and/or Y polysaccharide with *Haemophilus influenzae* type b polysaccharide). After immunization, peptides from the carrier protein are conventionally thought to be presented to peptide-specific T cells in association with major histocompatibility complex (MHC) class II molecules (some recent data suggesting that carrier protein peptide may actually be presented in association with an oligosaccharide and MHCII) by polysaccharide-specific B cells; the result is a T cell–dependent immune response that allows production of antibody and generation of an expanded B-cell memory pool. Unlike responses to booster doses of plain polysaccharides, responses to booster doses of conjugate vaccines have the characteristics of memory responses. Indeed, conjugate vaccines overcome the hyporesponsiveness induced by plain polysaccharides by replenishing the memory pool. The reactogenicity of conjugate vaccines is similar to that of plain polysaccharide vaccines.

The first widespread use of serogroup C meningococcal conjugate vaccine (MenC) came in 1999 in the United Kingdom after a rise in serogroup C disease. A mass vaccination campaign involving all individuals <19 years of age was undertaken, and the number of laboratory-confirmed serogroup C cases fell from 955 in 1998–1999 to just 29 in 2011–2012. The effectiveness of the immunization program was attributed both to direct protection of immunized persons and to reduced transmission of the organism in the population as a result of decreased rates of colonization among the immunized (herd immunity). Data on immunogenicity and effectiveness have shown that the duration of protection is short when the vaccine is administered in early childhood; thus booster doses are needed to maintain population immunity. In contrast, immunity after a dose of vaccine given in adolescence appears to be prolonged.

The first quadrivalent conjugate meningococcal vaccine containing A, C, Y, and W polysaccharides conjugated to diphtheria toxoid was initially recommended for all children >11 years of age in the United States in 2005. In 2007 the license was extended to high-risk children 2–10 years of age. In the same year, the vaccine was licensed in Canada for persons 2–55 years of age. Uptake was slow, but current U.S. data suggest an efficacy rate of 82% in the first year after vaccination, with waning to 59% at 3–6 years after vaccination. Limited data from the U.S. Vaccine Adverse Events Reporting System indicated that there might be a short-term increase in the risk of Guillain-Barré syndrome after immunization with the diphtheria conjugate vaccine; however, further investigation has not confirmed this finding. Quadrivalent conjugate vaccines with tetanus or CRM_{197} as carrier protein are now available in many countries.

A monovalent serogroup A vaccine, manufactured in India, was licensed in 2010 and rolled out to countries in the sub-Saharan African meningitis belt. There is strong evidence that this vaccine has been highly effective in controlling epidemic meningococcal disease in the region, with some evidence of a >90% reduction in disease in vaccinated populations. However, disease caused by serogroup X and W persists.

Vaccines Based on Subcapsular Antigens The lack of immunogenicity of the serogroup B capsule has led to the development of vaccines based on subcapsular antigens. Various surface components have been studied in early-phase clinical trials. Outer-membrane vesicles (OMVs) containing outer-membrane proteins, phospholipid, and LPS can be extracted from cultures of *N. meningitidis* by detergent treatment (Fig. 180-7). OMVs prepared in this way were used in efficacy trials with a Norwegian outbreak strain and reduced the incidence of group B disease among 14- to 16-year-old schoolchildren by 53%. Similarly, OMV vaccines constructed from local outbreak strains in Cuba and New Zealand have had reported efficacy rates of >70%. These OMV vaccines appear to produce strain-specific immune responses, with only limited cross-protection, and are therefore best suited to clonal outbreaks (e.g., those in Cuba and New Zealand as well as others in Norway and the province of Normandy in France).

Several purified surface proteins have been evaluated in phase 1 clinical trials but have not yet been developed further because of antigenic variability or poor immunogenicity (e.g., transferrin-binding proteins, neisserial surface protein A). Other vaccine candidates have been identified since sequencing of the meningococcal genome. A combination vaccine that includes the New Zealand OMV vaccine and three recombinant proteins (neisserial adhesin A, factor H–binding protein, and neisserial heparin-binding antigen) is immunogenic in infancy and has been licensed for use in Europe and Australia. Recommendations for its use are pending. Finally, a highly immunogenic vaccine based on two variants of the lipoprotein factor H–binding protein is undergoing clinical evaluation

FIGURE 180-7 Illustration of meningococcal outer-membrane vesicle containing outer-membrane structures.

MANAGEMENT OF CONTACTS

Close (household and kissing) contacts of individuals with meningococcal disease are at increased risk (up to 1000 times the rate for the general population) of developing secondary disease; a secondary case follows as many as 3% of sporadic cases. About one-fifth of secondary cases are actually co-primary cases—i.e., cases that occur soon after the primary case and in which transmission is presumed to have originated from the same third party. The rate of secondary cases is highest during the week after presentation of the index case. The risk falls rapidly but remains above baseline for up to 1 year after the index case; 30% of secondary cases occur in the first week, 20% in the second week, and most of the remainder over the next 6 weeks. In outbreaks of meningococcal disease, mass prophylaxis has been used; however, limited data support population intervention, and significant concerns have arisen about adverse events and the development of resistance. For these reasons, prophylaxis is usually restricted to (1) persons at greatest risk who are intimate and/or household contacts of the index case and (2) health care workers who have been directly exposed to respiratory secretions. In most cases, members of wider communities (e.g., at schools or colleges) are not offered prophylaxis.

The aim of prophylaxis is to eradicate colonization of close contacts with the strain that has caused invasive disease in the index case. Prophylaxis should be given to all contacts at the same time to avoid recolonization by meningococci transmitted from untreated contacts and should also be used as soon as possible to treat early disease in secondary cases. If the index patient is treated with an antibiotic that does not reliably clear colonization (e.g., penicillin), he or she should be given a prophylactic agent at the end of treatment to prevent relapse or onward transmission. Although rifampin has been