Conquering the Meningococcus

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Abstract

Since the first outbreaks of meningococcal meningitis were first described in Geneva in 1804 and in New England in 1806, and since the discovery of the causative agent by Weichselbaum in 1887 and the beginning of epidemics of meningococcal meningitis in the sub-Saharan Africa ~100 years ago, Neisseria meningitidis has been recognized as the cause worldwide of epidemic meningitis and meningococcemia. The massive epidemic outbreaks in sub-Saharan Africa in the 1990’s, the emergence since 1995 of serogroups Y, W-135 and X and the prolonged outbreak of serogroup B meningococcal disease in New Zealand over the last decade serve to remind us of the continued potential of the meningococcus to cause global morbidity and mortality. This report reviews new discoveries impacting prevention and future prospects for conquering the meningococcus as a human pathogen.

Advances in understanding meningococcal biology and epidemiology

Meningococcal disease incidence varies in human populations from rare to over 1000/100 000 population/year. Meningococcal disease occurs as sporadic cases, incidence < 1/100 000/year, hypersporadic disease 1–10/100 000/year occurring in regions or countries, localized outbreaks and case clusters, and epidemic and pandemic disease with rates > 10 to > 1000/100 000 (Vieusseux, 1805; Danielson & Mann, 1860; Greenwood et al., 1985; World Health Organization Working Group, 1995; Rosenstein et al., 1999; Tzeng & Stephens, 2000; Raghunathan et al., 2006). The incidence is influenced by the virulence potential of circulating meningococci, by factors, both host and environmental, which affect the human reservoir of meningococci and by host susceptibility to meningococcal disease.

In addition to the ability to cause disease, Neisseria meningitidis is also a common commensal, isolated from the nasopharynx of 8–20% of healthy individuals (Greenfield et al., 1971; Caugant et al., 1994; Stephens, 1999; Janda & Knapp, 2003) and more frequently in adolescents and other populations with close contact. Understanding how the meningococcus can be both a common commensal and a devastating human pathogen has been a major quest in the biology and in the design of prevention strategies for N. meningitidis. Thirteen serogroups of N. meningitidis, based on different capsular polysaccharide structure, are known but only six serogroups (A, B, C, W-135, Y and recently X) are currently associated with significant pathogenic potential (Rosenstein et al., 2001; Djibo et al., 2003; Apicella, 2005). Interestingly, the emergence and global importance of serogroups W-135, X and Y has been recognized only in the last 10 years. We now understand that these pathogenic serogroups are required for invasive meningococcal disease but also require expression in genetically defined virulent clonal strains that emerge and spread globally (Wang et al., 1992; Morelli et al., 1997; Raymond et al., 1997; Maiden et al., 1998; Aguilera et al., 2002) and that a large pool of meningococci are true commensals.

Classification of meningococcal isolates has been based on phenotypic characteristics of variable outer membrane-expressed structures such as capsule, serogroup: major outer membrane proteins, serotype: other outer membrane proteins, serosubtype: and lipooligosaccharide, immunotype (Frasch et al., 1985). B:2b:P1.5:L3,7,9 would be a strain designation. The last decade has witnessed the unraveling of the genetic basis of the meningococcus. Neisseria meningitidis strains MC58 (serogroup B) and Z2491 (serogroup A) have published genome sequences (Parkhill et al., 2000; Tettelin et al., 2000). Neisseria meningitidis strain FAM18 (serogroup C) (http://www.sanger.ac.uk/Projects/) and Neisseria gonorrhoeae strain FA1090 (GenBank AE004959) genome sequences are also available. Other genome-based sequencing projects are underway, complemented by studies using microarray-based comparative genome hybridizations and subtractive hybridization (Perrin et al., 2002) to identify genes that are unique to meningococci and to pathogenic...
Neisseria ssp. Multilocus sequence typing (MLST) of seven housekeeping genes (Maiden et al., 1998) is now a standard for genomic typing and identification of virulent clone complexes (e.g. ST-11, ST-5, ST-7, ST-23). MLST and other genomic studies have revealed much about the meningococcal epidemiology, population structure, carriage and transmission dynamics and genetic requirements for invasive meningococcal disease.

