MENINGITIS

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Recent outbreaks of meningitis in South Wales and elsewhere have led to calls for a more widespread immunisation programme for this disease.

This briefing note explains the causes of meningitis, examines the vaccines available and discusses the issues that arise.

WHAT CAUSES MENINGITIS?

Meninigitis is a condition associated with inflammation of the membranes (meninges) surrounding the brain. It can be caused by virtually any micro-organism (e.g. bacteria, viruses, fungi, parasites) that gains access to the cerebro-spinal fluid (CSF) that bathes these membranes. Historically however, most cases have been caused by one of three main types of bacteria:

- *Neisseria meningitidis* (meningococcus);
- *Streptococcus pneumoniae* (pneumococcus);
- *Haemophilus influenzae* type b (Hib).

Of these, Hib is no longer a common cause of the disease, as a result of the introduction of an effective vaccine in October 1992. This vaccine is now routinely given to all UK infants between the age of 2-4 months, and has reduced confirmed cases of Hib infections by at least 95% in recent years.

Information on the current numbers of cases and causes of the disease comes from two main sources:

- Notifications made to the Public Health Laboratory Service's (PHLS) Communicable Disease Surveillance Centre (CDSC) under the Public Health (Infectious Diseases) Regulations 1998.
- Laboratory reports from PHLS reference units identifying the micro-organisms responsible.

The single most common cause of meningitis remains *N. meningitidis*, which accounted for around 1 in 3 cases notified to CDSC between December 1996 and March 1998 (**Figure 1**). *S. pneumoniae* accounted for around 1 in 5 cases with the rest being linked to a wide range of other bacteria or to viruses (Figure 1).

FIGURE 1 MICROORGANISMS LINKED WITH MENINGITIS

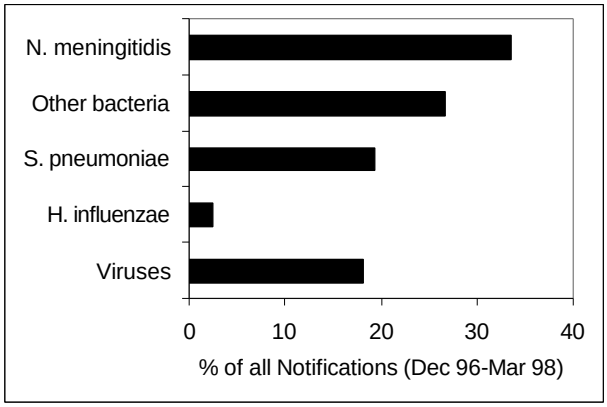
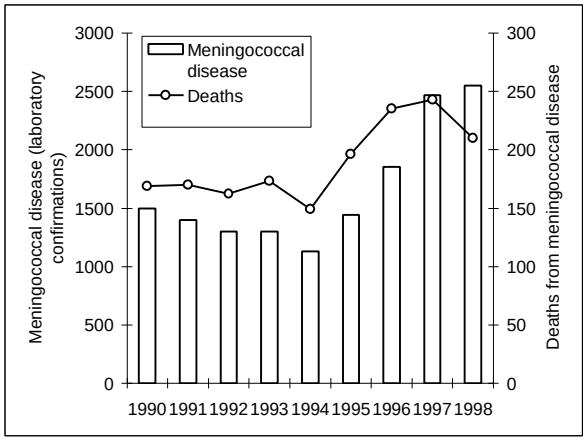


FIGURE 2 TRENDS IN MENINGOCOCCAL DISEASE



TRENDS

Meningococcal Disease

N. meningitidis is not only associated with infections of the CSF (meningitis) but also causes infections of the blood (septicaemia). Both may occur at the same time, and the criteria that doctors use to assign a meningococcal infection to the diagnostic categories of 'meningitis' or 'septicaemia' vary considerably. For this reason, **meningococcal disease** (i.e. all infections involving *N. meningitidis*) represents the most reliable indicator of overall trends. The number of such infections in England and Wales confirmed by the PHLS Meningococcal Reference Unit has increased significantly in recent years (**Figure 2**) and now stands at more than 2,500 cases (and over 200 deaths) a year. Around 1,100 of these unequivocally represent meningococcal meningitis, with the laboratory confirming the presence of *N. meningitidis* in CSF samples. For the remaining 1,400 or so, the presence of the bacterium has been confirmed in blood samples, and these may thus represent meningitis or septicaemia. These overall trends hide monthly fluctuations in the number of cases of meningococcal disease reported - the cyclical nature of these variations are shown in **Figure 3**, with infections peaking every December or January.

