

## Progress and challenges in bacterial meningitis

Bacterial meningitis is a devastating disease that is associated with substantial mortality and morbidity. The major causative bacteria are *Streptococcus pneumoniae* and *Neisseria meningitidis*, with case-fatality rates of 30% and 7%, respectively, in high-income countries.<sup>1</sup> In resource-poor countries, fatality rates can be as high as 50%.<sup>2</sup> Neurological sequelae, including hearing loss, developmental disorders, and neuropsychological impairment, occur in up to 50% of survivors of the disease.<sup>1,3</sup> Although routine vaccination against the three most common causative bacteria has had a notable effect on the prevalence of bacterial meningitis, an estimated 1.2 million cases occur worldwide every year, resulting in 180 000 deaths in children aged 1–59 months in 2010.<sup>4</sup>

The accompanying *Lancet* Series on bacterial meningitis updates present knowledge of three important aspects of this disease: dilemmas in diagnosis,<sup>5</sup> advances in treatment,<sup>6</sup> and the effect of vaccines on bacterial meningitis worldwide.<sup>7</sup> The Series emphasises substantial progress in clinical diagnostics, molecular diagnostic methods, adjunctive anti-inflammatory treatments, and preventive strategies. The authors also draw attention to evolving challenges: global emergence of multidrug-resistant bacteria, the scarcity of randomised studies to assess treatment strategies, and, perhaps most crucially, the fact that progress benefits mainly patients in high-income countries rather than resource-poor countries where the urgency of the problem is greatest. Further introduction of conjugate vaccines, especially in areas with high disease burdens, is essential for reduction of the global burden of acute bacterial meningitis. Novak and colleagues<sup>8</sup> have reported a promising effect of an affordable *N meningitidis* serogroup A meningococcal conjugate vaccine in sub-Saharan Africa.

The Series describes three main strategies to improve outcomes in patients with bacterial meningitis: early recognition and initiation of antibiotics,<sup>5</sup> optimisation of bacterial killing,<sup>6</sup> and reduction of the inflammatory response in the subarachnoid space.<sup>6</sup> In view of the devastating consequences of delayed antibiotic therapy, adequate antibiotics should be started as soon as possible. However, the global emergence of antibiotic-resistant pathogens threatens the

effectiveness of many inexpensive and widely available antibiotics.<sup>5</sup> New antibiotics can have a role in these situations, but clinical data for these new drugs have not kept pace with the rise of resistance.

Large randomised controlled trials are crucial to establish whether new drugs or treatment strategies have a place in the treatment of bacterial meningitis. For low-income countries with high attack rates of meningitis, randomised studies have examined continuous antibiotic infusion, paracetamol, and the adjunctive treatments glycerol and dexamethasone, but did not show a clear benefit for patients.<sup>6</sup> For high-income countries with low attack rates of meningitis, few randomised studies have been undertaken over the past 15 years. However, in this setting, these studies have shown favourable effects of adjunctive dexamethasone treatment for adults with bacterial meningitis.<sup>9</sup> Dexamethasone treatment has been implemented for pneumococcal meningitis in the Netherlands, which has led to a reduction in the case-fatality rate from 30% to 20%.<sup>10</sup>

In high-income countries in particular, leading bacterial meningitis research groups should collaborate to undertake large multicentre randomised studies to evaluate promising treatments. Solid scientific evidence, rather than beliefs about present practices,

See *Series* pages 1684, 1693, and 1703



Coloured scanning electron micrograph of *Streptococcus pneumoniae*

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should be used to decide which treatments to investigate. An improved understanding of disease pathogenesis and pathophysiology could help to identify such high-potential treatments. Many pre-clinical studies have been undertaken in animals, often with conflicting results.<sup>11</sup> Animal studies of new treatments should be designed carefully, analogous to standards used for clinical studies. The investigators should report how sample size was estimated, whether and how animals were randomised, whether investigators were masked to the treatment, and how data were handled.<sup>12</sup> Because drug-development companies are generally not interested in a disease that affects mainly patients in resource-poor countries, preclinical and clinical studies will need to be funded by governments or charitable foundations.

Genetic factors are major determinants of susceptibility to death from infectious diseases.<sup>13,14</sup> Investigation of the genetics of patients with bacterial meningitis and their causative bacteria could identify new targets for adjunctive treatments and vaccine development. Carefully designed multicentre prospective association studies with appropriate sample sizes are needed, in which clinical phenotypes, DNA of patients and controls, and causative pathogens are collected. We have started a prospective nationwide genetic association study for bacterial meningitis (MeninGene):<sup>15</sup> this ongoing study includes almost 1400 adult patients and their causative bacteria, and genetic analyses are pending. Data from the study will be made publicly available to all meningitis researchers, and we hope that others will join in this initiative towards an open-access biobank for this devastating disease.

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I am the principal investigator of MeninGene. I declare that I have no conflicts of interest.

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## Drug law reform: when bad policy is good politics

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The need for reform of drug laws is now growing in many countries, but change is slow because bad policy is still good politics. Thus, many political systems are unable to move forward with reform of drug laws, and change seems most likely to happen through pressure from civil society.<sup>1</sup>

The global prohibition of drugs developed over many decades, becoming entrenched when three international treaties were agreed between 1961 and

1988.<sup>2</sup> The political usefulness of a punitive approach to drugs first became apparent when President Richard Nixon's declaration of a "War on Drugs" in 1971 contributed to his landslide victory in the 1972 US Presidential election. This encouraged politicians around the world to emulate Nixon's effective political strategy.

During the 1980s, control of HIV among people who inject drugs was of paramount public health

## Bacterial Meningitis 1

# Dilemmas in the diagnosis of acute community-acquired bacterial meningitis

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See [Comment](#) page 1623

This is the first in a [Series](#) of three papers about bacterial meningitis

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Rapid diagnosis and treatment of acute community-acquired bacterial meningitis reduces mortality and neurological sequelae, but can be delayed by atypical presentation, assessment of lumbar puncture safety, and poor sensitivity of standard diagnostic microbiology. Thus, diagnostic dilemmas are common in patients with suspected acute community-acquired bacterial meningitis. History and physical examination alone are sometimes not sufficient to confirm or exclude the diagnosis. Lumbar puncture is an essential investigation, but can be delayed by brain imaging. Results of cerebrospinal fluid (CSF) examination should be interpreted carefully, because CSF abnormalities vary according to the cause, patient's age and immune status, and previous treatment. Diagnostic prediction models that use a combination of clinical findings, with or without test results, can help to distinguish acute bacterial meningitis from other causes, but these models are not infallible. We review the dilemmas in the diagnosis of acute community-acquired bacterial meningitis, and focus on the roles of clinical assessment and CSF examination.

### Introduction

Acute community-acquired bacterial meningitis is a medical emergency, and patients with this disease need immediate medical assessment and treatment. Dilemmas exist in the diagnosis of patients with bacterial meningitis, because clinical findings do not always accurately identify patients with meningitis, and cerebrospinal fluid (CSF) analysis is not always diagnostic. Furthermore, in resource-poor countries with high rates of tuberculosis and HIV, and poor laboratory diagnostics, establishment of the diagnosis of bacterial meningitis can be even more difficult. In this review, we focus on dilemmas in the diagnosis of acute community-acquired bacterial meningitis in children and adults; diagnostic dilemmas in patients with nosocomial bacterial meningitis have been reviewed previously.<sup>1</sup> We review the clinical presentation and differential diagnosis of the disease, use of lumbar puncture, and interpretation of CSF results, and draw

attention to advances in diagnostic markers and the use of prediction models in the diagnosis of acute community-acquired bacterial meningitis after the neonatal period.

