Acute bacterial meningitis in adults

Fiona McGill, Robert S Heyderman, Stavros Panagiotou, Allan R Tunkel, Tom Solomon

Summary
Over the past several decades, the incidence of bacterial meningitis in children has decreased but there remains a significant burden of disease in adults, with a mortality of up to 30%. Although the pathogenesis of bacterial meningitis is not completely understood, knowledge of bacterial invasion and entry into the CNS is improving. Clinical features alone cannot determine whether meningitis is present and analysis of cerebrospinal fluid is essential for diagnosis. Newer technologies, such as multiplex PCR, and novel diagnostic platforms that incorporate proteomics and genetic sequencing, might help provide a quicker and more accurate diagnosis. Even with appropriate antimicrobial therapy, mortality is high and so attention has focused on adjunctive therapies; adjunctive corticosteroids are beneficial in certain circumstances. Any further improvements in outcome are likely to come from either modulation of the host response or novel approaches to therapy, rather than new antibiotics. Ultimately, the best hope to reduce the disease burden is with broadly protective vaccines.

Burden of disease and epidemiology
The incidence of bacterial meningitis varies throughout the world. In the UK and western Europe, the incidence is 1–2 cases per 100 000 people per year, whereas it can reach 1000 cases per 100 000 people per year in the Sahel region of Africa (figure 1).1,2 A huge reduction in incidence has occurred over the past few decades, largely secondary to the introduction and widespread use of conjugate vaccines.1,3–4 Conjugate vaccines have a protein attached to purified bacterial capsular polysaccharide. This elicits a more robust and sustained immune response, especially in young children. Table 1 gives an overview of vaccines currently available to prevent meningococcal disease. Conjugate vaccines against meningococcal serogroups B and C have been licensed in the USA and Europe. The polysaccharide capsule; the target for all currently licensed vaccines.5–9 There are more than 90 antigenically different serotypes of S pneumoniae as determined by the polysaccharide capsule; the target for all currently licensed vaccines.

Pneumococcal conjugate vaccines (PCV) have been used for the past 15 years. PCV7 targeted seven pneumococcal serotypes and more recently PCV10 and PCV13 (covering ten and 13 serotypes, respectively) were licensed in the USA and Europe. The polysaccharide vaccine PPV23 covers 23 serotypes. Until recently, conjugate vaccines were largely used only in children but a recent placebo-controlled trial10 in people aged 65 years and older has shown good efficacy of PCV13 in preventing vaccine-type pneumococcal pneumonia, non-bacteraemic pneumonia, and invasive pneumococcal disease, with vaccine efficacies of 46%, 45%, and 75%, respectively. Although most studies on the immunogenicity of pneumococcal vaccines are non-comparative, there is some evidence that PCV is more immunogenic than polysaccharide vaccine.11 The conjugate vaccines also produce substantial herd immunity, when vaccination of part of the population provides protection for non-vaccinated individuals. Large studies have shown substantial reductions of disease caused by vaccine serotypes in both vaccinated and unvaccinated populations.12–15

Since conjugate vaccines were first introduced, serotype replacement has been reported. This is an increase in the incidence of disease or asymptomatic carriage caused by non-vaccine serotypes.16–19 However, the overall incidence of invasive pneumococcal disease has dropped. A meta-analysis from Europe, the Americas, and Australia showed a sustained reduction in the incidence of pneumococcal meningitis in children 7 years after vaccination (risk ratio for meningitis was 0.40, 95% CI 0.25–0.64). There was a similar, but smaller, reduction in adults with a relative risk of meningitis in 18–49-year-old people of 0.61 (95% CI 0.40–0.95) 7 years after vaccination. For adults aged 50–64 years, there was a decrease in meningitis caused by the vaccine serotypes but this was offset by a significant increase in non-vaccine serotype disease (rate ratio 2.83, 95% CI 1.46–5.47).20 Mathematical models have provided insights into the epidemiological outcomes of vaccination, namely that PCV7 has not caused a significant increase in disease caused by non-vaccine serotypes.21–23 It has been suggested that a single conjugate vaccine may not be sufficient to reduce the incidence of invasive pneumococcal disease.24–26 Consequently, the concept of pneumococcal conjugate vaccine–like antigen (PCV-LA) has been developed.27–29

Streptococcus pneumoniae
Pneumococcus is the commonest cause of bacterial meningitis in adults in much of the world.1,3,5 There are more than 90 antigenically different serotypes of S pneumoniae as determined by the polysaccharide capsule; the target for all currently licensed vaccines.

