Epidemiology of meningococcal disease

Keith AV Cartwright

In the UK, serogroup A strains disappeared 50 years ago, but in the 1990s, numbers of cases rose again to a 50-year high. Following the very successful introduction of conjugated meningitis C vaccines, effective meningitis B vaccines are now the highest priority.

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The epidemiology of meningitis in the UK is evolving and will continue to do so. Mumps vaccine, a component of the measles, mumps and rubella (MMR) vaccine, has almost eliminated the commonest cause of viral meningitis, and enteroviruses are the current most important agents. The incidence of viral meningitis is not known because most cases are mild; some are not treated in hospital, and in many, the diagnosis is not confirmed.

Before the introduction of conjugated *Haemophilus influenzae* type b (Hib) vaccines in the UK in 1992, there were more than 1000 cases of invasive Hib disease (of which rather more than half manifested as meningitis) in each year from 1989 to 1993, but numbers fell by more than two thirds in 1994, with a further substantial fall in 1995. Recently, this consistent downward trend has been reversed with small rises in numbers of Hib cases in the last 2 years, a trend that will require careful monitoring.

CLASSIFICATION OF MENINGOCOCCI

Neisseria meningitidis, the meningococcus, is a capsulated gram-negative diplococcus highly adapted to colonize humans. About 10% of healthy individuals carry the microbe in the nasopharynx at any one time, including up to 25–30% of teenagers and young adults. Occasionally, usually soon after acquisition, the organism may invade to cause meningitis (85%) or septicaemia (15%); the latter associated with much higher mortality. Most strains in the nasopharynx are of minimal invasive potential – carriage of virulent, invasive strains is unusual.

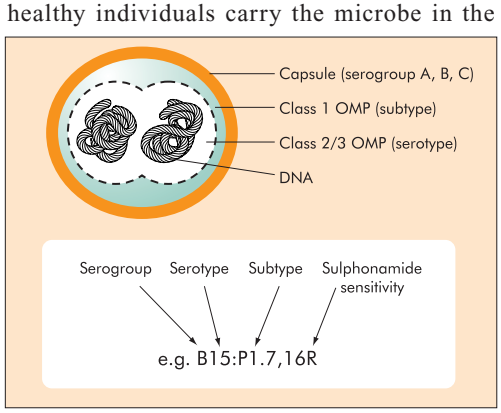


Figure 1. Meningococcal classification. OMP = outer membrane protein.

Variations in the capsular polysaccharide permit differentiation into more than 10 serogroups, including A, B, C, W-135, X and Y. The first three are responsible for the vast majority of cases of invasive meningococcal disease (MD) worldwide, although recently the USA has seen an increase in cases caused by serogroup Y, and the incidence of W-135 disease has been increasing, especially in association with the Haj pilgrimage to Saudi Arabia.

Meningococci may be serogrouped (variations in the capsule), serotyped (variations in the class 2/3 outer membrane protein) and subtyped (class 1 outer membrane protein, with two major variable regions in the class 1 protein – VR1 and VR2); sulphonamide sensitivity is another stable marker. A combination of these characteristics defines the phenotype, e.g. B15:P1.7,16R (*Figure 1*). Multilocus enzyme electrophoresis allows identification of clones of organisms all sharing a common ancestor, e.g. the ET-5 clone, which includes both B15:P1.16 and B4:P1.15 strains.

In the last few years, genetic classification has become more widely available, and the gold standard methodology is multilocus sequence typing (MLST) in which about 500 base pairs of each of seven housekeeping genes are sequenced. Following registration with a global meningococcal website (http://neisseria.org/nm/typing/mlst/), new sequences are allocated a number, permitting the assignment of a seven-figure numeral (a sequence type; ST) that char-

acterizes each strain with great accuracy, as well as providing information on its ancestry and its genetic relatedness to other meningococcal strains (Maiden et al, 1998).

SOURCES OF DATA ON THE INCIDENCE OF MD IN ENGLAND AND WALES

Data on MD incidence in England and Wales come from two main sources that are combined into a single database. These are notifications reported to the Public Health Laboratory Service Communicable Disease Surveillance Centre and microbiological data from the Meningococcal Reference Unit (MRU), Manchester Public Health Laboratory. Since 1999, all English regions have participated in a programme of enhanced surveillance of MD that was put in place to support the introduction of conjugated serogroup C (men C) vaccines.