### Clinical presentation

In view of the urgent need for antibiotic administration in patients with acute community-acquired bacterial meningitis, early recognition of the disease is essential. The sequence and development of signs and symptoms before hospital admission were retrospectively assessed in 448 children and adolescents with meningococcal diseases, encompassing the full range of disease from sepsis to meningitis.<sup>2</sup> Although limited by its retrospective design, this study showed that the classic symptoms of rash, neck stiffness, and impaired consciousness do not develop until late in the pre-hospital illness, if at all. Adults also displayed this absence of classic symptoms. In a prospective nationwide cohort of 696 adults with culture-proven acute bacterial meningitis, the classic triad of fever, neck stiffness, and altered mental status was present in only 44% of episodes; however, 95% of episodes were characterised by at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status.<sup>3</sup>

Investigators of several studies have assessed the usefulness of neck stiffness, Kernig's sign, and Brudzinski's sign for the diagnosis of community-acquired bacterial meningitis. A meta-analysis of prospective studies in children with suspected bacterial meningitis showed sensitivities of 51% for neck stiffness, 53% for Kernig's sign (likelihood ratio positive test [LR+] 3.5, 95% CI 2.10–5.70; LR negative test [LR–] 0.56, 0.41–0.75), and 66% for Brudzinski's sign (LR+ 2.5, 95% CI 1.80–3.60; LR– 0.46, 0.31–0.68) for the diagnosis of bacterial meningitis.<sup>4</sup> In adults, these clinical findings have low diagnostic accuracy for prediction of CSF pleocytosis (table 1),<sup>5–7</sup> suggesting that absence of these findings

### Search strategy and selection criteria

We searched the Cochrane Library (The Cochrane Library 2011, issue 1), Medline (1966 to March, 2012), and Embase (1974 to March, 2012) with the search terms “bacterial meningitis” or “meningitis” or “meningococcal disease” or “*Neisseria meningitidis*” or “pneumococcal disease” or “*Streptococcus pneumoniae*” in combination with the terms “diagnosis” or “diagnostic techniques” or “spinal puncture” or “cerebrospinal fluid” or “imaging”. We selected mainly articles published in the past 5 years, but did not exclude frequently referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those that we judged to be relevant. Review articles are cited to provide readers with more details and additional references. We modified our reference list on the basis of comments from peer reviewers.

	Thomas <sup>5</sup> (n=297)		Uchihara <sup>6</sup> (n=54)		Waghdhare <sup>7</sup> (n=190)		Combined			
	Meningitis*	No meningitis	Meningitis†	No meningitis	Meningitis*	No meningitis	Sensitivity	Specificity	PPV	NPV
Neck stiffness	24/80 (30%)	69/217 (32%)	5/34 (15%)	0/20 (0%)	39/99 (39%)	27/91 (30%)	31%	71%	41%	61%
Kernig's sign	3/66 (5%)	8/171 (5%)	3/34 (9%)	0/20 (0%)	14/99 (14%)	7/91 (8%)	11%	95%	60%	60%
Bruzinski's sign	3/66 (5%)	8/170 (5%)	NA	NA	11/99 (11%)	6/91 (7%)	9%	95%	50%	62%

Data are number of cases in which each clinical finding was present out of total number of cases in each group (%). PPV=positive predictive value. NPV=negative predictive value. NA=not assessed. \*Meningitis was defined as cerebrospinal fluid white blood cell count  $\geq 6$  cells per  $\mu\text{L}$ . †Meningitis was defined as cerebrospinal fluid white blood cell count  $\geq 5$  cells per  $\mu\text{L}$ .

**Table 1: Test characteristics of clinical findings in adults with suspected meningitis**

cannot be used to exclude the possibility of bacterial meningitis. Physicians should not rely on one test for the diagnosis of bacterial meningitis; the patient's history and physical examination findings should be used together to create a clinical impression that leads to selection of appropriate diagnostic studies.

Many patients with bacterial meningitis have predisposing disorders.<sup>3,8</sup> Ear, sinus, or lung infections precede pneumococcal meningitis in 40% of patients.<sup>3,8</sup> Endocarditis is a rare predisposing infection in patients with bacterial meningitis, but can coexist in those with *Staphylococcus aureus* or *Streptococcus pneumoniae* meningitis.<sup>9</sup> Patients with acute bacterial meningitis can also present with signs of septic shock (10–25% of cases),<sup>10,11</sup> especially those with meningococcal meningitis.<sup>10,12,13</sup> In these patients, meningitis can initially be overlooked because changed mental status is attributed to hypovolaemic shock or septic encephalopathy.

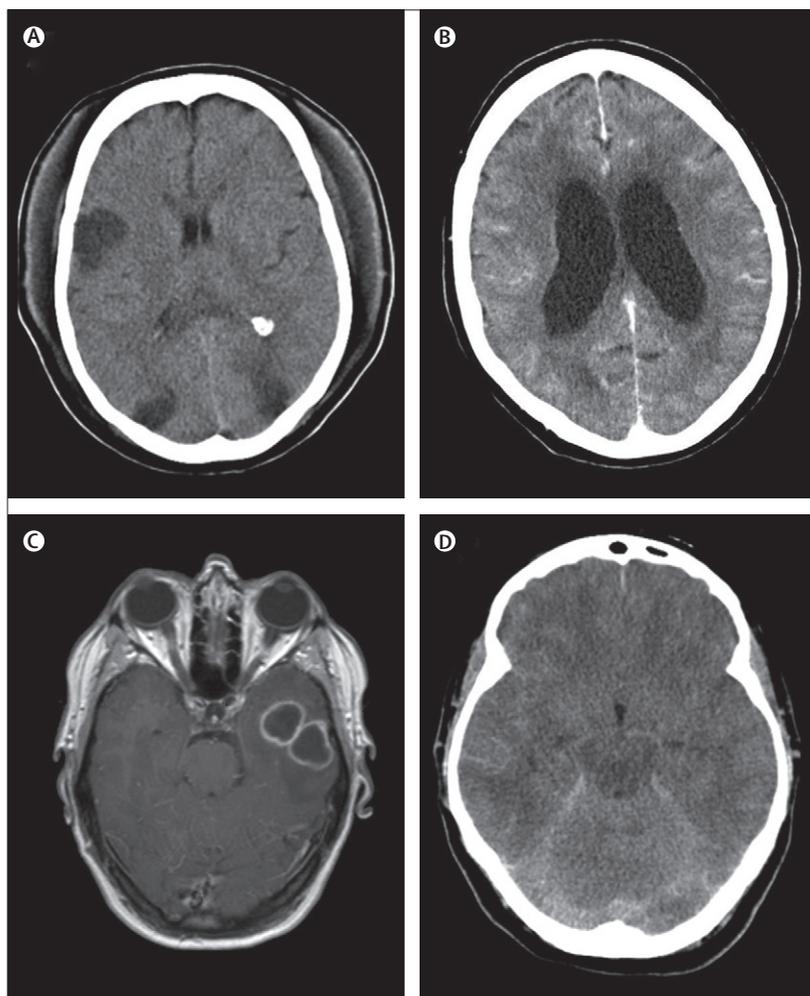
### Differential diagnosis

The differential diagnosis of the triad of fever, headache, and stiff neck includes bacterial or viral meningitis, fungal meningitis, tuberculous meningitis, drug-induced meningitis, carcinomatous or lymphomatous meningitis, meningitis associated with inflammatory diseases (eg, systemic lupus erythematosus, sarcoidosis, Behçet's disease, or Sjögren's syndrome), cerebral abscess, and subarachnoid haemorrhage (when the body temperature is normal or only moderately raised and the onset of headache is acute). The relative importance of these disorders can be measured by a careful neurological examination and a thorough patient history, including information about medical history, recent travel, vaccinations, the use of illicit and immunosuppressive drugs, and risk factors for HIV and sexually transmitted infections. Furthermore, the local epidemiology of rare microorganisms causing CNS infection, such as amoebae, *Trypanosoma cruzi*, *Leptospira* spp, and *Rickettsia* spp, should be considered. Patients with immunosuppression, especially those with HIV infection, have an increased risk of pneumococcal, tuberculous, and cryptococcal meningitis. In resource-poor settings where tuberculous and acute bacterial meningitis are both endemic, a duration of symptoms of more than 5 days before presentation predicts a diagnosis of

tuberculous meningitis.<sup>14–18</sup> Discrimination of bacterial from tuberculous meningitis is crucial, because death or severe neurological disability from tuberculous meningitis is strongly associated with delays in initiation of antituberculosis chemotherapy.<sup>19</sup> If patients have a history of cancer, leukaemia, lymphoma, or autoimmune diseases, physicians should include in the differential diagnosis meningeal or cerebral localisation of these diseases. If no specific risk factors are present, viral meningitis (eg, caused by enteroviruses, herpes simplex virus type 2, or mumps virus) is the most common diagnosis.<sup>20,21</sup> The clinical distinction between viral and acute bacterial meningitis is difficult in the acute phase of illness; therefore, some of these patients are admitted to the hospital and treated with antibiotics until CSF culture results are available or the diagnosis of viral meningitis has been confirmed.<sup>22</sup>