Pneumococcal Disease

Pneumococcal disease covers a range of conditions resulting from *S. pneumoniae* infection. In 1997, the PHLS Reference Unit confirmed 5,114 reports of *S.*

pneumoniae, the vast majority of which (4,832) were present in blood. Such cases are much more likely to represent pneumococcal pneumonia or septicaemia, than meningitis. Only in 235 cases was a definite diagnosis of pneumococcal meningitis supported, with laboratory confirmation of *S. pneumoniae* in CSF. Unlike meningococcal disease, there is little reason to suppose that cases of pneumococcal meningitis are on the increase.

Trends in Bacterial Strains

A common feature of all the bacteria closely associated with meningitis is that they are wrapped in capsules made of cross-linked chains of sugars (poly-saccharides). The exact composition of this capsule varies from one strain of bacteria to another. As explained later, this has implications for vaccine research, since each vaccine is only effective against the particular strain(s) it was designed to counter.

In the case of *S. pneumoniae*, scores of different strains are known, and the composition of vaccines is 'tweaked' to protect against the current most predominant strains. *N. meningitidis* is rather more straightforward, since while more than a dozen different strains are known, only two of these (groups B and C) are implicated to any significant extent in cases of meningococcal meningitis. Of these, group B has historically been linked with causing most (2 in 3 cases in 1990) cases of meningococcal disease, although the proportion of group C disease has risen substantially in the last 5 years (**Figure 4**). However, part of this rise may be due to the introduction of improved diagnosis and 'typing' methods[1] in 1996/97.

WHO IS MOST AT RISK?

Many people carry the bacteria that cause meningitis with no apparent adverse health effects. For instance, some 5-10% of the population carry *N. meningitidis* and as many as 30% *S. pneumoniae* in their nose or throat. Scientists do not understand the process by which these bacteria gain access to the blood or CSF, and turn a harmless 'cohabitation' into a potentially life-threatening disease. But they do know that some age groups are more at risk from certain types of bacteria than others, as illustrated in **Figure 5**.

As far as meningococcal disease is concerned, cases are spread throughout the younger age range, with two main peaks - one among infants under 5 years old, and one in young people age 15-19 (Figure 5). While group B predominates among infants, group C is now most commonly isolated from 15-19 year old sufferers of meningococcal disease. In contrast, pneumococcal meningitis (Figure 5) is most commonly found in people at opposite ends of the age spectrum, particularly in infants under 1 year of age, with virtually no cases affecting teenagers or young adults.

FIGURE 3 FLUCTUATIONS IN MENINGOCOCCAL DISEASE

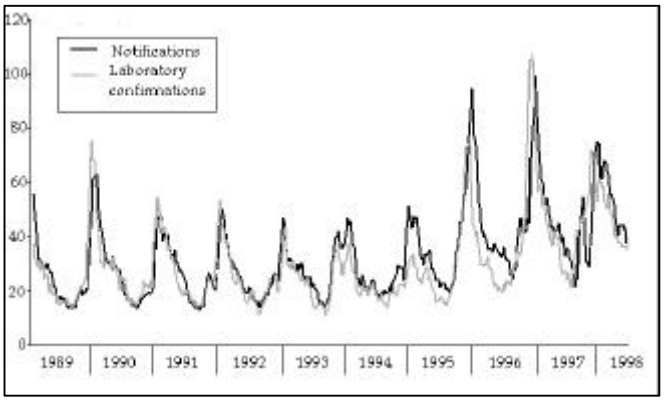


FIGURE 4 MENINGOCOCCAL DISEASE BY GROUP

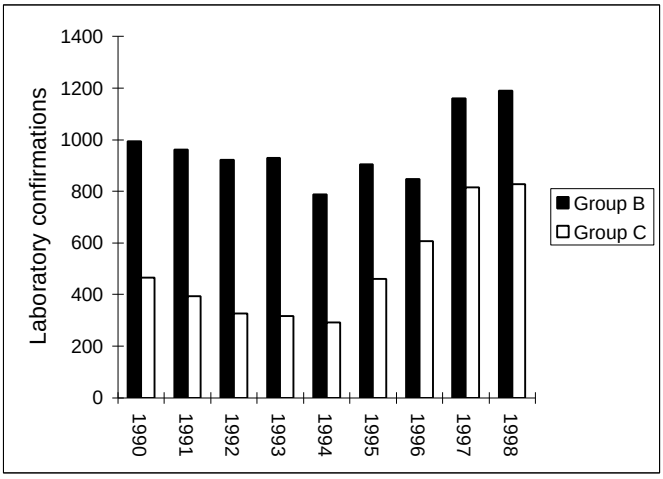
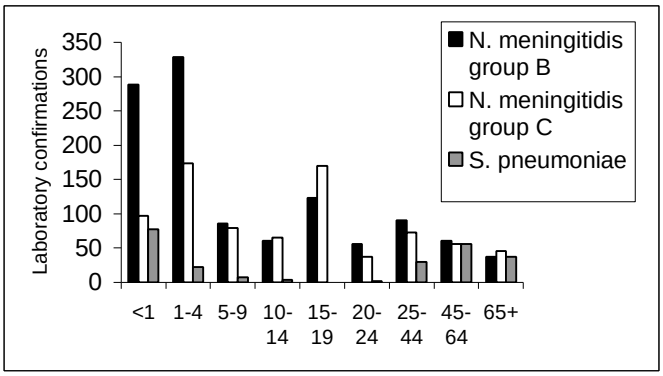