The MRU receives meningococcal strains and clinical material from confirmed and suspected cases. Meningococcal DNA can be extracted from blood or CSF, amplified by polymerase chain reaction (PCR) and then detected, providing a non-culture serogroup designation as well a confirmation of the diagnosis in many cases (Kaczmarski et al, 1998). Non-culture diagnostic methods of disease confirmation are of ever-increasing importance because of the declining use of lumbar puncture as an investigation (Wylie et al, 1997) and because an increasing proportion of patients with suspected MD are given a dose of benzylpenicillin by their GP before they arrive in hospital; this renders blood cultures sterile in almost all cases (Cartwright et al, 1992). The use of the PCR test has grown rapidly since its introduction in 1996 (*Figure 2*).

Despite attempts to improve the quality of the data, MD incidence is still underascertained, possibly by as much as 30–40%. MD deaths are determined by the Office for National Statistics using information from death certificates and are thought to be notified more efficiently (i.e. completely) than the ascertainment of surviving cases. This gives rise to a spuriously high apparent case fatality rate.

THE INCIDENCE OF MD

MD is relatively common worldwide; substantial epidemics occur in sub-Saharan Africa (the 'meningitis belt', *Figure 3*) every 5–10 years. During epidemics, attack rates may be as high as 500 cases per 10^5 per annum. This compares with the current UK incidence of about 5 cases per 10^5 per annum.

Since the establishment in 1912 of a national system for infectious disease notification in

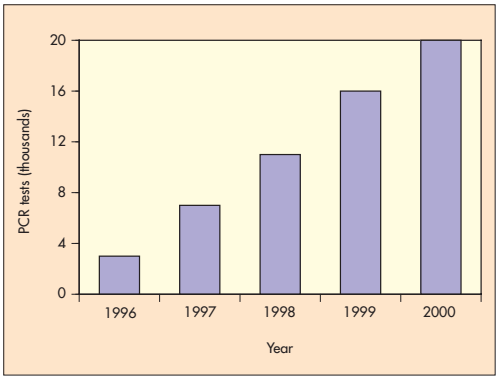


Figure 2. Meningococcal polymerase chain reaction (PCR) tests in England and Wales 1996–2000.

England and Wales, there have been three notable periods of high MD incidence (*Figure 4*). Two were associated with the World Wars and though to be caused (at least initially) by enhanced transmission of meningococci among military recruits with subsequent spillover into the civilian population. Other World War II combatant countries experienced similar high rates of MD including the USA, France and Germany. A third period of high incidence was seen in the UK during the Depression years (1929–33), a phenomenon also observed locally in the USA.

The meningococci circulating in the UK during these periods of high incidence in the first half of the last century were of serogroup A. In the 1950s, this serogroup disappeared (for ill-understood reasons) to be replaced by strains of serogroup B and C, an epidemiological picture that has prevailed up to the present time. For almost all of the last 40 years, serogroup B has accounted for 60–75% of cases of MD, with

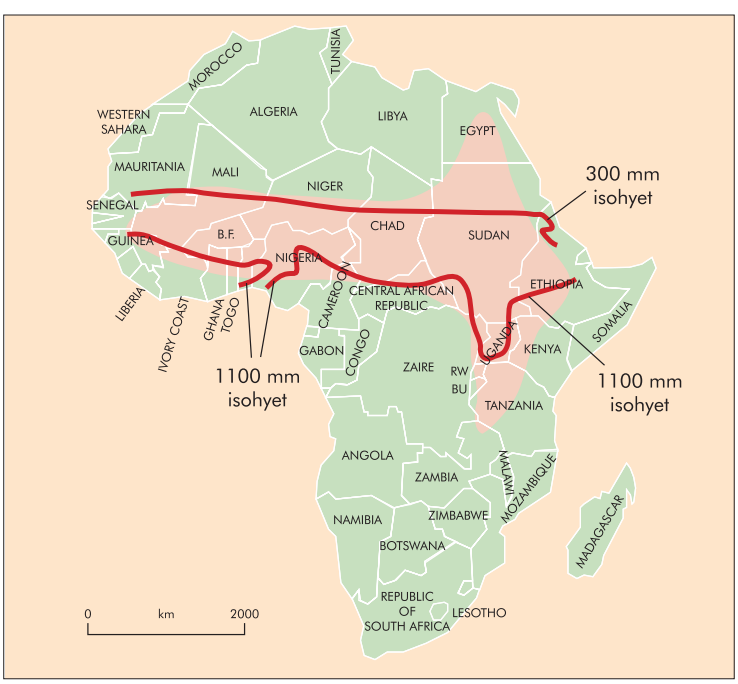


Figure 3. The meningitis belt.