### Lumbar puncture

Because of the urgent and essential need for a lumbar puncture to obtain CSF for diagnostic studies, physicians need to establish whether cranial imaging is needed before doing a lumbar puncture to minimise the potential risks of this procedure. Patients with space-occupying intracranial lesions can present with symptoms identical to acute community-acquired bacterial meningitis or these lesions can complicate acute bacterial meningitis early in the disease course (eg, subdural empyema, epidural abscess, brain abscess, cerebral infarctions, or obstructive hydrocephalus; figure 1); in these patients, brain herniation can complicate lumbar puncture.<sup>23–25</sup> Withdrawal of CSF at the lumbar point causes a cranial–caudal pressure gradient, with the potential to increase the existing brain shift caused by a space-occupying lesion. The incidence of brain herniation after lumbar puncture in patients with meningitis has been debated.<sup>26–28</sup> Investigators of retrospective cohort studies from the USA and the UK reported a cerebral herniation rate after lumbar puncture proven by post-mortem examination in two (1%) of 252 children with meningococcal meningitis and five (1%) of 439 adults with bacterial meningitis.<sup>29,30</sup> However, cerebral herniation also occurs in patients with acute bacterial meningitis without lumbar puncture, which complicates this dilemma further.



**Figure 1:** Cranial CT findings in patients with bacterial meningitis that potentially contraindicate a lumbar puncture

(A) Cerebral infarction. (B) Hydrocephalus. (C) Cerebral abscesses. (D) Diffuse brain oedema.

Physicians can use cranial imaging to help to identify patients at risk of brain herniation after lumbar puncture, but this method is associated with delayed therapy and increased mortality.<sup>21,31,32</sup> A retrospective Canadian study of 123 patients showed that a substantial **delay** of more than **6 h** in initiation of **antibiotic** treatment occurred in 15 (63%) of 24 adult patients in whom **cranial CT** was done before the lumbar puncture.<sup>32</sup> Therefore, empirical treatment should **always** be **started before** the patient is sent for **brain imaging**.

To avoid diagnostic delays, conserve resources, and reduce radiation exposure and unnecessary treatment, **clinical examination** can be used to select patients who **need CT before lumbar puncture**.<sup>21</sup> In a prospective study of 301 adults with suspected acute bacterial meningitis, 235 patients had a CT scan before lumbar puncture. Abnormalities were identified in 52 (24%) patients, and lesions causing brain shift in 11 (5%).<sup>21</sup> New-onset **seizures**, an immunocompromised state

(patients with **HIV/AIDS**, those receiving immunosuppressive therapy, or those who have undergone transplantation), history of a CNS lesion (mass lesion, stroke, or focal infection), signs that suggest space-occupying lesions (papilloedema, **focal** neurological deficits, or evolving signs of brain tissue shift), or **moderate-to-severe** impairment of consciousness can **predict** brain imaging **abnormalities** and can therefore be used to identify patients with suspected acute bacterial meningitis who **need imaging** before lumbar puncture.<sup>21,27</sup> When none of these risk factors is present in adults, brain imaging before the lumbar puncture is **not needed**. Although studies of the selection of children with suspected acute bacterial meningitis who need imaging before lumbar puncture are scarce, criteria similar to those in adults have been recommended.<sup>28</sup> A normal CT scan on admission does not exclude the possibility that the patient will develop brain herniation during the meningitis episode. Other contraindications for doing a lumbar puncture are coagulation disorders such as disseminated intravascular coagulation, use of anticoagulant drugs, or significant thrombocytopenia in patients receiving chemotherapy or those with haematological diseases.<sup>33,34</sup> If a patient presents with septic shock or respiratory failure, the lumbar puncture should be postponed until the patient has been stabilised.

In settings with a high HIV seroprevalence, many patients with suspected acute community-acquired bacterial meningitis would qualify for cranial imaging before lumbar puncture because of the high likelihood of HIV infection,<sup>35–37</sup> yet CT equipment can be scarce in these settings.<sup>38</sup> The risk of death resulting from an inaccurate diagnosis through lumbar puncture deferral is considered greater than the risks that are associated with the procedure, irrespective of focal signs or a reduced state of consciousness, and therefore lumbar puncture should not be deferred.<sup>38</sup>

### CSF examination

CSF examination is essential to establish the diagnosis of bacterial meningitis, identify the causative organism, and undertake in-vitro antibiotic susceptibility testing. Characteristic CSF findings for acute community-acquired bacterial meningitis are a polymorphonuclear **pleocytosis**, **hypoglycorrhachia**, and **raised CSF protein** concentrations.<sup>3,34,39,40</sup> More than 90% of cases of acute bacterial meningitis present with a CSF **white** cell count of **more than 100 cells per  $\mu\text{L}$** .<sup>3</sup> In immunocompromised patients, CSF white cell counts are often low, although an **acellular** CSF is rare, except in patients with **tuberculous meningitis**.<sup>14,19</sup> Polymorphonuclear cells can predominate in the acute phase of many other meningeal infections, including those caused by viruses and ***Mycobacterium tuberculosis***, although, unlike in untreated acute bacterial meningitis, they **rarely exceed 80%** of the total white blood cell counts.<sup>14,41</sup> CSF protein concentrations are

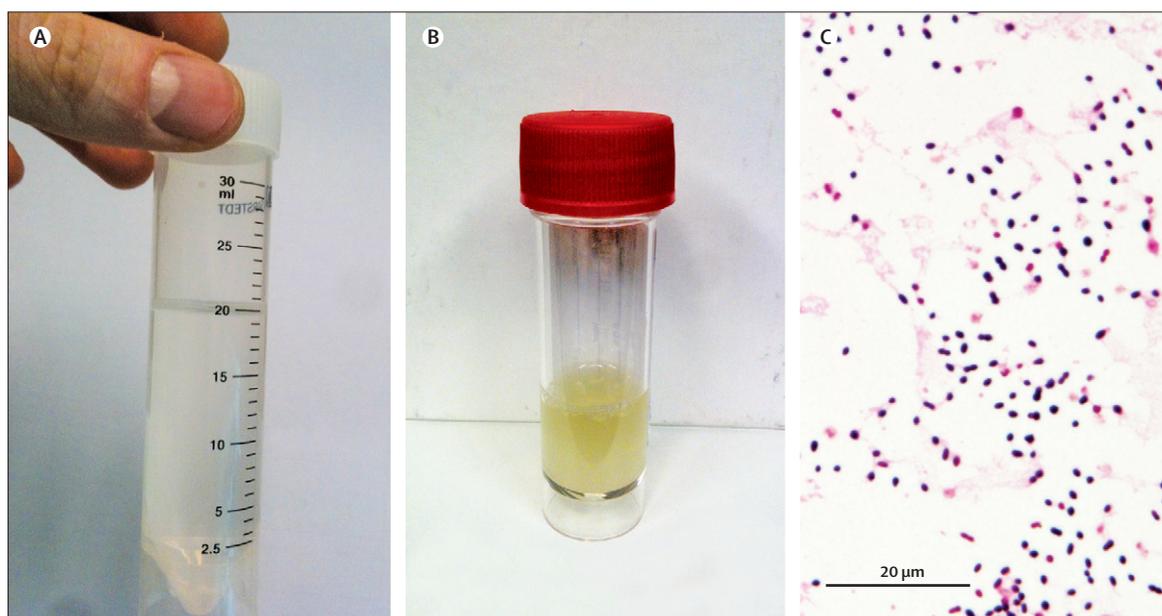


Figure 2: Cerebrospinal fluid appearances of bacterial meningitis

(A) Normal cerebrospinal fluid (CSF). (B) Yellow turbid CSF. (C) CSF Gram stain showing Gram-positive diplococci (*Streptococcus pneumoniae*).