FIGURE 5 BACTERIA ASSOCIATED WITH DISEASE IN DIFFERENT AGE GROUPS



TREATMENT AND MANAGEMENT

Antibiotics (notably penicillin) are used to treat bacterial meningitis, but their effectiveness is increasingly being compromised by the spread of

[1] **A DNA amplification technique (PCR) is now used to diagnose and assign meningococci into the various different groups.**

antibiotic resistance factors throughout the microbial world[2]. The key challenge is to start treatment as soon as possible after symptoms (**Box 1**) emerge, because of the rate at which the disease can progress. This means that doctors have to work 'blind', treating suspected cases with antibiotics before they know what type of microbe they are dealing with, or whether it is resistant to any antibiotics commonly used in treatment.

Meningitis tends to occur as an isolated event, or as outbreaks involving relatively small numbers of people. Transmission of the various bacteria from one person to another requires direct close contact with nose or throat discharges. Close contacts (household members, intimate partners, etc.) of people suspected or diagnosed as having meningitis may also be treated with antibiotics as a prophylactic measure. Depending on the species and strain of bacteria involved, other contacts such as people attending the same school, college, workplace, etc. may also be immunised if appropriate vaccines are available (see below).

ISSUES

The recent outbreaks of meningitis in South Wales and elsewhere, coupled with rising trends in meningococcal disease have prompted calls for a more widespread immunisation programme. The issues surrounding use of current vaccines and the need to develop better ones are discussed in more detail below.

Existing Vaccines

Meningitis vaccines currently licensed for use in the UK are summarised in **Table 1**. As outlined in **Box 2**, the **capsular** vaccines currently available for *N. meningitidis* group C and *S. pneumoniae* are suitable for use only in children aged 2 years or above, and offer only relatively short-term protection (~3 years). More recently however, scientists have developed ways of boosting the effectiveness of capsular vaccines in young children, and of extending the longevity of the immune response. Such approaches led to the Hib **conjugate** (Box 2) vaccine (Table 1) currently given to children in the UK, which is effective in infants as young as 2 months, and leads to long-lasting immunity. **No vaccine is currently available to protect against the single most common cause of meningitis (*N. meningitidis* group B).**

The main issue surrounding currently licensed vaccines is whether to introduce universal immunisation of young people against *N. meningitidis* group C. Some doctors advocate such a course of action because of the rise in group C meningococcal disease among teenagers in recent years (Figures 4 and 5). They argue that vaccinating children when they start primary school, with booster jabs every 3 years or so until age 19, could prevent more than 300 cases of group C disease each year in England and Wales alone. However, such an option would require an initial 'catch up' campaign to immunise every person in the

BOX 1 MENINGITIS SYMPTOMS

Among the main symptoms of meningitis are:

- fever;
- headache;
- vomiting;
- stiffness in the neck;
- dislike of bright lights;
- drowsiness;
- red rash.

TABLE 1 CURRENTLY LICENSED MENINGITIS VACCINES

Microbe	Vaccine type	Age group	Longevity
N. meningitidis group C	Capsular	>2 years	Temporary (~3 years)
S. pneumoniae	Capsular	>2 years	Temporary
Hib	Conjugate	>2 months	> 15 years
N. meningitidis group B	No vaccine available		

BOX 2 CAPSULAR AND CONJUGATE VACCINES

The bacteria that cause meningitis are sheathed in polysaccharide capsules, the structure of which varies from one species (and strain) to another. These capsules obscure the unique **antigens** (complex molecular 'fingerprints' that alert the immune system) present on the surface of bacterial cells that would normally be the prime targets for vaccine development. This leaves researchers little option but to use the capsules themselves (or components of them) as the basis of anti-meningitis (capsular) vaccines.

