acid and therefore have the potential to be autoreactive in humans, although no deleterious effects have been noted in early human trials (P. Fusco, Baxter, 2001, personal communication). Nonetheless, there is a strong sense that the strategy of PS-protein conjugation is not attractive to vaccine developers who anticipate ethical and regulatory difficulties that may be difficult, if not impossible to resolve in taking forward these vaccines as commercially viable propositions. However, other antibodies that arise after immunization with a conjugate N-propionylated serogroup B PS vaccine do not cross-react with human tissues. A derivative approach that might avoid the cross-reactivity issue is to use molecular mimetics of non-autoreactive epitopes as potentially safe serogroup B vaccine antigens (36).

The problems encountered in the development of MenB PS-based vaccines has resulted in consideration of a variety of alternative candidates, notably outer membrane vesicle (OMV) vaccines, recombinant outer membrane (lipo)protein vaccines, and lipopolysaccharide (LPS) vaccines.

However, while so far evaluation of the potential utility of these alternative MenB vaccine candidates has been difficult because of the lack of an accepted laboratory surrogate of protection at a recent consensus meeting held in Atlanta (37), it was concluded that serum bactericidal antibodies (dilutions of serum that can kill meningococci in the laboratory in the presence of complement) are ''a good surrogate for predicting the effectiveness of a meningococcal group B vaccine'' and that ''immunogenicity based on functional SBA activity will be the primary end point for evaluating vaccines'' (16), as clearly described for serogroup C meningococci (38). It is not clear whether other assays, such as opsonophagocytosis or protection in animal models, might better reflect protection of humans against MenB disease. An important question is the degree of serological cross-protection required before a vaccine could be licensed and used widely. It is therefore noteworthy that the MenC vaccine when introduced in various regions reduced the burden of meningococcal disease by 30% to 50%, and this might be a reasonable target for a first-generation MenB vaccine.

OUTER MEMBRANE PROTEIN VACCINES

The outer membrane proteins (OMPs) of MenB have been extensively studied as potential vaccine constituents since the 1970s. A drawback to their candidacy as vaccines is that these proteins tend to be highly variable not only among different MenB isolates but also within clonal populations of the same strain. As a consequence, any OMP from a single strain is unlikely to provide cross-protection to all other MenB strains. Furthermore, the antigenic regions of many of these protein structures evolve rapidly within bacterial populations because of the natural selection on carriage strains, especially through the acquired host immune clearance mechanisms mediated by local and systemic B cells. However, despite these reservations, there is good evidence for conservation of OMPs within clonal complexes, so that a small number of variants of certain OMPs are stably associated with a particular lineage over long periods of time and in different geographic locations (39,40), providing the possibility that a relatively small number of proteins, particularly in combinations of different proteins, might constitute a cross-protective vaccine.