We searched Scopus with the terms “meningitis”, “meningo”*, and “neurological infection” together with “aetiology”, “epidemiology”, “treatment”, “management”, “antibiotic”, “antimicrobial”, “investigation”, “therapy”, “prevention”, “vaccin”*, and “lumbar puncture” for articles published between Jan 1, 2010, and Dec 31, 2015. We also included any studies referenced within these articles if deemed relevant. In addition, any older references known to the authors were also included, as were abstracts of articles not written in English. Review articles are included to guide the reader to a more extensive reference list.

Search strategy
predicted a substantial reduction in disease following the introduction of PCV13, even taking serotype replacement into account.21,22 Observational studies23 accord with these predictions, showing a 32% reduction in invasive pneumococcal disease following the introduction of PCV13, but a 25% increase in non-PCV13 serotypes.

Neisseria meningitidis

Meningococci are categorised into 13 serogroups; five (A, B, C, W135, and Y) are responsible for most cases of invasive disease. Serogroup B is the commonest strain across Europe, including England and Wales where it is responsible for most cases.29,30 Serogroup Y is predominant in the USA27 and the second most common in parts of Europe.28 The prevalence of serogroup W135 is increasing in the UK, which has been linked with a South American clone. Disease caused by this clone is associated with a higher mortality because they are part of the more deadly ST11 clonal complex (or cc11).31 The same clonal complex is responsible for recent outbreaks of meningococcal C disease among men who have sex with men.32,33

Serogroup C was previously responsible for most meningococcal disease in western Europe but incidence has substantially declined since the introduction of the meningococcal C conjugate vaccine. In the Netherlands, incidence has declined from 4·5 cases per 100 000 people in 2001, to 0·6 cases per 100 000 people in 2012.27 Similar results have been seen in other countries.10 In 2015, serogroup C disease appeared for the first time in the Sahel region of Africa.34 Serogroup A has been responsible for large outbreaks in the meningitis belt of Africa; however, massive reductions have occurred in recent years following widespread vaccination.32,33 The Meningitis Vaccine Project—a collaboration between WHO and the Programme for Applied Technology in Health—set out to vaccinate 250 million people in Africa with the new serogroup A conjugate vaccine. The project has been a massive public health triumph. In Burkina Faso, there was a risk reduction of 99·8% and similar results occurred in Niger, where serogroup A disease had virtually disappeared by 2011.33,34 Meningococcal A is also responsible for epidemics in parts of Asia, including India, Indonesia, Nepal, Mongolia, and Pakistan.35

Other bacteria

Haemophilus influenzae type b was a significant cause of meningitis, especially in infants and young children, before the widespread use of conjugate vaccines.6 As with meningococcal disease, H influenzae type b has virtually disappeared in areas where immunisation has been implemented, but remains a problem where vaccination is not commonplace.36 The incidence of invasive haemophilus disease due to non-type b strains has, however, increased. Most of these cases are due to non-typeable organisms but some due to other encapsulated forms of H influenzae, in particular types e and f.37–39

Streptococcus suis is a major cause of meningitis in some parts of Asia, especially Thailand and Vietnam. It is a pathogen of pigs, and close contact with pigs or pork is a significant risk factor for disease. Although the case fatality rate is only 4%, some degree of hearing loss occurs in more than 50% of survivors.40 It has also been reported from many other parts of the world.41–43 Other causes of meningitis include the Enterobacteriaceae, Staphylococcus aureus,44 and Listeria monocytogenes which normally occurs in patients with risk factors such as older adults, alcoholics, diabetics, patients with malignancies, and those taking immunosuppressive drugs.45–48