Serogroup A *N. meningitidis* is linked to the highest incidence of meningococcal disease, causes very large epidemics, especially in sub-Saharan Africa, and remains a major challenge (Greenwood et al., 1985, 1987, 1999; World Health Organization Working Group, 1995; Outbreak News, 2006) (Fig. 1). In the regions of the African meningitis belt, outbreaks occur during the dry season and diminish with the onset of the rainy season (Greenwood et al., 1985). Over 150 000 cases year$^{-1}$ were reported during the serogroup A outbreaks of the mid-late 1990s in areas of the belt (e.g. Burkina Faso, Mali, Niger, Nigeria and Chad) and these numbers likely reflect only part of the magnitude of the outbreaks (World Health Organization Working Group, 1995; Tzeng & Stephens, 2000). Molecular epidemiology and genetic analysis suggests serogroup A meningococci causing these outbreaks are highly clonal, emerge and spread rapidly, such as ST-5 or ST-7 complexes, and may have descended from a common ancestor in the 19th century (Morelli et al., 1997). This correlates with the appearance of meningococcal outbreaks in sub-Saharan Africa in 1905.

Serogroup B is a major cause of sporadic or endemic disease but prolonged outbreaks in Europe, Cuba, Chile, in the US Pacific Northwest and recently in New Zealand have caused significant morbidity and mortality (Swartley et al., 1997; Tzeng & Stephens, 2000; Dyet & Martin, 2006). Outer membrane protein types and subtype and specific genotypes ET-5 or ST-32 and ST41/44 complexes (Dyet & Martin, 2006) distinguish these outbreaks but these types also cause endemic disease. Serogroup C (especially ET-37/ST-11 complexes) has caused major epidemic outbreaks (e.g. sub-Saharan Africa, Brazil), case clusters and local outbreaks in the US, Canada and Western Europe, especially among adolescents and young adults (Jackson et al., 1995; Raymond et al., 1997; Rosenstein et al., 1999). Serogroup W-135 (also ET-37/ST-11 complexes) caused worldwide outbreaks in 2000–2002 associated with the Hajj pilgrimage and significant disease in parts of the African meningitis belt (Aguilera et al., 2002; Outbreak News, 2006; Raghunathan et al., 2006). Since the mid-1990s, serogroup Y (ET-501/ST-23 and related STs) strains have caused increased rates of disease in the US and Israel, and serogroup X has been responsible for localized recent outbreaks in parts of sub-Saharan Africa such as Niger (Racoosin et al., 1998; Djibo et al., 2003). Some parts of the world, for reasons not well understood, persistently have very low rates of meningococcal disease (Mexico, Japan and other parts of Asia and areas of South and Central America) and few or no outbreaks. Both population carriage and invasive disease susceptibility
factors as well as not fully understood environmental factors may be explanations. In the US and Europe large outbreaks of serogroup A meningococcal disease occurred in the first part of the 20th century but since World War II serogroup A disease has virtually disappeared from the US and Western Europe. However, serogroup A has caused outbreaks in China, Nepal and Russia over the last 25 years. The rates of meningococcal disease have been 0.6–1.8/100,000 in the United States since World War II (Rosenstein et al., 1999) but endemic rates have been persistently higher in some Western European countries (e.g. Great Britain). Rates of meningococcal disease are highest in young children (related to waning of protective maternal antibody) and increase again in adolescents and young adults aged 14–24 (Goldschneider et al., 1969a, b) probably related to increased transmission and acquisition.

**Advances in understanding meningococcal pathogenesis**

The epidemiology and pathogenesis of *N. meningitidis* meningococcal disease is defined by:

1. the virulence characteristics of different *N. meningitidis* strains or clonal groups;
2. the human reservoir and dynamics of meningococcal exposure (e.g. human transmission, acquisition and carriage);
3. human susceptibility (Tzeng & Stephens, 2000).