raised in 90% of patients with acute community-acquired bacterial meningitis.<sup>3,30,40,42,43</sup>

CSF culture is the gold standard for diagnosis of bacterial meningitis and is positive in 80–90% of patients with acute community-acquired bacterial meningitis before the start of treatment.<sup>39</sup> CSF Gram staining is a rapid, inexpensive, and well validated method to assess the presence of bacteria in CSF (figure 2); the reported yield of CSF Gram staining in both children and adults ranges from 69% to 93% in pneumococcal meningitis and from 30% to 89% in meningococcal meningitis.<sup>39</sup> The specificity of the CSF Gram stain was 97% in a cohort study including 696 adults with culture-proven acute bacterial meningitis.<sup>3</sup> Blood cultures should always be done on admission and are especially helpful in patients in whom antibiotics are started before the lumbar puncture is undertaken, including when cranial CT is indicated.<sup>39</sup> Blood cultures identify the causative organism in 50–80% of paediatric and adult cases.<sup>39</sup> The yield of blood cultures decreases by 20% if the patient has been pretreated with antibiotics.<sup>44,45</sup>

Because CSF Gram stain and culture do not always identify the causative agent in all patients with bacterial meningitis, molecular diagnostic methods have been studied. Nucleic acid amplification tests, such as PCR, have proven their incremental value compared with Gram stain and CSF culture to identify the causative microorganism, especially in patients with acute community-acquired bacterial meningitis who received antibiotic treatment before lumbar puncture.<sup>39</sup> PCR facilitated diagnosis in 33% of 409 patients aged between 1 month and 67 years in Burkina Faso who could not be

	Number of patients (BM/controls)	Sensitivity	Specificity	PPV	NPV
<b>Corless:<sup>47</sup> CSF culture-confirmed cases (control samples: other bacteria or viruses)</b>					
<i>Neisseria meningitidis</i>	32/0	89%	100%	NA	NA
<i>Streptococcus pneumoniae</i>	23/0	91%	100%	NA	NA
<i>Haemophilus influenzae</i>	6/0	100%	100%	NA	NA
<b>Tzanakaki:<sup>48</sup> CSF culture-confirmed cases (control samples: other bacteria or viruses)</b>					
<i>N meningitidis</i>	33/0	94%	100%	100%	99.1%
<i>S pneumoniae</i>	26/0	88%	100%	100%	99.1%
<i>H influenzae</i>	8/0	92%	100%	100%	99.1%
<b>Parent du Châtelet:<sup>46</sup> CSF culture-confirmed cases (control samples: patients with negative cultures)</b>					
<i>N meningitidis</i>	85/349	95%	95%	NA	NA
<i>S pneumoniae</i>	16/418	79%	95%	NA	NA
<i>H influenzae</i>	34/400	81%	97%	NA	NA
<b>Sacchi:<sup>49</sup> CSF culture-confirmed cases (control samples: specimens positive for other pathogens)</b>					
<i>N meningitidis</i>	90/51	100%	100%	98–100%*	99–100%*
<i>S pneumoniae</i>	46/94	98%	100%	98–100%*	99–100%*
<i>H influenzae</i>	3/139	67%	100%	98–100%*	99–100%*
<b>Boving:<sup>39</sup> CSF culture-positive cases or Gram stain-positive cases (control samples: CSF culture-negative cases)</b>					
<i>N meningitidis</i>	21/1166	91%	99.1%	68%	100%
<i>S pneumoniae</i>	6/1181	100%	99.7%	67%	100%

BM=bacterial meningitis. PPV=positive predictive value. NPV=negative predictive value. CSF=cerebrospinal fluid. NA=not available. \*Individual values per pathogen not presented.

Table 2: Test characteristics for multiplex CSF PCR in the diagnosis of bacterial meningitis

diagnosed with conventional methods.<sup>46</sup> Broad-range PCR can be used to detect the most common microorganisms in one test, and has adequate sensitivity and excellent specificity (table 2).<sup>46–50</sup> PCR techniques have evolved rapidly and can now be done within 2 h in most

industrialised countries; however, the availability of PCR in resource-poor settings is scarce.

An immunochromatographic test is available for the detection of *S pneumoniae* in CSF. In one study including 450 children with suspected acute bacterial meningitis, this test was 100% sensitive and specific for the diagnosis of pneumococcal meningitis;<sup>51</sup> the overall sensitivity of this test ranges from 95% to 100%.<sup>52</sup> Despite these promising results, more studies are needed to establish the usefulness of this test in non-specialist laboratories.

### Prediction models

In patients without a positive CSF Gram stain or culture, the diagnosis of acute bacterial meningitis is often difficult to establish or reject. A combination of clinical findings with or without test results has been assessed to develop models that allow accurate prediction of the likelihood of acute bacterial meningitis compared with other possible causes (especially viral meningitis). Oostenbrink and colleagues<sup>53–55</sup> developed a prediction model to guide decisions about the use of lumbar puncture and empirical antibiotic therapy in children aged between 29 days and 15 years with suspected acute bacterial meningitis. The model included assessment of variables from patients' history, physical examination, and measurement of serum C-reactive protein (table 3). In both the derivation and validation sets, none of the children with risk scores less than 9.5 had acute bacterial meningitis, and lumbar puncture could be withheld in about 35% of children with meningeal signs without a single case of acute bacterial meningitis being missed. In a follow-up study, the same investigators reported that the addition of CSF polymorphonuclear cell count and ratio of CSF to blood glucose to their diagnostic model was useful for the decision to start empirical antibiotic therapy in children with meningeal signs.<sup>54</sup> These prediction models were subsequently analysed in an external population from four paediatric hospitals in the Netherlands.<sup>53</sup> In the derivation part of the study, the

investigators used a clinical score of 9.5 to discriminate between children with or without acute bacterial meningitis; however, application of this score to prospective validation yielded two children with acute bacterial meningitis with a clinical score of 8.5. Bacterial meningitis was diagnosed in none of the 205 children with a score less than 8.5, 13% with a score of 8.5–14.9, 52% with a score of 15–19.9, and 87% with a score greater than 20. The frequency of acute bacterial meningitis increased with the CSF score, although there was no threshold value at which the CSF score could be used to exclude a diagnosis of acute bacterial meningitis.

Other investigators have examined specific CSF variables to predict the likelihood of acute bacterial meningitis. In one analysis of the records of 422 immunocompetent patients older than 1 month with acute bacterial or viral meningitis,<sup>43</sup> a CSF glucose concentration less than 1.9 mmol/L, a ratio of CSF to blood glucose less than 0.23, a CSF protein concentration above 2.2 g/L, more than 2000 CSF leucocytes per  $\mu\text{L}$ , or more than 1180 CSF neutrophils per  $\mu\text{L}$  predicted bacterial rather than viral meningitis with 99% certainty or higher (table 3). This model was validated in a retrospective review of 160 adult patients with bacterial or viral meningitis,<sup>58</sup> which showed that the model was robust when applied to a geographically distinct adult population. Further validation was achieved in another retrospective review of 500 consecutive cases of community-acquired meningitis in children older than 1 month and adults; when the probability of acute bacterial meningitis was equal to 0.1, the negative and positive predictive values of this model were 99% and 68%, respectively.<sup>59</sup> These investigators also created a new model with four slightly different independent variables (CSF protein concentration, total CSF polymorphonuclear cell count, blood glucose concentration, and leucocyte count); the negative and positive predictive values of this model were 99% and 85%, respectively. When this model was used in patients younger than