Pathogenesis

Many aspects of the pathogenesis of bacterial meningitis have yet to be understood; however, there are four main processes: colonisation, invasion into the bloodstream, survival in the bloodstream, and entry into the subarachnoid space. The subsequent inflammation and neurological damage is caused by a combination of bacterial and host factors. Figure 2 shows the pathogenesis of S pneumoniae and N meningitidis meningitis.

Many bacteria that cause meningitis initially colonise the mucous membranes of the upper respiratory tract.
Colonisation involves a combination of the bacteria adhering to the cell surfaces and avoidance of the host’s defence mechanisms. Many organisms have fimbriae (a fringe) or pili (hair-like appendages) that assist in their attachment to the epithelium. The main requirement for meningococcal adhesion is the type IV pili (tfp). Tfp adhere via various receptors including PAFR, β2 adrenoceptor receptors, and CD147. The meningococcal outer membrane proteins including lipopolysaccharide and the opacity proteins (OpC and OpA) have also been proposed to contribute to the maintenance of adhesion. Three main receptors have been proposed for pneumococcal adhesion to epithelial surfaces: PAFR, laminin receptors, and PIGR.

Invasion into the bloodstream occurs either transcellularly (passing through the cells) or pericellularly (between cells). Pneumococci utilise both of these methods via receptors such as PAFR, β2 adrenoceptor receptors, and CD147. The meningococcal outer membrane proteins including lipopolysaccharide and the opacity proteins (OpC and OpA) have also been proposed to contribute to the maintenance of adhesion. Three main receptors have been proposed for pneumococcal adhesion to epithelial surfaces: PAFR, laminin receptors, and PIGR.

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Because of a lack of host defences in the subarachnoid space, bacteria multiply there relatively unhindered. Bacterial components are recognised by pattern recognition receptors, present on microglia and other brain cells. A cascade of events is then triggered that ultimately leads to the release of pro-inflammatory mediators such as TNFα, interleukin 6, and interleukin 1β. Many of these molecules are released in greater quantity in pneumococcal meningitis than in meningitis caused by other organisms and could account for the worse prognosis associated with pneumococcal meningitis. Following the release of the cytokines, granulocytes cross the blood–brain barrier and it becomes more permeable. Bacterial lysis occurs in response to antibiotics or, in the case of pneumococci, when the bacteria reach the stationary growth phase (autolysis). Lysis leads to the release of pro-inflammatory agents, such as lipopolysaccharide, lipoteichoic acid, and peptidoglycans, from the cell wall of the bacterium and augments the inflammatory process.

<table>
<thead>
<tr>
<th>Pathogen covered</th>
<th>Serotypes or serogroups covered</th>
<th>Type of vaccine</th>
<th>Protein conjugate</th>
<th>Vaccines available</th>
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<td>Tetanus toxoid</td>
<td>MenHibrix (also contains Haemophilus type b polysaccharide)</td>
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<td>Tetanus toxoid</td>
<td>MenHibrix (also contains Haemophilus type b polysaccharide)</td>
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<td>Conjugate, monovalent</td>
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<td>Pediacel, Menitorix</td>
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CRM197 is inactive, non-toxic dipheria toxin. Protein D is derived from non-typeable Haemophilus influenzae.

Table 1: Vaccines for bacterial meningitis
Neutrophils have been implicated in much of the neurological damage that occurs in meningitis and MRP-14, a protein expressed in myeloid cells, has been found in the cerebrospinal fluid of patients with pneumococcal meningitis; inhibition of MRP-14 reduced sequelae in a mouse model. Matrix metalloproteinases (MMPs) are released by white blood cells in the CSF. They are present very early in infection and aid the release and activation of pro-inflammatory cytokines, the degradation of extracellular matrix components, and the recruitment of further leucocytes into the subarachnoid space. As with other inflammatory mediators, the levels of MMP-9 are especially high in pneumococcal meningitis compared with meningitis caused by other organisms.