The incidence of meningococcal disease will increase when meningococci of high virulence are encountered, when factors that increase meningococcal transmission are present and when host resistance to invasive meningococcal disease is decreased.

**Virulence**

Meningococcal strain virulence can be defined by the number of cases of disease that occur in a population after acquisition (Raymond et al., 1997; Stephens, 1999; Yazdankhah et al., 2004). Some meningococcal clonal groups are characterized by high rates of disease following nasopharyngeal acquisition, especially when first introduced into a population. For example, members of the ST-11 clonal complex, usually serogroup C, B or W-135, may cause invasive meningococcal disease in one in 20 to one in 400 acquisitions (Raymond et al., 1997). By contrast, clonal groups found in the nasopharynx of symptom-free carriers who are not case contacts rarely cause meningococcal disease, even in settings of high rates of transmission and acquisition (Jones et al., 1998). Although the calculations are estimates based on cross-sectional carriage rates and the incidence of disease in a community, some meningococcal strains or clonal groups rarely if ever cause disease. Epidemic and most sporadic meningococcal disease is caused by a limited number of defined genomic clonal complexes such as ET-37, ET-5, A4 cluster, and these can express one or more capsule types (Raymond et al., 1997; Swartley et al., 1997; Maiden et al., 1998; Vogel et al., 2000; Yazdankhah et al., 2004).

The ~2.2 mbp meningococcal genome contains >2000 ORFs with ~83% of the genome coding sequence (Parkhill et al., 2000; Tettelin et al., 2000). Recombination events including transfer of genes among meningococci, gonococci and commensal *Neisseria* species and other areas of low G + C content associated with virulence determinants characterize the genome, indicating reassortment by horizontal genetic exchange (Davidson & Tonjum, 2006). The core meningococcal genome encoding essential metabolic functions is about 70% of the genome. The meningococcus has the metabolic pathways to survive in oxygen-limited environments such as intracellularly. Large genetic islands, 5–33 kb, in different strains contain bacteriophage homologs, remnants of bacteriophages and numerous restriction enzymes related to overall genomic structure (Linz et al., 2000; Parkhill et al., 2000; Tettelin et al., 2000; Feil et al., 2001; Kahler et al., 2001; Masignani et al., 2001; Perrin et al., 2002; Davidsen & Tonjum, 2006). In addition, over 60 other coding regions of low G + C content, 224 bp–11.3 kb, have been identified. These data indicate that the gene pool of meningococci is large and that meningococcal virulence may be related to a different distribution of genetic determinants present in different pathogenic clonal strains.

Many of the genetic islands are predicted to encode hypothetical surface proteins and virulence factors (e.g. capsule biosynthesis and transport). The meningococcal genome also contains multiple genetic switches that influence pathogenesis including: slipped-strand mispairing of repetitive nucleotides, regulation of promoters, intergenic recombination events, IS element movement and two-component systems. There are > 50 phase variable genes. For example, IS elements [e.g. IS1301 (Hilse et al., 1996), IS1016] and other repetitive DNA (Kahler et al., 2001) are associated with sequence polymorphisms and gene expression (e.g. capsule assembly). The potential structural variability of the meningococcus is quite remarkable due to gene and genomic rearrangements, and indicates the evolutionary capability is high.