	Studies	Population	Prediction rule	Scored items
Oostenbrink meningitis score	Oostenbrink (o/p, n=286; v=74), <sup>55</sup> Oostenbrink (o/r, n=227), <sup>54</sup> Oostenbrink (v/p, n=226) <sup>53</sup>	Children aged 1 month–15 years	No bacterial meningitis cases if score <8.5 on 44-point scale (range 0–44)	Duration of complaints=1 point per day (maximum 10), vomiting=2, meningeal irritation=7–5, cyanosis=6–5, petechiae or ecchymosis=4, disturbed consciousness=8, CRP=0.5 points per 10 mg/L increase, CSF PMN count=0–4*†, CSF to blood glucose ratio=0.5 points per 0.1 decrease*
Bacterial meningitis score	Nigrovic (o/r, n=456, v=240), <sup>56</sup> Nigrovic (v/r, n=3295), <sup>20</sup> Dubos (v/r, n=198) <sup>57</sup>	Children and young adults aged 29 days–19 years (16 years in Dubos study)	Bacterial meningitis unlikely if score 0 on 6-point scale (range 0–6)	Positive CSF Gram stain=2, CSF protein $\geq 0.8$ g/L =1, peripheral absolute neutrophil count $\geq 10\,000$ cells per $\mu\text{L}$ =1, seizures before or on admission=1, CSF absolute neutrophil count >1000 cells per $\mu\text{L}$ =1
Spanos CSF prediction model	Spanos (o/r, n=422), <sup>43</sup> McKinney (v/r, n=160), <sup>58</sup> Hoen (v/r, n=500), <sup>59</sup> Leblebicioglu (v/r, n=30) <sup>60</sup>	Children aged >1 month and adults (in McKinney study, defined as >17 years)	Bacterial meningitis likely if one CSF characteristic present	CSF glucose concentration <1.9 mmol/L, CSF to blood glucose ratio <0.23, CSF protein concentration >2.2 g/L, CSF leucocyte count >2000/ $\mu\text{L}$ , CSF neutrophil count >1180/ $\mu\text{L}$
Hoen CSF prediction model	Hoen (o/r, n=500), <sup>59</sup> Leblebicioglu (v/r, n=30), <sup>60</sup> Baty (v/p, n=109) <sup>64</sup>	Children aged >1 month and adults	Bacterial meningitis unlikely if score <0.1	Risk of bacterial meningitis formula = $1/(1+e^{-L})$ , in which $L=32.13 \times 10^{-4} \times \text{CSF PMN count } (10^6/\text{L}) + 2.365 \times \text{CSF protein } (\text{g/L}) + 0.6143 \times \text{blood glucose } (\text{mmol/L}) + 0.2086 \times \text{white blood cell count } (10^9/\text{L}) - 11$

o=original study, p=prospective study, n=number of included patients, v=validation study, r=retrospective study, CRP=C-reactive protein, CSF=cerebrospinal fluid, PMN=polymorphonuclear leucocyte. \*Added to original score after follow-up study. †<10 cells per  $\mu\text{L}$ =0 points, 10–99 cells per  $\mu\text{L}$ =1 point, 100–999 cells per  $\mu\text{L}$ =2 points, 1000–9999 cells per  $\mu\text{L}$ =3 points, >10 000 cells per  $\mu\text{L}$ =4 points.

Table 3: Clinical prediction models for community-acquired acute bacterial meningitis

3.5 years, the positive and negative predictive values were 96% and 97%, respectively.

Other prediction models based on similar and other variables have also been developed and validated.<sup>56,62,63</sup> Nigrovic and colleagues<sup>56</sup> reviewed records of a cohort of 696 children and young adults aged between 29 days and 19 years diagnosed with meningitis. The investigators used multivariable logistic regression and recursive partitioning analyses to identify predictors from the derivation set, which led to development of a bacterial meningitis score (table 3) to distinguish bacterial from aseptic meningitis. Patients with none of these parameters were given a score of 0 and identified as low risk for acute bacterial meningitis, with a negative predictive value of 100% (95% CI 97–100) and a specificity of 73% (51–100). A score above 2 had a sensitivity of 87% (72–96) and a positive predictive value of 87% (72–96) for acute bacterial meningitis. These figures need to be interpreted with some caution, because the prediction model includes a positive CSF Gram stain that adds 2 points to the risk score. Patients with positive Gram stains, in whom there is no diagnostic uncertainty, should ideally be excluded from studies of prediction models to differentiate bacterial from viral meningitis. The investigators validated the score externally with a large retrospective cohort of 3295 patients aged between 29 days and 19 years in 20 academic medical centres in the USA;<sup>20</sup> of the 1714 patients categorised as low risk by the bacterial meningitis score, only two had acute bacterial meningitis (negative predictive value 99.9%, 95% CI 99.4–100), providing further help for decision making for children and young adults who present at emergency departments with CSF pleocytosis.

Although another study<sup>57</sup> has confirmed the usefulness of the Nigrovic bacterial meningitis score compared with other models, universal applications of bedside prediction models are not always appropriate. In a retrospective study of the application of the bacterial meningitis score to 21 children aged 0–15 years with acute bacterial meningitis, five did not have all criteria and would have been considered low risk and not treated.<sup>64</sup> These investigators developed a new score using a C-reactive protein concentration less than 20 mg/L, CSF glucose concentration above 2.89 mmol/L, and CSF protein concentration less than 1 g/L. A score of 0 points distinguished viral meningitis from acute bacterial meningitis in 54 of 70 children (100% accuracy and 100% specificity); with this formula, only 16 patients with viral meningitis would have received antibiotics compared with the 41 patients in their series who were actually treated.<sup>64</sup>

The benefit of the use of these prediction models in patients with suspected acute bacterial meningitis is to guide decision making for those in whom further diagnostic studies and therapy could be appropriately withheld. In individual patients with suspected acute bacterial meningitis, a prediction model could have value, but clinicians' judgment (to include the presence of other

presenting symptoms, signs, and laboratory variables) should continue to be used in decisions about the need for CSF analysis and administration of empirical antibiotic and adjunctive therapy. The use of these models should also be limited to the age cohort in which they were developed. Another important limitation of the described prediction models is that they all differentiate between viral and acute bacterial meningitis, but in clinical practice many other causes (eg, fungal or mycobacterial meningitis) might need to be considered. These prediction models might be most useful in doubtful cases, when they can be used to suggest a reconsideration of the diagnosis.

### Diagnostic markers

Studies have examined other markers for their diagnostic use in patients with acute bacterial meningitis (table 4); these studies have focused mainly on the differentiation of acute bacterial from viral meningitis. Determination of the CSF lactate concentration is a widely available, straightforward, cheap, and rapid diagnostic test.<sup>73,74</sup> Two meta-analyses, one including 25 studies with 1692 patients (adults and children)<sup>73</sup> and the other including 31 studies with 1885 patients (adults and children),<sup>74</sup> both concluded that the diagnostic accuracy of CSF lactate is better than that of CSF white blood cell

	Number of patients (BM/AM/HC)	Sensitivity	Specificity	PPV	NPV
<b>CSF analytes</b>					
Stahel <sup>65</sup> (A)					
Complement factor 3	18/21/64	100%	100%	94.7%	100%
Complement factor B	18/21/64	100%	92.5%	100%	100%
Linder <sup>66</sup> (A)					
Heparin-binding protein	37/29/97	100%	99.2%	96.2%	100%
Holub <sup>67</sup> (A)					
Cortisol	47/37/13	100%	82%	NA	NA
Determann <sup>68</sup> (A)					
sTREM1	92/8/9	73%	77%	94%	34%
Tang <sup>69</sup> (C)					
Interleukin 1 $\beta$	23/26/95	78%	96%	95%	83%
Tumour necrosis factor $\alpha$	23/26/95	74%	81%	77%	78%
Hsieh <sup>70</sup> (C)					
Interleukin 6	12/41/42	96%	51%	19%	98%
Interleukin 12	12/41/42	96%	75%	24%	98%
<b>Serum analytes</b>					
Sormunen <sup>71</sup> (C)					
C-reactive protein	325/182/0	86%	100%	100%	80%
Dubos <sup>72*</sup> (C)					
Procalcitonin	96/102/0	99%	86%	NA	NA
C-reactive protein	96/102/0	86%	67%	NA	NA

CSF=cerebrospinal fluid. BM=bacterial meningitis. AM=aseptic meningitis. HC=healthy controls. PPV=positive predictive value. NPV=negative predictive value. A=adults. C=children. NA=not available. sTREM1=soluble triggering receptor expressed on myeloid cells 1. \*Meta-analysis of six retrospective European studies.