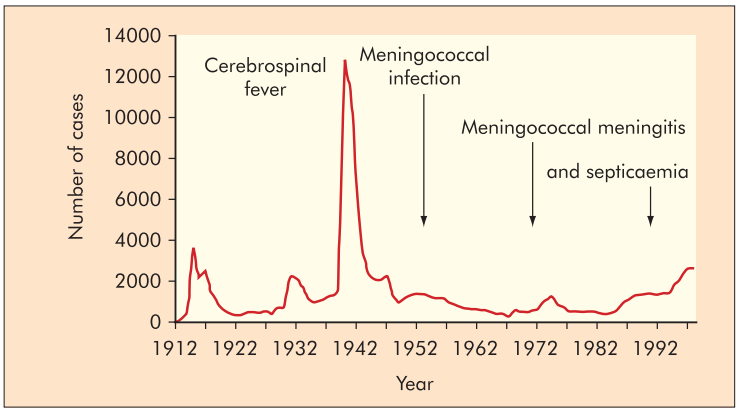


Figure 4. Notifications of meningococcal disease England and Wales 1912–1998.

serogroup C accounting for the great majority of the rest. In each year, there are a few cases caused by other serogroups (*Figure 5*).

In England and Wales, there have been more than 1000 notified cases annually for each of the last 10 years. In 1995, 1996 and 1997, there was a substantial increase in disease incidence associated with a rise in the proportion of cases caused by strains of serogroup C. In 1999, there was a further rise to 2974 cases – a 50-year high. In 2000, the impact of the new men C vaccine (introduced in November 1999) began to become apparent, with a small reduction in the total to 2778 cases, despite a further rise in the incidence of men B disease (*Figure 6*). The rise in the proportion of cases notified as 'septicaemia' reflects changes in notification practices rather than any true change in the pattern of clinical presentation.

Overall mortality is between 5 and 10%. This has reduced recently, probably in part a result of more complete notification, but also a result of earlier recognition and improved management. Local clusters and outbreaks are a perplexing but well recognized feature of MD. When these occur in educational settings, they are usually caused by men C strains.

Meningococci in the UK have become slightly more insensitive to penicillin in recent years. This development is not yet therapeutically important, but the prevalence is rising and the trend needs careful monitoring. Very rare strains that produce β-lactamase (and are therefore penicillin resistant) have been reported from Canada, South Africa and Spain, but to date there have been no cases of treatment failure or patient deaths as a consequence of infection with a β-lactamase producing strain.

Treatment with parenteral penicillin by the GP reduces mortality by about 50%, although it makes the organism harder to isolate. Non-culture methods of diagnosis (such as PCR) are now of great importance in monitoring disease incidence. A CSF sample (where clinically indicated), blood cultures and a throat swab should be obtained from all new cases of the disease. Meningococci isolated from cases should be sent to a reference laboratory in order to confirm serogroup and type and to provide epidemiological information.

CLUSTERS

Although the relative risk of disease following exposure to a case of meningococcal disease is high (500–1000x), the absolute risk is still extremely low – only 2% or so of all cases of invasive disease are secondary; about 1 of 200 close family contacts will develop secondary meningococcal infection if untreated. Chemoprophylaxis (rifampicin, ciprofloxacin or ceftriaxone) for close contacts reduces the risk of secondary disease, but if follow-up is extended beyond the normal 30–60 days, it can be shown to be incompletely efficient. If the index case strain is of serogroup A or serogroup C, contacts should be offered both chemoprophylaxis and vaccine. Chemoprophylaxis alone should be offered to contacts of cases of serogroup B disease but may merely defer rather than reduce the risk of secondary cases. All contacts, irrespective of the serogroup of the index case strain, should be reminded that an increased risk of secondary disease may persist for many months. The intro-

Figure 5. Clinical meningococcal isolates sent to the Meningococcal Reference Unit July 1997–June 1998.

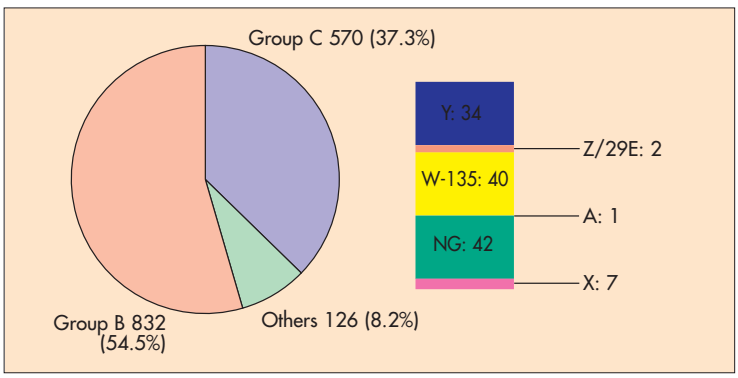
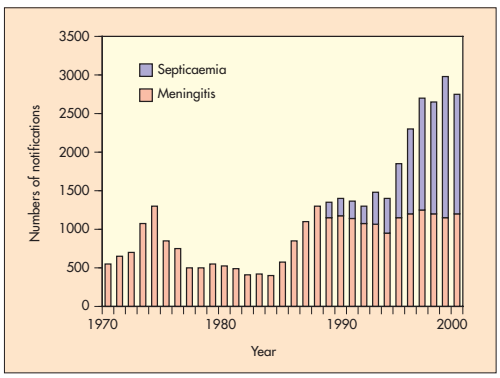


Figure 6. Meningococcal disease, England and Wales: annual number of notifications.



duction of conjugated men C vaccines has reduced the incidence of clusters dramatically.