The surface structures capsule polysaccharide, outer membrane proteins and endotoxin are major virulence components (Kahler & Stephens, 1998; Tzeng & Stephens, 2000; Rosenstein et al., 2001; Apicella, 2005). Other virulence-related mechanisms include rapid doubling time and release of outer membrane blebs or vesicles (Andersen, 1989; Hackett et al., 2002; Øvstebø et al., 2004; Brandtzæg, 2006), phase and antigenic variation related to genetic switches,
molecular mimicry and, less defined, the possible release of toxins. Capsule is a major if not the major virulence factor of *N. meningitidis* (Frosch et al., 1989; Swartley et al., 1997). Although there are case reports of true encapsulated meningococci causing disease, many of the rare ‘nongroupable’ stains isolated from CSF or blood often show evidence of recombination events in the capsule genetic locus that may have occurred during *in vitro* passage after isolation. As noted, the repertoire of capsules associated with meningococcal disease remains small but is greater than previously believed (e.g. recognition in the last decade of significant disease due to serogroups Y, W-135 and X) (Racocisin et al., 1998; Aguiler et al., 2002; Djibo et al., 2003). The genetic basis for the different capsules expressed by meningococci has been defined (Frosch et al., 1989; Swartley et al., 1997). Capsule expression varies *in vivo* (Swartley et al., 1997; Vogel et al., 2000; Dolan-Livengood et al., 2003) and meningococci with otherwise identical genetic types (e.g. MLST) can express different amounts or different capsular polysaccharides, or no polysaccharides (Swartley et al., 1997; Dolan-Livengood et al., 2003).

Capsule protects the meningococcus from phagocytic killing, opsonization and complement-mediated bactericidal killing, is a major protective antigen (Gotschlich et al., 2003). OMP can be regulated by iron limitation (Delany et al., 2006). Outer membrane proteins are involved in host cell interactions and as targets for bactericidal antibodies (Tzeng & Stephens, 2000; Massari et al., 2003). OMP can be regulated by iron limitation (Delany et al., 2006) or other environmental signals. Newly identified OMP including conserved surface proteins, adhesion/invasion proteins and putative toxins have been identified in the genome searches and are promising vaccine candidates (Giuliani et al., 2006).

Endotoxin or lipooligosaccharide of *N. meningitidis* is also a major virulence factor involved in inflammatory signaling, in close adherence and colonization and is a key mediator of the pathogenesis of fulminant sepsis and meningitis (Virji et al., 1995; Kahler & Stephens, 1998).

Capsule and lipooligosaccharide structures also can mimic human cell structures (e.g. the 2-8-linked polysialic acid capsule of serogroup B meningococcus is identical to the neural cell adherence molecule (NCAM) (Finne et al., 1983) and the z-chain structures of endotoxin are identical to the human I and i antigens (Mandrell et al., 2007).

### Transmission and carriage

The dynamics of meningococcal transmission, acquisition and carriage in humans are a second major influence on the incidence and likelihood of meningococcal disease (Goldschneider et al., 1969b; Greenfield et al., 1971; Cartwright et al., 1987; Caugant et al., 1994; Cartwright et al., 1991; Cartwright, 1995; Jones et al., 1998; Stephens, 1999; Tzeng & Stephens, 2000; Dolan-Livengood et al., 2003; Mueller et al., 2006). The natural habitat and reservoir of the meningococcus are the upper respiratory nasopharyngeal mucosal membranes. As noted, *N. meningitidis* is carried by ~8–20% of the normal population, but the prevalence of carriage varies widely and does not directly predict disease. However, without meningococcal carriage there is no meningococcal disease and the rates of meningococcal disease are influenced by factors that enhance exposure and transmission, carriage rates of strains with different virulence potential, and host factors. Transmission is by direct contact with or inhalation of meningococcus in large droplet nuclei that are acquired through very close contact with respiratory secretions and saliva. Acquisition of meningococci may be transient, result in invasive disease or lead to colonization (carriage). Meningococcal disease usually occurs 1–14 days after acquisition. The inoculum size required for infection is unknown but, based on infection of *N. gonorrhoeae* in a human urethral challenge model (Cohen et al., 1994), may be 103–106 organisms mL⁻1. Transmission is facilitated by close contact, coughing and spreading of secretions. Once meningococci reach human epithelial cells, a series of interactions with host epithelial cells occurs, leading to effacement of the epithelial surface, microcolony formation and/or epithelial cell invasion (Stephens et al., 1983).