**Table 4: Test characteristics for CSF and serum diagnostic markers in different studies**

count, glucose, and protein concentration in the differentiation of bacterial from aseptic meningitis (sensitivities of 93% [95% CI 89–96] and 97% [95–98], and specificities of 96% [93–98] and 94% [93–96], respectively). In patients who received antibiotic treatment before the lumbar puncture, CSF lactate concentration had a substantially lower sensitivity of 49% (23–75) compared with those not receiving antibiotic pretreatment (98%, 96–100).<sup>74</sup> CSF lactate concentration is less accurate in patients with several other CNS diseases, such as stroke and head trauma, in which the concentrations are raised. Therefore, the usefulness of CSF lactate concentrations in patients pretreated with antibiotics, or those with some other CNS diseases, is probably limited.<sup>73,74</sup>

CSF concentrations of cortisol, heparin-binding protein, soluble triggering receptor expressed on myeloid cells 1, interleukin 6, interleukin 12, interleukin 1 $\beta$ , tumour necrosis factor  $\alpha$ , complement component B, and complement component 3 have been studied as markers for acute bacterial meningitis in single studies of children or adults (table 4).<sup>65–70</sup> Most of these studies included fewer than 40 patients, limiting the generalisability of the results. The concentration of CSF complement component B had 100% sensitivity and specificity in adults, and the performance of complement component 3 and heparin-binding protein was excellent (complement component 3 sensitivity 100%, specificity 95%; heparin-binding protein sensitivity 100%, specificity 99.2%) in the differentiation of bacterial from aseptic meningitis.<sup>65,66</sup>

Retrospective studies have shown that serum concentrations of C-reactive protein and procalcitonin are highly discriminatory between paediatric bacterial and viral meningitis.<sup>71,72</sup> A study of 507 children showed a specificity of C-reactive protein of 100% (95% CI 97–100) for patients with a C-reactive protein concentration greater than 40 mg/L, and a sensitivity of 93% (90–96) for identification of acute bacterial meningitis cases.<sup>71</sup> A meta-analysis of six retrospective studies in 198 children showed that increased serum procalcitonin ( $\geq 0.5$   $\mu\text{g/L}$ ) and C-reactive protein ( $\geq 20$  mg/L) concentrations were associated with acute bacterial meningitis, with an odds ratio of 434 (95% CI 57.0 to  $>1000.0$ ) for increased procalcitonin, and 9.9 (4.8–20.8) for increased C-reactive protein concentrations.<sup>72</sup> However, whether these additional CSF and serum tests add any value to standard tests is unclear.

### Additional diagnostic dilemmas

In resource-poor settings, the differentiation between acute bacterial meningitis, cryptococcal meningitis, tuberculous meningitis, and cerebral malaria can be very difficult when patients have received prehospital antibiotic treatment.<sup>38,75</sup> Abnormalities in the CSF white blood cell count and CSF protein and glucose concentrations are usually less pronounced in patients with acute bacterial meningitis who are receiving antibiotics than in those who are not, and could therefore resemble

CSF abnormalities that are typical for patients with tuberculous meningitis. Molecular diagnostic methods (eg, PCR) can help to identify the causative microorganism in these patients,<sup>76</sup> but are often not available in resource-poor settings and, if available, are not helpful if the result is negative. In these patients, treatment for both bacterial and tuberculous meningitis is usually started, and repeated lumbar puncture is done to assess the treatment effect.

Antibiotics kill susceptible bacteria in the CSF rapidly, rendering the sample sterile within about 8 h of administration.<sup>77</sup> In a retrospective case series of 92 patients with suspected acute bacterial meningitis, CSF culture was positive in 73% of patients who had a lumbar puncture up to 4 h after start of antibiotic treatment, compared with 11% of patients who had a later lumbar puncture.<sup>77</sup> Antibiotic treatment also causes the CSF white blood cell count to decrease in the subsequent 48–72 h, with a rise in the proportion of mononuclear cells, and an increase in CSF glucose, which is usually very low in untreated acute bacterial meningitis, to normal concentrations.<sup>14</sup>

When the suspicion of acute bacterial meningitis in a patient is sufficiently high to start empirical antibiotic treatment, but the diagnosis has not been confirmed directly by characteristic CSF findings or Gram stain, the diagnosis needs to be reassessed after admission. Results of blood and CSF cultures, cryptococcal antigen testing, Ziehl–Neelsen or India ink stains, and, when available, PCR results of CSF, will subsequently become available in the days after admission. If these tests remain negative or are unavailable, and the patient has no response to the initiated therapy, diagnostic uncertainty continues, particularly in patients in resource-poor settings. In these patients, cryptococcal, tuberculous, and partly treated acute bacterial meningitis are difficult to distinguish apart, and physicians often start empirical treatments for tuberculous and acute bacterial meningitis simultaneously.<sup>38</sup> A repeated lumbar puncture could be necessary to repeat microbiological tests on CSF and to assess the response to therapy. A rapid decrease in CSF cell count and protein, and an increase in glucose, is expected in patients with acute bacterial meningitis but not in those with tuberculous meningitis.<sup>14</sup>

### Conclusions and future directions

Early recognition of acute community-acquired bacterial meningitis is essential to improve the prognosis of the disease. Clinical assessment alone is insufficient to exclude acute bacterial meningitis, and a lumbar puncture with CSF analysis is needed in all patients with suspected acute bacterial meningitis. In some cases, cranial imaging is needed before lumbar puncture to detect brain shift; in these patients, empirical antibiotic treatment should be given before imaging. Molecular diagnostic methods have emerged in the diagnostic process for acute bacterial meningitis, although costs

restrict their use worldwide. Well designed studies of diagnostic accuracy are needed for new CSF variables that add potential value to standard laboratory tests. Prediction models can be used to estimate the risk of acute bacterial meningitis, but these models need to be refined and validated further in several settings and populations. Clinical judgment of individual patients by their physicians remains the most important factor in the diagnosis of acute bacterial meningitis.

#### Contributors

All authors contributed to writing and editing of the review, and all authors approved the final version.

#### Conflicts of interest

We declare that we have no conflicts of interest.

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## Bacterial Meningitis 2

### Advances in treatment of bacterial meningitis

Diederik van de Beek, Matthijs C Brouwer, Guy E Thwaites, Allan R Tunkel

Bacterial meningitis kills or maims about a fifth of people with the disease. Early antibiotic treatment improves outcomes, but the effectiveness of widely available antibiotics is threatened by global emergence of multidrug-resistant bacteria. New antibiotics, such as fluoroquinolones, could have a role in these circumstances, but clinical data to support this notion are scarce. Additionally, whether or not adjunctive anti-inflammatory therapies (eg, dexamethasone) improve outcomes in patients with bacterial meningitis remains controversial; in resource-poor regions, where the disease burden is highest, dexamethasone is ineffective. Other adjunctive therapeutic strategies, such as glycerol, paracetamol, and induction of hypothermia, are being tested further. Therefore, bacterial meningitis is a substantial and evolving therapeutic challenge. We review this challenge, with a focus on strategies to optimise antibiotic efficacy in view of increasingly drug-resistant bacteria, and discuss the role of current and future adjunctive therapies.

#### Introduction

Acute bacterial meningitis is a life-threatening infectious disease, the epidemiology of which has changed substantially since the introduction of conjugate vaccines.<sup>1-3</sup> Nevertheless, the disease continues to inflict a heavy toll, including in high-income countries, causing substantial morbidity and mortality.<sup>1,4</sup> Early administration of antibiotics saves lives, but the global emergence of multidrug-resistant bacteria threatens the effectiveness of many inexpensive and widely available antibiotics. The role of adjunctive anti-inflammatory therapies is uncertain, especially in resource-poor settings. For these reasons, bacterial meningitis is an evolving therapeutic challenge. In this review, we discuss the various treatment strategies available, and draw attention to advances in antibiotic and adjunctive therapy.

#### Initial empirical antibiotics

Early clinical suspicion of bacterial meningitis and rapid administration of antibiotics is important to increase survival and reduce morbidity. In a prospective study of 156 patients with pneumococcal meningitis admitted to an intensive-care unit,<sup>5</sup> a delay in antibiotic treatment of longer than 3 h after arrival at the hospital was associated with increased 3-month mortality.