MD CAUSED BY W-135 STRAINS ASSOCIATED WITH THE HAJ

In 1987, cases of MD caused by serogroup A were noted in Muslim pilgrims visiting Mecca in Saudi Arabia for the Haj religious festival. This led the Saudi authorities to require evidence of vaccination against serogroup A in Haj pilgrims before issuing a visa. Following this, there was no problem with MD in Haj pilgrims until 2000, when cases caused by serogroup W-135 were noted in returning pilgrims (Hahné et al, 2002) and in a small number of their close contacts. Cases of Haj-associated W-135 disease were documented in many European, Middle and Far Eastern countries, and in the USA. The responsible strains were highly homogeneous, forming part of the ET-37 (sequence type 11) clonal complex. Following further W-135 cases in Haj pilgrims and in their close contacts in 2001, the Saudi authorities now require pilgrims to provide evidence of immunization with quadrivalent A, C, Y, W-135 vaccine.

THE IMPACT OF INTRODUCTION OF CONJUGATED MEN C VACCINES IN ENGLAND

The UK was the first country in the world to introduce conjugated men C vaccines. Starting in November 1999, the new vaccine was offered to all infants (three doses starting at age 2 months) with a single dose offered to older children and teenagers up to the age of 18 years. Although these conjugated vaccines were thought likely to reduce nasopharyngeal carriage of men C strains, an immediate herd immunity effect was not expected because the peak age incidence of carriage is around 20–24 years, just above the upper age limit of those targeted for immunization.

Initial calculations of efficacy made after 9 months showed that the new vaccines were 97% effective in teenagers and 92% in toddlers (Ramsay et al, 2001). Subsequently, there has been clear evidence of a major reduction in men C incidence in the age groups targeted for immunization, in comparison with those aged 20 years or more, in whom there has been little change in men C incidence (*Figure 7*). Numbers of cases of men B disease, which had been rising steadily for some years before 1999, have continued to rise, but despite careful searching, there has been no evidence to date of serogroup replacement, i.e. emergence of strains expressing a capsular polysaccharide other than men C, yet otherwise genetically similar to the men C strains circulating before the introduction of the new vaccines.

THE FUTURE

As the use of men C vaccines is extended in the UK to those aged 20–24 years, a further reduction in men C incidence can be expected. Numbers of cases of men B disease are currently continuing to rise, and a men B vaccine is urgently required. The recent increases in the numbers of cases of W-135 disease in the UK and of serogroup Y cases in the USA give cause for concern, as does the possibility that virulent strains of meningococci may acquire genes conferring high-level penicillin resistance through the production of β-lactamases. Careful monitoring in the UK and development of good international networks will help to give early warning of any important new trends. **HM**

Conflict of interest: none.

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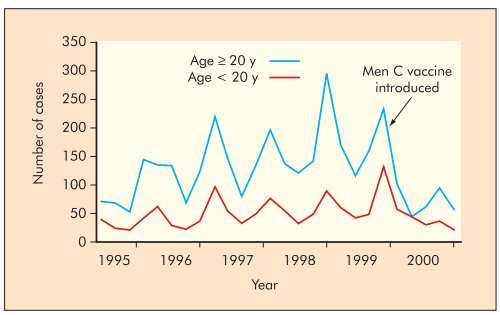

Figure 7. Laboratory-confirmed cases of meningitis C (men C) disease by quarter, England and Wales, by age group.

KEY POINTS

- Before the introduction of conjugated meningitis C vaccines in the UK in 1999, there were about 3500 cases of invasive meningococcal disease annually.
- Most UK cases are caused by strains of serogroup B, for which there is currently no vaccine.
- Meningococci remain universally sensitive to penicillin throughout the world.
- Major epidemics of meningococcal disease caused by serogroup A strains occur at 5–10 year intervals in sub-Saharan countries – the so-called 'meningitis belt'.
- Chemoprophylaxis is used to prevent secondary cases, but these are uncommon. About 98% of cases of meningococcal infection are primary and sporadic.
- Conjugated meningitis C vaccines have caused a dramatic fall in the incidence of meningitis C disease in the UK; other countries including Spain, Eire and Belgium are now using these vaccines.