In some cases, vaccines based on these capsules alone do elicit strong immune responses in humans, causing the release of antibodies that can recognise and bind to the capsular material, and thus protect against the bacteria from which the capsule was derived. However, such vaccines do not work in children under around 2 years of age, because their immune systems are not sufficiently developed. Another drawback is that they stimulate only one arm of the immune system - so-called humoral immunity. They do not stimulate the cell mediated ('memory') responses needed for long-lasting protection, and their effects thus wear off as levels of the antibody decline in the blood. This is why current capsular vaccines against *N. meningitidis* group C, and *S. pneumoniae* protect against meningitis only for around 3 years.

One way round these problems is to develop conjugate vaccines, where capsular material is 'grafted' onto immunologically active proteins, specially chosen to boost the body's immune response. Conjugate vaccines such as the Hib vaccine in current use are sufficiently powerful to elicit immune responses in children as young as 2 months. Furthermore, because they stimulate both arms of the immune system, they offer much longer-lasting protection.

[2] **See POST report Diseases Fighting Back, October 1994.**

country between the age of 5-19 years. As summarised in **Table 2**, this would involve nearly 10M people, and the vaccine costs alone (i.e. ignoring the substantial additional costs of delivering it through GPs or school health services) would run to some £70M in the first year. Thereafter, in addition to the 'running costs' (~£4.5M a year in vaccine alone to immunise each new cohort of 650,000 or so 5 year olds), further periodic large-scale investment would be needed to deliver the booster jabs. While the Department of Health (DH) sees group C meningococcal disease as a priority, it considers development of new vaccines as a more cost-effective option.

The Need for Better Vaccines

Following the successful introduction of the Hib vaccine in 1992, the DH made the development of better conjugate vaccines against other causes of meningitis a major priority. As outlined in Box 2, they offer the advantages of effectiveness in infants older than 2 months (the main group at risk of meningitis), and of being 'one-off' vaccines (lasting for >15 years). DH has thus collaborated with vaccine manufacturers and has been funding a 3 year, £1M programme since April 1997 to accelerate research in this area. Recent progress is outlined below.

N. meningitidis group C

The DH sees the development of group C conjugate vaccines as an urgent priority. Such vaccines would not only help protect infants from menigococcal meningitis, but would also help to stem the rising number of group C infections among 15-19 year olds. Three manufacturers are currently developing such vaccines, and (DH funded) Phase II clinical trials are currently nearing completion. Results so far suggest that the new vaccines are safe and highly effective in infants from the age of 2 months upwards. DH estimates that the new vaccines could be licensed within 1-2 years, and the commercial collaborators are now starting to consider manufacturing capacity.

However, the introduction of a new conjugate vaccine in the near future has considerable resource implications. Assuming that the vaccine would be targeted at all those who would benefit from it most, the launch would require a 'catch-up' campaign involving all people age 2 months to 19 years - some 12.5M people in England and Wales alone (Table 2). The overall cost of launching the new vaccine depends on the number of people vaccinated (12.5M) x the number of doses required for full immunity (3 in the case of the Hib vaccine) x the cost per dose (no details on cost are available yet). While this is likely to add up to a very substantial figure, it would be a 'one-off' cost - no booster jabs would be required since the vaccine grants long-lasting immunity. Thereafter, 'running costs' would be more manageable, involving immunising around 650,000 infants a year.

TABLE 2 POTENTIAL RECIPIENTS OF GROUP C MENINGOCOCCAL VACCINE

Age Group (years)	Population Estimate (M, 1997 figures)	Cases of group C disease (1998)
<1	0.65M	97
1-4	1.96M	174
5-9	3.47M	79
10-14	3.28M	65
15-19	3.15M	170

S. pneumoniae

Given that very young children are one of the groups at highest risk of pneumococcal disease, the development of conjugate vaccines protecting under-2s against *S. pneumoniae* is another high priority area identified by the DH. Several such vaccines have now been developed, protecting against up to a dozen of the most common pneumococcal strains. One of these has already performed well in efficacy trials in the US, although the DH estimate that it will take 3-4 years of further trials before the new conjugate pneumococcal vaccines are licensed for use in the UK. The cost implications of launching any new pneumococcal vaccine are likely to be similar to those associated with the Hib vaccine, with a 'catch-up' programme aimed at all infants under 4 years.

N. meningitidis group B

There are currently no vaccines available that protect against group B meningococcal disease because the polysaccharide capsule surrounding the group B strains does not appear to trigger antibody responses in humans. This may be because these capsules closely resemble natural polysaccharides found in the human brain. The lack of antibody response to group B capsules has forced researchers to seek alternative approaches. Most research to date has concentrated on finding bacterial proteins that protrude through the capsule. Several promising candidates have been identified including iron scavenging proteins (transferrins) that the bacterium needs to poach iron from its host. DH and the Medical Research Council are both funding research in this area, although the DH estimates that commercial group B vaccines are still some 5-10 years away.