Meningococcal carriage can be prolonged (months) in ~25% of carriers, brief (days to several weeks) in ~33%, or, despite exposure, very transient or does not occur in ~30–40% (Stephens, 1999). Carriage is an immunizing event leading to protective immunity against the organism (Goldschneider et al., 1969b). Some meningococcal strains may be highly transmitted but prolonged carriage is infrequent or less transmissible but more virulent (e.g. ST-11 serogroup C). Other meningococci, although they may be less virulent, are well transmitted, result in higher carriage prevalence and thus can be associated with increased disease rates (e.g. serogroup Y strains in the US) (Dolan-Livengood et al., 2003). Serogroup A strains in sub-Saharan Africa
during outbreaks can be associated both with high virulence, rapid transmission and acquisition and high carriage rates during outbreaks.

Meningococcal carriage and acquisition is influenced by age, close contacts or crowding, and important cofactors such as smoking (Tseng & Stephens, 2000). Meningococcal carriage is low in young children (*Neisseria lactamica* predominates), highest in adolescents, and increases in settings of closed populations, for example, military recruits and Hajj pilgrims. Other cofactors that increase the incidence of carriage and meningococcal disease include infections such as mycoplasma, influenza and other respiratory viral infections, smoking, and environmental damage to the upper respiratory tract (very low humidity, drying of mucosal surface and trauma induced by dust) (Artenstein et al., 1967; Young et al., 1972; Greenwood et al., 1985; Moore et al., 1990). While human susceptibility also may be a factor contributing to meningococcal acquisition and carriage, in a recent large UK study, social behaviors such as attendance at pubs/clubs, intimate kissing and cigarette smoke or exposure to passive smoke, were most highly associated with the risk of meningococcal carriage but not age or sex (MacLennan et al., 2006).

**Human susceptibility**

The lack of protective bactericidal antibodies (e.g. increased risk to young children due to waning of maternal antibody) has long been recognized as the single most important predisposing host factor for systemic meningococcal disease (Goldschneider et al., 1969a). However, opsonization and phagocytic function also appear to be important host defenses as demonstrated by disease reduction after polysaccharide vaccination in individuals with complement deficiencies. Genetic factors also determine human susceptibility and outcome (Emonts et al., 2003). Defects in the complement system may lead to rapid fatal meningococcaemia in patients who lack properdin in the alternative complement pathway and recurrent meningococcal infections are seen in patients with defects in the terminal pathway (C5-C9) (Sjoholm et al., 1982; Fijen et al. 1999). Polymorphisms in genes coding for the Fcε-receptor II (CD32), Fcγ-receptor III (CD16), mannose binding lectin (MBL), PAI-1 inhibitor levels and Toll-like receptor 4 (TLR4) are also associated with increased risk or severity of meningococcal sepsis (Hibberd et al., 1999; Fijen et al., 2000; Read et al., 2001; Smirnova et al., 2003; Faber et al., 2006; Tully et al., 2006). Meningococcal disease is also linked to immune suppression such as that seen in the nephritic syndrome, hypogammaglobulinaemia, HIV disease (but not serogroup A epedemics) and splenectomy.

**New insights into invasive meningococcal disease, diagnosis and treatment**

Features of the clinical presentation and new insights into the pathophysiology and molecular pathways of meningococcal meningitis, meningococcal sepsis and accompanying disseminating intravascular coagulation (DIC) have been defined in the last decade in a series of important studies and reviews (Brandtzaeg et al., 1989, 1992, 1996, 2001; van Deuren et al., 1995; Baines et al., 1999; Bjerre et al., 2000, 2003; van Deuren et al., 2000; Faust et al., 2001; Hackett et al., 2002; Haralambous et al., 2003; van der Ley & Steeghs, 2003; Øvstebo et al., 2004; Zughair et al., 2004; Moller et al., 2005; Thompson et al., 2006). Further, PCR and improved antigen detection systems are enhancing diagnostic accuracy in both industrialized and developing countries (Borel et al., 2006; Diggle & Clarke, 2006). In the UK a significant number of all cases are now diagnosed without culture (Gray et al., 2006) and in the African meningitis belt, new molecular diagnostic techniques (Borel et al., 2006) are improving meningococcal disease and serogroup surveillance and molecular epidemiology.