Administration of empirical antibiotics for patients with bacterial meningitis should be based on local epidemiology, the patient's age, and the presence of specific underlying diseases or risk factors (table 1).<sup>4,6</sup> In geographical regions with *Streptococcus pneumoniae* (pneumococcal) strains that are resistant to penicillin and cephalosporins (figure), patients older than 1 month with community-acquired bacterial meningitis should receive vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone). The decision of whether to use vancomycin depends on the rate of resistance to third-generation cephalosporins. In areas where the prevalence of cephalosporin-resistant *S pneumoniae* is low (<1% resistance), a third-generation cephalosporin (either cefotaxime or ceftriaxone) usually suffices as empirical

therapy. Furthermore, vancomycin is expensive and rarely available in low-income countries.<sup>7</sup> Alternative agents in these settings include an antipneumococcal fluoroquinolone (eg, moxifloxacin) and rifampicin, although clinical data to support the use of these drugs are scarce. Rifampicin is inexpensive, widely available, penetrates reasonably well into cerebrospinal fluid (CSF), and usually has in-vitro activity against ceftriaxone-resistant pneumococcal strains.<sup>4,8</sup>

*Listeria monocytogenes* is noteworthy because of its resistance to cephalosporins. Amoxicillin or ampicillin are effective against *Listeria* spp and should be given to immunosuppressed patients with meningitis who are at risk of this infection, including pregnant patients and those older than 50 years.

#### Optimisation of the delivery and effectiveness of antibiotics

Optimisation of the delivery and effectiveness of antibiotics are two key therapeutic challenges in bacterial meningitis. Penetration across the blood-brain barrier is important for successful treatment and depends on the amount of disruption of the barrier's integrity by inflammation, and the size, charge, lipophilicity, protein-binding ability, and interaction with efflux pumps of the antibiotic (table 2).<sup>8,9</sup> However, clinical efficacy also

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See [Comment](#) page 1623

This is the second in a [Series](#) of three papers about bacterial meningitis

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#### Search strategy and selection criteria

We searched the Cochrane Library (The Cochrane Library 2011, issue 1), Medline (1966 to March, 2012), and Embase (1974 to March, 2012). We used the search terms "bacterial meningitis" or "meningitis" with the terms "therapy" or "antibiotics" or "antimicrobial" or "treatment". We mainly selected articles published in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those that we judged to be relevant. Review articles and book chapters are cited to provide readers with more details and more references than can be included in this paper. We modified our reference list on the basis of comments from peer reviewers.

	Bacterial pathogens	Empirical therapy	Intravenous dose (dose interval)
<b>Community-acquired meningitis</b>			
Age <1 month	<i>Streptococcus agalactiae</i> , <i>Escherichia coli</i> , <i>Listeria monocytogenes</i>	Amoxicillin/ampicillin plus cefotaxime, or amoxicillin/ampicillin plus an aminoglycoside	Age <1 week: ampicillin 150 mg/kg per day (8 h); cefotaxime 100–150 mg/kg per day (8–12 h); gentamicin 5 mg/kg per day (12 h) Age 1–4 weeks: ampicillin 200 mg/kg per day (6–8 h); gentamicin 7.5 mg/kg per day (8 h); tobramycin 7.5 mg/kg per day (8 h); amikacin 30 mg/kg per day (8 h); cefotaxime 150–200 mg/kg per day (6–8 h)
Age 1–23 months	<i>Sagalactiae</i> , <i>E coli</i> , <i>S pneumoniae</i> , <i>Neisseria meningitidis</i>	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)*	Vancomycin 60 mg/kg per day (6 h) to achieve serum trough concentrations of 15–20 µg/mL; cefotaxime 225–300 mg/kg per day (6–8 h); ceftriaxone 80–100 mg/kg per day (12–24 h)
Age 2–50 years	<i>S pneumoniae</i> , <i>N meningitidis</i>	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)*	Children as above; adults: vancomycin 30–60 mg/kg per day (8–12 h) to achieve serum trough concentrations of 15–20 µg/mL; ceftriaxone 4 g per day (12 h); cefotaxime 8–12 g per day (4–6 h); cefepime 6 g per day (8 h); ceftazidime 6 g per day (8 h); amoxicillin or ampicillin 12 g per day (4 h); penicillin 24 million units per day (4 h); meropenem 6 g per day (8 h)
Age >50 years	<i>S pneumoniae</i> , <i>N meningitidis</i> , <i>L monocytogenes</i> , aerobic Gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)	As for adults above
Immunocompromised state	<i>S pneumoniae</i> , <i>N meningitidis</i> , <i>L monocytogenes</i> , <i>Staphylococcus aureus</i> , <i>Salmonella</i> spp, aerobic Gram-negative bacilli (including <i>Pseudomonas aeruginosa</i> )	Vancomycin plus ampicillin plus either cefepime or meropenem	..
Recurrent	<i>S pneumoniae</i> , <i>N meningitidis</i> , <i>Haemophilus influenzae</i>	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)	..
<b>Health-care-associated meningitis</b>			
Basilar skull fracture	<i>S pneumoniae</i> , <i>H influenzae</i> , group A β-haemolytic streptococci	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)	..
Head trauma; post-neurosurgery	Staphylococci ( <i>S aureus</i> and coagulase-negative staphylococci), aerobic Gram-negative bacilli (including <i>P aeruginosa</i> )	Vancomycin plus ceftazidime, cefepime, or meropenem	..

Preferred daily intravenous doses (and dosing intervals) apply to patients with normal renal and hepatic function. In patients with impaired renal function, the loading (initial) dose of the antibiotic is based on the extracellular fluid volume and is not changed in the case of decreased renal function; subsequent doses or dosing intervals need to be changed in patients with impaired renal function. \*Add amoxicillin or ampicillin if meningitis caused by *L monocytogenes* is also suspected.

**Table 1: Empirical antibiotics for presumed bacterial meningitis by demography and risk factor**

depends on the antibiotic CSF concentration and its bactericidal activity against causative bacteria.<sup>8</sup> For example, although β-lactam antibiotics penetrate poorly into the CSF, very effective bactericidal concentrations can be achieved by administration of frequent and high systemic doses, which are generally well tolerated.<sup>8</sup> Toxicity makes dose escalation difficult for the aminoglycosides, glycopeptides, and polymyxins; therefore, intrathecal or intraventricular administration of these agents might be needed to reach effective CSF concentrations, although data to support the safety and efficacy of this approach are scarce.<sup>10</sup> The intrathecal route resulted in high CSF aminoglycoside concentrations in young children with gram-negative meningitis,<sup>11</sup> but a controlled, non-randomised study of intrathecal versus intravenous gentamicin in 117 infants with Gram-negative meningitis did not show clinical benefit.<sup>12</sup> Furthermore, in a randomised controlled trial of intraventricular versus systemic gentamicin, investigators reported a substantially higher mortality rate in patients receiving intraventricular gentamicin therapy (43% vs 13%).<sup>13</sup>

A better understanding of the relation between CSF concentration and antibiotic effectiveness could improve clinical outcomes. Almost 60 years ago, Eagle and colleagues<sup>14</sup> showed that penicillin killed bacteria more effectively when given continuously rather than by bolus injections; the best predictor of successful treatment was the time that concentrations were maintained above the minimum inhibitory concentration (MIC). Some studies have investigated whether continuous infusions of these antibiotics improve outcomes in patients with bacterial meningitis.<sup>15</sup> A possible benefit of continuous cefotaxime infusion was suggested in a study of 723 African children with bacterial meningitis randomly assigned to either cefotaxime boluses or continuous cefotaxime infusion for the first 24 h of therapy;<sup>16</sup> 272 (38%) children died, but the mode of cefotaxime administration did not significantly change the proportion of children who died or were severely disabled by hospital discharge. However, a planned subgroup analysis showed that children with pneumococcal meningitis given continuous cefotaxime infusion were significantly less likely to die or have sequelae than were those given cefotaxime boluses.

