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Can we control all-cause meningococcal disease in Europe?

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ABSTRACT

Invasive disease caused by *Neisseria meningitidis* is potentially devastating, with a case fatality rate of 5–15% and high rates of significant sequelae among survivors after septicaemia or meningitis. Capsular group C (MenC) conjugate vaccines have been highly successful in achieving control of MenC disease across Europe, and some countries have also introduced quadrivalent MenACWY conjugate vaccines to reduce disease caused by groups A, W and Y in addition to C. These vaccines putatively elicit protective levels of bactericidal antibodies in all age groups, induce immunologic memory and reduce nasopharyngeal carriage, thereby leading to herd protection. Protein-based meningococcal vaccines based on subcapsular components, and designed primarily to target capsular group B (MenB) disease, have recently been licensed. These vaccines are highly immunogenic in infants and adolescents, inducing bactericidal antibodies against strains expressing high levels of vaccine antigens which are identical to the variants present in the vaccines. Effectiveness of these vaccines at a population level will be determined by whether vaccine-induced antibodies provide cross-protection against variants of the vaccine antigens present on the surface of the diverse collection of circulating invasive strains. The level of serum bactericidal activity induced against strains also seems to depend on the level of expression of the vaccine antigens. The duration of protection and the impact on carriage of meningococci will have a major bearing on the overall effectiveness of the programme. In September 2015 the UK became the first country to introduce the multicomponent meningococcal serogroup B vaccine (4CMenB) into a national routine immunization schedule, and data on the effectiveness of this programme are anticipated in the next few years. **M. Sadarangani, CMI 2016;22:S103**

Introduction

Neisseria meningitidis (meningococcus) is a Gram-negative diplococcus, categorized into capsular groups on the basis of the polysaccharide capsule. Six of the 12 groups (A, B, C, W, X and Y) are responsible for almost all cases of invasive disease worldwide [1]. It is a common nasopharyngeal commensal, found in approximately 10% of the population, but bacteria occasionally enter the bloodstream to cause devastating invasive diseases such as meningitis and septicaemia [2]. In Europe it is a rare endemic disease, although hyperendemic and epidemic disease patterns also occur. Onset of disease in susceptible individuals may be very rapid, and the case fatality rate (CFR) is high, especially in those with septic shock [3,4]. There are high rates of long-term neurologic and nonneurologic sequelae among survivors [5–12]. Individual susceptibility involves a complex relationship among environmental, host and bacterial factors, and prevention of disease through vaccination offers the only realistic prospect for disease control. The recent licensure of vaccines designed to control endemic disease caused by capsular group B (MenB) organisms has made the possibility of control of disease caused by all groups a step closer.

Why should we want to control meningococcal disease?

The spectrum of meningococcal infection ranges from asymptomatic nasopharyngeal carriage to fulminant septic shock, which can result in death within a few hours. Septicaemia and acute meningitis are the commonest manifestations of invasive disease. Classical meningococcal septicaemia is one of the most recognizable clinical syndromes, with fever and widespread purpura, with

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or without shock. Occult bacteraemia and chronic meningococcemia can also occur. A small number of individuals develop focal infections such as pneumonia, septic arthritis, osteomyelitis, myocarditis, pericarditis, peritonitis, conjunctivitis, endophthalmitis, sinusitis and otitis media.

A major reason for the poor outcomes from invasive disease, and hence the importance of achieving disease control through prevention, is the rapid progression from a nonspecific febrile illness indistinguishable from minor viral infections to fulminant septicaemia and/or severe meningitis. In children who ultimately develop septicaemia, the most frequent early symptoms are fever, nausea, vomiting and lethargy. A blanching, salmon-coloured, maculopapular rash, similar to viral exanthema, may also be present [13]. As disease progresses, signs of shock start to become apparent. A rash is present in 70–80% of meningococcal bacteraemia cases at hospital presentation and is usually non-blanching (i.e. petechial or purpuric). A study of prehospital symptoms showed that most affected patients have only nonspecific symptoms in the first 4 to 6 hours, with the typical features of petechial/haemorrhagic rash, meningism and impaired consciousness developing later at a median of 13 to 22 hours [14]. In those with meningitis, the classical manifestations observed in older children are rarely present in infants and young children, when disease is most common. The illness usually begins with fever, nausea and vomiting, photophobia and severe headache. Occasionally the first sign is a seizure, but this can also occur later in disease. Irritability, delirium and altered level of consciousness develop as central nervous system inflammation progresses. The most specific signs are neck stiffness, associated with Kernig and Brudziński signs, but these are often absent in children. Focal neurologic abnormalities may also occur [13]. In some cases of meningitis, signs of raised intracranial pressure occur. Where septicaemia and meningitis coexist, neurologic symptoms and signs are due to a combination of cerebral ischaemia and meningeal inflammation.