Without treatment 70–90% of patients with systemic meningococcal disease will die (Flexner, 1913). The use of antibiotics has reduced this figure to ~10%. Early recognition by family and health personnel, prehospital antibiotic treatment, rapid transportation to a local hospital or clinic, stabilization if possible in an intensive care unit, and rapid institution of established treatment protocols (van Deuren & Brandtzaeg, 2000; Booy et al., 2001) may further reduce individual morbidity and morbidity. Still, the overall case fatality rate has remained at ~10% in economically developed countries over the last several decades (Goldacre et al., 2003) and most patients who die in these areas have fulminant septic shock. In developing countries more patients die of meningitis. Prehospital antibiotic treatment is now advocated in many countries based on the present knowledge of the pathophysiology (Welch & Nadel, 2003). Effective antibiotics immediately stop the proliferation of *N. meningitidis* in the vasculature and CSF (Wang et al., 2000; Welch & Nadel, 2003) and may aid in prevention.

In developing countries, one dose of ceftriaxone injected intramuscularly can be sufficient treatment (Nathan et al., 2005) and is prophylaxis for carriage. The choice of antibiotics and data for and against the use of adjuvant therapy in meningococci including use of fluids, plasma, heparin, activated protein C, steroids, endotoxin neutralization, plasmapheresis, blood exchange and extra corporal membrane oxygenation are covered in other reviews (van Deuren et al., 1998; Derkx et al., 1999; Levin et al., 2000; de Kleijn et al., 2002, 2003; Trotter et al., 2002; Saez-Llorens & McCracken, 2003; Barton et al., 2004; Gupta & Tuladhar, 2004; Luyt et al., 2004; Zenz et al., 2004; Annane et al., 2005;
Meningococcal control and prevention

Understanding the virulence, pathogenesis and pathophysiology of invasive meningococcal disease has not yet in the antibiotic era significantly altered overall mortality or mortality once disease occurs. Given the rapid onset and progression of meningococcal sepsis and the delays and limited access to care in developing countries for patients with meningococcal meningitis or sepsis, achieving major reductions without effective prevention strategies will be difficult if not impossible.

Chemoprophylaxis to eliminate meningococcal carriage is recommended for close contacts of cases as the incidence of meningococcal disease in these individuals is 400–800-fold higher than the normal population (Rosenstein et al., 2001). Rifampin, ceftriaxone, azithromycin and the quinolones all have activity against meningococci in the nasopharynx. However, resistance to rifampin can develop rapidly and quinolone resistance in meningococci has recently been reported. While chemoprophylaxis is effective in known contacts and in limited outbreak settings (residential schools, barracks, etc.), the issues of resistance, access to and availability of drugs, and large epidemic outbreaks limit this approach. Prevention of meningococcal disease by vaccination is the best control strategy.

Based on the importance of capsular polysaccharide in pathogenesis and natural immunity, effective vaccines to decrease A, C, Y, and W-135 meningococcal disease were introduced in the 1970s and 1980s based on the classic studies of Gotschlich, Gold, Goldschneider and Artenstein (Goldschneider et al., 1969a,b; Artzten et al., 1970; Gold et al., 1975) (Fig. 2). These vaccines are safe, with mild local adverse events, and have good efficacy (> 85%) in older children and adults. The serogroup C polysaccharide vaccine is poorly immunogenic in children < 18–24 months, and does not affect long-term meningococcal carriage or induce immunological memory. The serogroup A polysaccharide has different immunologic properties in young children and can provide short-term protection. Also, immunity to the polysaccharide vaccines is limited to 3–5 years of protection and immunologic hyporesponsiveness is a complication of repeated doses.