**Genetic predisposition**

Several studies have suggested a genetic predisposition to bacterial meningitis, with most related to deficiencies that affect the complement system. In particular, C2 deficiency has been reported in 58% of patients with pneumococcal meningitis, factor D deficiency predisposes to meningococcal disease, and susceptibility to meningococcal serogroups W135 and Y arises in people with properdin deficiency. Case-control studies showed that polymorphisms in mannose-binding lectin and cfh are associated with susceptibility to pneumococcal and meningococcal disease, respectively. Roughly a fifth of patients with meningococcal disease were defined as having meningitis. Because of variations in definitions, no analysis could be done excluding patients who did not have meningitis. Genome wide association studies have confirmed that a polymorphism in cfh predisposes to meningococcal disease, just over a third of patients in these studies had meningitis, and a polymorphism in the C3 gene predisposed to pneumococcal meningitis.

**Figure 2: Mechanistic pathways in the pathogenesis of bacterial meningitis**

Colonisation by pneumococcus is achieved by various stepwise mechanisms. The opaque capsule of the bacteria prevents sIgA to remove the bacteria from the nasopharynx (1). Release of the PLY toxin from lysed bacteria reduces ciliary contractility of the upper airway (2), whereas deglycosylation of the mucus reduces further cilia activity (3). The negative charge surrounding the capsule, opposes the negative charge of the sialic acid in mucus (4). Additionally, the phase variation of the capsule from opaque to transparent enables adhesion molecules to bind to the epithelium (5). Invasion of pneumococci into the bloodstream is achieved by transcytotic or paracellular mechanisms (6) and degradation of the extracellular matrix (7). The pneumococci then enter the nervous system by following similar mechanistic pathways to the upper airway (8, 9, 10). For meningococcal meningitis, colonisation is achieved by inhibiting sIgA function similarly to the pneumococci (11). Secretion of endotoxins (12) and capsular saccharides (13) as well as the use of meningococcal pili (14), enables the bacteria to bind on the epithelial cells. Invasion into the bloodstream is achieved by the encapsulation of bacteria by phagocytes (15). The bacteria enter the bloodstream and further invade the nervous system transcellularly or paracellularly either binding to fibronectin or laminin (16). For both pneumococcal and meningococcal meningitis, the blood–brain barrier breaks down and cytokines and white blood cells cross into the brain, initiating further inflammatory responses. Intracranial pressure is increased and lysis of the bacteria promotes the creation of free radicals, which can lead to oxidative stress and neuronal damage.
Diagnosis

Diagnosing bacterial meningitis clinically can be difficult because many illnesses present with similar symptoms. The classical triad of neck stiffness, fever, and altered consciousness occurs in less than 50% of patients with acute bacterial meningitis.6 However, any two of headache, fever, neck stiffness, and altered consciousness are much more common, in up to 95% of patients.8 Kernig’s and Brudzinski’s signs have been used in the clinical assessment of meningitis for many years, but their usefulness is doubtful. They have been reported to have high specificity (up to 95%), although this is dependent on the clinician, but the sensitivity can be as low as 5%.64 They should not be relied on to exclude, or depend on the clinician, but the sensitivity can be as high specifi city (up to 95%), although this is.

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The gold standard for diagnosing meningitis is examination of the cerebrospinal fluid (table 2). Measuring the opening pressure at the time of lumbar puncture is useful and is often high in patients with bacterial meningitis. A high white blood cell count in the cerebrospinal fluid can indicate inflammation of the meninges, although some patients might have bacteria in their cerebrospinal fluid without an elevated white blood cell count. These patients have a poor prognosis.