Despite advances in critical care and specific therapy with β-lactam antibiotics, the case-fatality rate (CFR) in resource-rich countries has remained around 5–15% since the 1950s. This varies depending on disease presentation—meningitis has a CFR of approximately 1% in Europe [3,15] and 4% in the meningitis belt of sub-Saharan Africa [16], while septic shock in the absence of meningitis has a CFR of 16–52% [3,4]. Some specialist centres have recently published improved survival data (CFR of 5%) after early aggressive circulatory support [17,18]. Complications of disease occur during both the early, acute phase and later, resulting in long-term sequelae (Table 1). In the long term, survivors have high rates of significant sequelae (up to 20–30% in most studies), leading to long-term disability [5]. Studies with long-term follow-up of up to 15 years have found rates of sequelae up to 50–60%, including physical and neuropsychiatric problems [6–12]. Significant emotional problems in close family members have also been found in these studies, highlighting the societal impact of this disease.

The rapid onset, difficulty in early diagnosis, severity of disease and high CFR are features of meningococcal disease which support the use of vaccines as an appropriate public health strategy for disease control. The recent license of vaccines targeting MenB have now made control of disease caused by all capsular groups a possibility.

Table 1
Complications of invasive meningococcal disease [5,19]

Early neurologic complications[a]
• Seizures.
• Syndrome of inappropriate antidiuretic hormone secretion.
• Subdural effusions and empyema.
• Hydrocephalus.
• Raised intracranial pressure.
• Focal neurologic abnormalities.
• Cerebral venous sinus thrombosis.
• Cerebral infarction.
Early complications resulting from severe shock and tissue hypoperfusion
• Skin necrosis.
• Gangrene of parts or entire limbs, possibly requiring amputation.
Long-term neuropsychologic complications
• Sensorineural hearing loss.
• Epilepsy.
• Learning difficulties.
• Motor/cognitive impairment.
Long-term complications resulting from severe shock and tissue hypoperfusion
• Severe skin scarring—may need skin grafting.
• Growth plate damage—may require multiple surgical procedures until growth is complete.
• Arthritis with or without joint damage.

[a] Caused by meningitis and cerebral hypoxic-ischemic damage resulting from shock.

Epidemiology of Meningococcal Disease in Europe

Invasive disease is rare in Europe, with rates of 0.11 to 1.77 cases per 100 000 population, depending on the country (Fig. 1). Between 2008 and 2012 there was a slight decrease in the overall incidence rate, from 0.95 per 100 000 per year to 0.68 per 100 000 per year, with highest rates in the UK, Ireland and Lithuania. The highest disease incidence rates occur in infants under 1 year of age (>10 per 100 000 per year), followed by 1- to 4-year-olds and adolescents/young adults aged 15 to 24 years (Fig. 2). The majority of cases in 2012 were caused by group B organisms (68%), followed by group C (17%), Y (8%) and W (4%). Between 2008 and 2012 there was a decrease in the number of cases caused by group B and C organisms. In part this can be attributed to introduction of capsular group C (MenC) conjugate vaccines in a number of countries (Fig. 3); however, until 2015 there have been no licensed vaccines targeting MenB, and this decrease is probably part of the natural fluctuations in disease incidence [23]. Other factors which could have contributed to this decrease include changes in other known risk factors, such as reduction in the prevalence of smoking in many countries [24] and more widespread use of influenza vaccines. Disease rates also fluctuate as a result of changes in population immunity relating to the arrival and disappearance of new clones, some of which have much higher virulence. Almost all European countries include one to three doses of the monovalent MenC conjugate vaccine in the routine childhood immunization schedule (http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx). In Austria and Greece an adolescent booster of the quadrivalent MenACWY conjugate vaccine is used, and in the Czech Republic the quadrivalent vaccine is used for all three doses. In the UK there has been an increase in capsular group W (MenW) disease as a result of the expansion of a hypervirulent strain, from 22 cases in 2009 to almost 180 in 2014–2015 (https://www.gov.uk/government/publications/meningococcal-disease-laboratory-confirmed-cases-in-England-and-Wales) [25]. In 2013–2014 MenW was responsible for 15% of all cases of invasive disease, compared to historical levels of 1–2% [26]. In response to this increase, the adolescent booster dose in the UK was changed from the monovalent MenC vaccine to quadrivalent MenACWY vaccine in September 2015 [27]. The dynamic nature of meningococcal disease epidemiology highlighted here emphasizes the need for continued high-quality surveillance systems across Europe as well as National Immunisation Technical Advisory Groups that are able to rapidly respond to epidemiologic changes, utilizing all available vaccines to achieve optimal disease control, irrespective of capsular group.