Major advances in the prevention of meningococcal disease are the meningococcal polysaccharide-protein conjugate vaccines. Meningococcal C and A, C, Y, W-135 polysaccharide-protein conjugate vaccines have been licensed and introduced into the UK, other parts of Europe, Canada and recently the US (Committee on Infectious Diseases, 2000; Ramsay et al., 2003; Trotter et al., 2004; Bilukha & Rosenstein, 2005; Larrauri et al., 2005) (Table 1). These vaccines are so far safe and immunogenic, are anticipated to provide long duration of protection and are effective in young children. In the UK and other

### Timeline of Meningococcal Vaccine Development

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<td><strong>Serogroup A, C, Y, W-135 Meningococcal Vaccines</strong></td>
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<td>1969-1971 - Meningococcal A &amp; C polysaccharide vaccines</td>
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<td>1978 - Quadrivalent A, C, Y, W-135 polysaccharide vaccine</td>
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<td>2000 - Conjugate serogroup C meningococcal vaccines</td>
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<td>2005-and beyond</td>
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<td><strong>Serogroup B Meningococcal Vaccines</strong></td>
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<td>1980s-present - OMV Vaccines</td>
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<td>• Norwegian National Institute of Public Health Vaccine (NIPH)</td>
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<td>• Netherlands Vaccine Institute</td>
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<td>2000- Multivalent protein-based (in development) and other novel strategies</td>
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<td>• Lipooligosaccharide-based (in development)</td>
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Fig. 2. Timeline of meningococcal vaccine development. OMV, outer membrane vesicle.
Table 1. Meningococcal vaccines

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<th>Serogroups</th>
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<td>Menomune® (Sanofi-Pasteur)</td>
<td>A, C, Y and W-135</td>
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<td>ACWY Vax® (GlaxoSmithKline)</td>
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<td>Mengiva A+C® (Sanofi-Pasteur)</td>
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<td>AC Vax® (GlaxoSmithKline)</td>
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<td>Trivalent ACW vaccine</td>
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<th>Polysaccharide-protein conjugates</th>
<th>Meningitec® (Wyeth)</th>
<th>C conjugated to CRM&lt;sub&gt;197&lt;/sub&gt;</th>
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<td>NeisVac-C® (Baxter)</td>
<td>C conjugated to tetanus toxoid</td>
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<td>New meningococcal conjugate vaccines</td>
<td>Menactra (MVC4) (Sanofi-Pasteur)</td>
<td>A, C, Y, W-135 CRM&lt;sub&gt;197&lt;/sub&gt;</td>
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<td>DTPwHb/HibMenAC (GlaxoSmithKline) (MVA) in development</td>
<td>A conjugate</td>
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<td>(Novartis) in development</td>
<td>A, C, Y W-135 conjugate</td>
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Meningococcal polysaccharide-protein conjugate vaccines have shown significant success in reducing the incidence of serogroup C disease in the UK. The vaccine demonstrated 90% effectiveness at 3 years in 11–18-year-olds. A major protective effect of the C conjugate vaccines is by herd immunity (Ramsay et al., 2003). Rates of serogroup C carriage and disease in nonvaccinated individuals are reduced by more than 50% by this mechanism. A serogroup A, C, Y and W-135 polysaccharide-protein conjugate meningococcal vaccine was recently introduced into the US for adolescents (Bilukha & Rosenstein, 2005). Important issues remain for meningococcal conjugate vaccines and the prevention of meningococcal disease. Currently, no broadly protective A, C, Y, W-135 meningococcal conjugate vaccine is available for infants and young children. Also, because the number of vaccines and antigens given in infancy is rapidly increasing, there is a need to develop combination vaccines containing protective meningococcal antigens that do not create immunological interference. Also, the schedule for meningococcal conjugate vaccine administration in infants appears important to maintain protection (Trotter et al., 2004). Conjugate vaccines induce memory responses but memory response alone may not protect against meningococcal disease (Trotter et al., 2004), likely because of rapid onset of disease after acquisition. Further, the dose of conjugate vaccines both in children and adolescents, the best conjugates and conjugate methodology to use and the need for subsequent boosting with conjugates or polysaccharides remain important issue.