Cerebrospinal fluid protein and glucose should also be measured. Patients with bacterial meningitis typically have high protein and low glucose. Cerebrospinal fluid glucose is influenced by the serum glucose concentration and, therefore, a concurrent serum sample must also be taken. Cerebrospinal fluid lactate may have advantages over glucose in that it is unaffected by the serum concentration. Cerebrospinal fluid lactate, if taken before antibiotic treatment, has a sensitivity of 0·93 (95% CI 0·89–0·96) and specificity of 0·96 (0·93–0·98) in differentiating bacterial from viral meningitis.69 Serum

and cerebrospinal fluid procalcitonin concentrations have also been suggested as useful tests to indicate a likely bacterial cause but well-designed diagnostic accuracy studies, including cost-effectiveness analyses, are needed before recommending the routine use of procalcitonin for diagnosis of bacterial meningitis.

Gram stain and culture of the cerebrospinal fluid enable both the identification of the causative pathogen and assessment of antimicrobial susceptibilities. If the lumbar puncture is delayed until after antibiotics have been given, the likelihood of identifying an organism might be reduced by up to 44%.65,66 Molecular methods are, therefore, becoming increasingly important for diagnosis. The most common of these is PCR, which can detect organisms in blood or cerebrospinal fluid for several days after antibiotics have been given.49,68 It has high sensitivity (87–100%) and specificity (98–100%).69–72 Dried spot cerebrospinal fluid PCR tests, which could be useful in the absence of a laboratory, have shown a 90% sensitivity in diagnosing bacterial meningitis caused by S pneumoniae, S suis, and N meningitidis.73 In addition to cerebrospinal fluid analysis, blood cultures might identify the cause and should be taken before antibiotics are given.

There has been interest in the ability to detect multiple pathogens with one platform, such as multiplex PCR, 16S PCR, MALDI-TOF, and whole genome sequencing.74–76 The 16S rRNA gene is present in almost all bacteria; one meta-analysis75 showed 16S rRNA PCR to be both sensitive and specific for the diagnosis of bacterial meningitis compared with standard culture (pooled sensitivity of 92% and specificity of 94%). The commonest method for species identification after 16S PCR was sequencing. MALDI-TOF is now commonplace in many clinical laboratories. It utilises the protein mass of the organism to identify the bacteria. This has revolutionised clinical microbiology by reducing the time to identification of an organism; it normally requires a cultured organism but there are reports of success direct from cerebrospinal fluid.77 Whole genome sequencing has been used to investigate outbreaks, but as it becomes faster and cheaper, it may be incorporated into routine surveillance and diagnosis.78–79
Preferred choice | Alternative if anaphylaxis to β-lactams
--- | ---
Adults <60 years of age
Cefotaxime 2 g intravenously every 4–6 h or ceftriaxone 2 g intravenously every 12 h
As above; plus amoxicillin or amoxicillin or ampicillin 2 g intravenously every 4 h | Chloramphenicol 25 mg/kg intravenously every 6 h
Vancomycin 15–20 mg/kg intravenously every 8–12 h or plus moxifloxacin 400 mg intravenously every 24 h
As above; plus co-trimoxazole 5 mg/kg (of the trimethoprim component) intravenously every 6–12 h

Adults ≥60 years of age
Cefotaxime 2 g intravenously every 4–6 h or ceftriaxone 2 g intravenously every 12 h; plus vancomycin 15–20 mg/kg intravenously every 8–12 h
As above; plus amoxicillin or ampicillin 2 g intravenously every 4 h | Chloramphenicol 25 mg/kg intravenously every 6 h
Vancomycin 15–20 mg/kg intravenously every 8–12 h; plus moxifloxacin 400 mg intravenously every 24 h
As above; plus co-trimoxazole 5 mg/kg (of the trimethoprim component) intravenously every 6–12 h

Doses are given as a guide only and should not be relied on for prescribing purposes. They also reflect the doses suitable for patients with normal renal and hepatic function.

*Eg, USA, southern and eastern Europe, Asia. †Amoxicillin (or co-trimoxazole if allergic to penicillin) should be added in patients younger than 60 if listerial infection is suspected—eg, in immunocompromised patients. ‡Maintain serum trough concentrations of 15–20 mg/L. §Some authorities would recommend either vancomycin or rifampicin. ¶No clinical data available on optimum dosage in patients with bacterial meningitis.

Table 3: Suggested empirical antibiotic choices for patients with bacterial meningitis

Loop-mediated isothermal amplification is another method of DNA amplification and detection. The method is quick, with results in less than 2 h, and a positive result can be seen with the naked eye. This technique has shown good sensitivity for detection of *N meningitidis*, *S pneumoniae*, *H influenzae*, and *Mycobacterium tuberculosis*. It has also been assessed as a bedside test in the UK, for which it had a positive predictive value of 100% and a negative predictive value of 97%. The speed and ease of diagnosis makes this a very attractive diagnostic tool, especially in resource poor settings.

The use of neuroimaging before lumbar puncture has generated considerable debate with some recommending that cerebral imaging is done before lumbar puncture for all patients. However, this approach has been associated with delays in antibiotic administration, reduced likelihood of identifying a pathogen, and an increase in mortality.84,85 The reason for neuroimaging is to detect cerebral herniation syndromes, or shift of brain compartments. If these are present and a lumbar puncture is done, there is the theoretical concern that a reduction in pressure caused by the lumbar puncture can precipitate a further brain shift, which could lead to fatal herniation. Neuroimaging should therefore be done for patients who have clinical signs that might suggest brain shift and, if shift of brain compartments or herniation is found, lumbar puncture should be delayed. Indications that brain shift might be present include focal neurological signs and reduced level of consciousness. The exact level of consciousness at which a lumbar puncture is safe is debated and different authorities recommend different cutoff points ranging between 8 and 13 on the Glasgow coma scale.88–91

No study has identified features associated with an increased risk of herniation after lumbar puncture. One study showed that certain features (age >60 years, immunocompromised, history of neurological disease, recent seizure, and some abnormal neurological examination findings) were associated with abnormalities on imaging, but the risk of herniation or brain shift was not assessed.86 A retrospective study87 showed that removing impaired mental status as a contraindication for lumbar puncture was associated with significantly earlier treatment and a favourable outcome; however, there are several limitations to this study and cause and effect cannot be attributed. Every patient with suspected bacterial meningitis should be carefully assessed to ascertain whether they have signs or symptoms consistent with brain shift. If they do not, lumbar puncture should be done as soon as possible without prior neuroimaging (appendix).

**Treatment**

Antibiotics should be given as soon as possible to patients with suspected bacterial meningitis, ideally after both blood and cerebrospinal fluid have been obtained for culture. Early antibiotic treatment is associated with a lower mortality.88 If sampling is delayed, the priority is for treatment to be given. Many antibiotic regimens are based on data from animal models or clinical experience rather than randomised trials. The choice of antibiotic depends on the likely pathogen, local patterns of antibiotic resistance, and the cerebrospinal fluid penetration of the drug (table 3). Penicillin and other β-lactams are effective against the commonest pathogens and the cerebrospinal fluid concentration (even with uninflamed meninges) tends to be close to the minimum inhibitory concentrations for moderately susceptible bacteria.92 The worldwide emergence of antimicrobial resistance, especially against *S pneumoniae*, affects the choice of empirical treatment in many countries. This is especially important in the poorer regions of the world, where newer antibiotics might not be available or affordable.

Penicillin-resistant pneumococci have been reported from all parts of the world and have been associated with an increase in mortality.93 Vancomycin is widely recommended when penicillin-resistant pneumococci might be present, but because it crosses the blood–brain barrier poorly it should be used in conjunction with another antimicrobial, often a cephalosporin.