In addition to children, populations with increased risk for meningococcal diseases who should benefit from the new conjugate vaccines are military recruits, patients with complement or other immune deficiencies, microbiologists who are routinely exposed to isolates of *N. meningitidis*, and persons who travel to or reside in countries in which *N. meningitidis* is epidemic. However, the greatest need for these new vaccines is in areas afflicted by large epidemics of serogroups A, C and W-135 including sub-Saharan and other parts of Africa. Additional work on new meningococcal conjugate vaccines (serogroup A vaccines for Africa such as the MVA project and combination vaccines specific for sub-Saharan Africa), the rapid and broad introduction of conjugate vaccines currently approved and developed should be emphasized. These vaccines hold great potential for control of meningococcal and other important bacterial diseases in the developing world and should be a global priority for development and introduction.

Vaccines for serogroup B *N. meningitidis* have lagged behind the development of vaccines for the other serogroups. The serogroup B capsule is of identical structure to polysialic structures expressed in fetal neural tissue (Finne et al., 1983), thus strategies have focused on meningococcal noncapsular surface antigens such as OMP, OMV and lipooligosaccharide (Pizza et al., 2000; Zimmer & Stephens, 2006), cross-reacting antigens found on *N. lactamica*. Diversity of major outer membrane structures among meningococci has limited these approaches, but recent success in the control of strain-specific serogroup B epidemics and the identification of conserved novel surface proteins (Pizza et al., 2000) for use in combination vaccines (Giuliani et al., 2006), the discovery of novel group B capsule-specific antigens (Moe et al., 2005) and progress in lipooligosaccharide vaccines indicate that vaccine prevention of serogroup B meningococcal disease may be near.

For example, an OMV strain-specific vaccine (MeNZB<sup>®</sup>) has been given to 1 million young people in New Zealand to control the 15-year epidemic of ST40/41 serotype-specific serogroup B meningococcal disease, with promising safety and efficacy results. This vaccine and the efforts to develop a conjugate serogroup A vaccine for Africa point out the increasing role of public-private partnerships in development of targeted vaccines. Conserved minor OMV, such as the interesting factor H binding protein, GNA1870 (Madico et al., 2006), or NadA, which can be overexpressed, are another important approach to serogroup B vaccine development. Other approaches include multivalent PorA OMV for broad coverage (examples are HexaMen and NovaMen), *N. lactamica* OMV, and iron-regulated protein-based vaccines. The development of serogroup B vaccines will require standardized methodologies (Borrow et al., 2006) and better definition of the role of activity other than the serum bactericidal assays such as opsonophagocytosis assays will require additional effort. Lipooligosaccharide inner core structures also appear to be viable serogroup B meningococcal vaccine candidates.
**Future perspectives**

As we begin the third century following the clinical recognition of meningococcal disease and the quarter century after introduction of the first generation of successful vaccines for prevention, the meningococcus remains a global threat. Biologically, *N. meningitidis* has become a model organism for understanding bacterial pathogens that colonize and infect only humans. The novel mechanisms of meningococcal virulence and genetic variability, the diversity of the *Neisseria* ssp. gene pool, the acquisition of genes outside the *Neisseria* gene pool, the evolutionary potential of meningococcus and its adaptation as a human commensal are intriguing examples of the complex relationships of human hosts and the microbial world. Further dissection of the genetics and pathogenicity of the meningococcus and of the *Neisseriaceae* family will reveal more about how the meningococcus evolved, spreads globally and causes disease. Environmental factors such as smoke, coinfections and humidity are now recognized as major elements in the transmission and acquisition of the meningococcus, and the risk for and severity of meningococcal disease is clearly linked to specific human genetic polymorphisms. These findings provide new opportunities for identification of risk, control and prevention.

Early clinical recognition and treatment of meningococcal disease are recognized as important to reduce individual morbidity and mortality but effective control will require the greater widespread use of broadly immunogenic, broadly protective and long-lasting meningococcal vaccines. The expanded introduction and use of meningococcal polysaccharide conjugate vaccines, the development of broadly effective serogroup B vaccines, the defining of precise correlates of protection for these vaccines including bactericidal antibody, opsonophagocytosis and memory responses, and the introduction of these vaccines into areas of greatest need like sub-Saharan Africa carry the hope to eliminate the meningococcus as a major threat to human health.

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