Fluoroquinolones might be good alternatives in the era of penicillin-resistant pneumococci. Experimental...
mouse models have shown moxifloxacin to be equivalent to cephalosporins for treatment of pneumococcal meningitis and cerebritis. Caution should be exercised in using fluoroquinolones as single drugs because organisms might rapidly develop resistance and clinical data are lacking. There are several case reports and case series showing the efficacy of other antibiotics in meningitis, such as ceftaroline, linezolid, daptomycin, and doripenem. Without evidence from comparative trials, these drugs should be used with caution and only when other better tested drugs cannot be used either because of resistance, patient intolerance, or allergy.

Efforts should be made to identify local patterns of antibiotic resistance to determine the best empirical treatment for each geographical area. In the UK, where penicillin resistance is rare, third-generation cephalosporins (cefotaxime or ceftriaxone) remain the empirical choice. However, many parts of the world have penicillin-resistant pneumococci (minimum inhibitory concentration ≥0·12 μg/mL). It occurs in roughly 25% of cases in the USA and parts of Europe (eg, Spain, Croatia, Romania), and more than 50% in Asia; 100% of isolates are resistant in parts of Central Africa (including the Democratic Republic of Congo), and more than 50% in many poorer nations. The high concentration of antibiotic-resistant pneumococci in some countries might benefit from adjunctive dexamethasone, although post-hoc analyses did suggest that there might be some benefit in HIV-negative adults and a lower rate of hearing loss among all survivors.

Another meta-analysis of 25 studies, in both adults and children, showed a small reduction in hearing loss in adults treated with corticosteroids compared with placebo (16% vs 22%; risk ratio 0·74, 95% CI 0·56–0·98) but no difference in mortality. A subgroup analysis showed a slight decline in mortality in all patients with pneumococcal meningitis (risk ratio 0·84, 95% CI 0·72–0·98) with no effect on H influenzae or meningococcal meningitis (although numbers in these groups were very small). This benefit did not remain when a random-effects model was used (which may have been more appropriate given the heterogeneity of the studies; P 47%).

Both these meta-analyses compared very diverse studies and populations including children and adults, high and low socioeconomic status, and differences in comorbidities. This variation is reflected in the heterogeneity of the analyses and possibly accounts for the conflicting conclusions. However, there should be a balance between the risks and potential benefits of corticosteroid use. Overall, corticosteroids seem to offer a small benefit in adults with regard to reducing hearing loss and might slightly lower mortality in pneumococcal meningitis. In most studies, there is no increase in side-effects when corticosteroids were given in comparison to placebo. Therefore, steroids are recommended for all adults with suspected bacterial meningitis in resource-rich countries. Although the meta-analyses did not show a difference between countries of high and low income, there was considerable heterogeneity and in lower income countries the benefits are probably less
pronounced; therefore, corticosteroids are not recommended in this group.

The dose of corticosteroids differs between trials, but the one that was used in the large European trial is 10 mg of dexamethasone given four times a day.125 The Cochrane review124 recommends administration with or just before the first antimicrobial dose.124 Subgroup analyses in both meta-analyses showed no statistical differences in terms of mortality when corticosteroids were given before or with antibiotics compared with when they were given afterwards.124,127 There were differences when hearing loss was the outcome of interest and the effect size was bigger in the group who received corticosteroids after antibiotics compared with the group who received corticosteroids before or concurrently (risk ratio 0·62, 95% CI 0·43–0·89 vs 0·8, 0·7–0·92).124

Glycerol and hypothermia have been trialled as potential adjunctive therapies in bacterial meningitis. Theoretically, osmotic substances such as glycerol can draw extravascular fluid from the brain into the vascular space and reduce intracranial pressure. One clinical study in adults,121 done in a resource-limited setting with a high HIV prevalence, showed no benefit. Induced hypothermia is used as a treatment for cerebral hypoxaemia following cardiac arrest and animal models have shown it to reduce intracranial hypertension in meningitis. Observational clinical studies128,129 also suggested it might be beneficial. However, a randomised controlled trial130 was stopped early because of an increased risk of death in patients in the intervention group. It is unlikely that hypothermia or glycerol will be widely implemented without adaptation and further controlled trials.

Prognosis and sequelae
Features associated with a poor prognosis include older age, reduced conscious level, tachycardia, a cerebrospinal fluid leucocyte count of less than 1000 × 10⁹ cells per mL, and reduced platelet count.3 Prognosis can be improved by instigating both antibiotic and steroid treatment early.1 Sequelae are more common in pneumococcal meningitis than meningococcal meningitis. Hearing loss is one of the most common problems after meningitis, particularly pneumococcal meningitis, and a prompt hearing assessment with cochlear implants can be beneficial for patients. Other sequelae include limb loss, especially if meningococcal sepsis occurs, subdural empyema, hydrocephalus, and seizures. Other less life-threatening sequelae include neurocognitive dysfunction such as sleep disorders.

The future
Many of the pneumococcal vaccines in development are protein based (rather than being based on the capsular polysaccharide), to be given either in addition or as an alternative to conjugate vaccines. This approach could provide pan-serotype protection and eliminate the problem of serotype replacement. Several early phase studies have been done, one of which (combining pneumolysin toxoid and histidine triad protein D, a pneumococcal surface protein thought to be involved in complement inhibition) has provided good evidence of immunogenicity with an acceptable safety profile in both younger and older adults.131–133

The search for a widely effective vaccine against meningococcal serogroup B has been difficult because of
the poorly immunogenic capsule. Vaccines were developed that targeted subcapsular proteins (figure 3) and were used with some success in epidemics in Norway, Cuba, Brazil, New Zealand, and France. However, they were poorly immunogenic in young children and strain specific, and so could not be rolled out on a larger scale. Using a novel genome sequencing method, a multicomponent serogroup B meningococcal vaccine has been produced. It contains four immunogenic components: three proteins (NadA, which is involved in the adhesion of Neisseria to the nasal epithelium; NHBA, thought to be involved in serum resistance; and fHbp) in combination with outer membrane vesicles from the New Zealand vaccine strain. The vaccine is immunogenic in young infants and older children. It might also reduce carriage of other meningococcal serogroups (because some of the subcapsular antigens in the vaccine are also present in non-B serogroups), indicating that it could affect transmission once fully implemented and have a significant effect on disease in adults as well as children. The vaccine has been estimated to provide coverage against 88% of circulating serogroup B strains in England and Wales, and was permitted for investigational use in the USA in late 2013 and early 2014 in two outbreaks. In September, 2015, the UK Department of Health incorporated it into their childhood immunisation schedule. The US Food and Drug Administration have also approved another serogroup B vaccine for adolescents and young adults. This vaccine is a bivalent vaccine that utilises two families of fHbp.

New treatments are needed. Research is focused on adjunctive therapy targeting the host inflammatory response. Some areas of interest include MMP inhibitors and MRP-14 inhibitors such as paquinimod, which has anti-inflammatory effects without affecting bacterial mediators. Some are also being investigated as well as compounds that can modulate the leucocyte response (eg, G-CSF).

Finally, surveillance around the world remains important. The global epidemiology of bacterial meningitis is continually changing, especially with the introduction of new vaccines, and surveillance is needed to determine the breadth of coverage, monitor for serotype replacement, and follow the emergence of new meningococcal serogroups. Robust epidemiological studies should document clearly the causative agents in low-resource settings, especially Asia, to determine what vaccination strategies are necessary. Surveillance for antimicrobial resistance is also of utmost importance. Epidemiological research into risk factors for disease in adults and preventive strategies is also needed.

Effective control of bacterial meningitis is still some way off. Because the disease is both rare and deadly, it requires the vigilance of the clinician to identify and treat it in a timely manner, and the continued support of research partners to develop new vaccines and treatments.

Contributors
FM and TS decided on the scope and plan for the Seminar. FM searched the published work and drafted the first version of the Seminar. All authors then contributed to further drafts and approved the final submitted version. SP gave specific input to the pathogenesis section and designed figures 2 and 3.

Declaration of interests
We declare no competing interests.

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