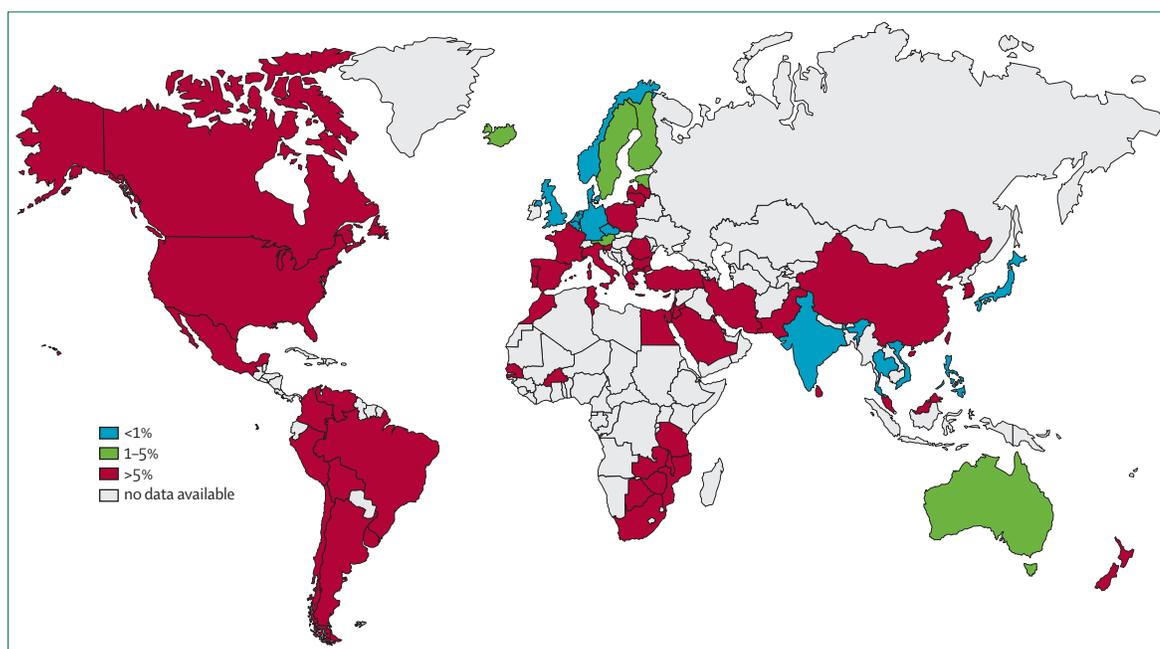


Figure: Global rates of pneumococcal penicillin resistance

### Antibiotics for specific organisms

Once a bacterial pathogen has been identified on a CSF Gram stain, or isolated and in-vitro susceptibility testing done, antibiotic therapy can be modified further for optimum treatment (tables 3 and 4).

#### *Streptococcus pneumoniae*

The treatment of pneumococcal meningitis has changed since the emergence of strains with reduced susceptibility to penicillin (figure); the prevalence of reduced susceptibility ranges from 25% to more than 50% in some US regions and is even higher in many other countries.<sup>17</sup> Penicillin resistance is a marker of decreased susceptibility to other antibiotics, which could lead to treatment failures in patients with pneumococcal meningitis.<sup>18</sup> In areas with cephalosporin resistance, empirical therapy for pneumococcal meningitis should consist of vancomycin combined with either cefotaxime or ceftriaxone, pending results of in-vitro susceptibility testing. Although rates of pneumococcal meningitis have decreased since the introduction of the heptavalent pneumococcal conjugate vaccine, the number of patients with meningitis caused by serotypes not covered by the vaccine, including resistant strains, has increased.<sup>19</sup> Non-vaccine serotypes are generally more susceptible to antibiotics than are vaccine serotypes, except for serotype 19A.<sup>19</sup>

Adequate doses of vancomycin are important to achieve appropriate CSF concentrations, because concomitant use of adjunctive dexamethasone could reduce vancomycin penetration into CSF. In a study of 14 patients with bacterial meningitis who were receiving adjunctive dexamethasone, administration of intravenous vancomycin

(15 mg/kg loading dose, followed by a continuous infusion of 60 mg/kg per day), led to adequate CSF vancomycin concentrations (mean 7.9 µg/mL).<sup>20</sup> Although clinical data on the efficacy of rifampicin in patients with pneumococcal meningitis are scarce, some authorities use this agent in combination with a third-generation cephalosporin, with or without vancomycin, in patients with pneumococcal meningitis caused by strains that are likely to be highly resistant to penicillin or cephalosporins.<sup>4</sup>

Once the MIC of penicillin and third-generation cephalosporins is known, treatment can be modified accordingly (table 4). The Clinical and Laboratory Standards Institute has redefined the in-vitro susceptibility breakpoints for pneumococcal isolates from patients with meningitis as either susceptible (MIC ≤0.06 µg/mL) or resistant (MIC ≥0.12 µg/mL) to penicillin;<sup>21</sup> for penicillin-resistant strains, the therapeutic approach depends on the degree of in-vitro susceptibility to the third-generation cephalosporins.

#### *Neisseria meningitidis*

The current treatment recommendation for meningococcal meningitis is penicillin G, amoxicillin, or ampicillin.<sup>3,4,6</sup> However, meningococcal strains with reduced susceptibility to penicillin have been identified in many countries. In a Spanish study,<sup>22</sup> the investigators reported an increase in the prevalence of meningococcal strains with reduced susceptibility to penicillin from 9.1% in 1986, to 71.4% in 1997. By contrast, intermediate susceptibility to penicillin (MIC >0.1 µg/mL) has been reported in 3–4% of US meningococcal isolates and 2% of isolates in sub-Saharan Africa.<sup>23,24</sup> In one study,<sup>25</sup> investigators recorded an association between reduced susceptibility to

	CSF penetration (CSF:plasma)* in uninfamed meninges	CSF penetration (drug in CSF:plasma)* in inflamed meninges	Comments on use of antibiotic class for meningitis treatment
<b>β-lactams</b>			
Benzylpenicillin	0.02	0.1	Poor CSF penetration, but high systemic doses are well tolerated and attain CSF concentrations that greatly exceed the MIC of susceptible bacteria. 40% of cefotaxime vs 90% of ceftriaxone is protein bound. Avoid imipenem because it could lower the seizure threshold. Continuous infusions could enhance bacterial killing
Amoxicillin/ampicillin	0.01	0.05	
Cefotaxime	0.1	0.2	
Ceftriaxone	0.007	0.1	
Meropenem	0.1	0.3	
<b>Aminoglycosides</b>			
Gentamicin	0.01	0.1	Poor CSF penetration and toxicity limits increases in systemic doses. Consider intraventricular/intrathecal delivery if needed
Amikacin	No data	0.1	
<b>Glycopeptides</b>			
Vancomycin	0.01	0.2	Poor CSF penetration and toxicity limits increases in systemic doses. Continuous infusions could enhance bacterial killing. Limited data for intraventricular/intrathecal delivery
Teicoplanin	0.01	0.1	
<b>Fluoroquinolones</b>			
Ciprofloxacin	0.3	0.4	Good CSF penetration. Moxifloxacin is an alternative agent for the treatment of penicillin-resistant pneumococcal meningitis
Moxifloxacin	0.5	0.8	
Levofloxacin	0.7	0.8	
<b>Others</b>			
Chloramphenicol	0.6	0.7	Excellent CSF penetration, although toxicity concerns limit its use 80% protein bound; CSF concentrations greatly exceed MIC of susceptible bacteria
Rifampicin	0.2	0.3	
<b>Newer agents</b>			
Cefepime	0.1	0.2	Effective against penicillin-resistant pneumococcal meningitis
Linezolid	0.5	0.7	Case report/series suggest effectiveness for pneumococcal, staphylococcal, and enterococcal meningitis, although high interindividual variability in CSF pharmacokinetics suggests therapeutic drug measurements could be needed
Daptomycin	No data	0.05	Poor penetration, but CSF concentrations exceed MIC of susceptible bacteria; case reports/series suggest efficacy in staphylococcal and enterococcal meningitis
Tigecycline	No data	0.5	Good CSF penetration, but concentrations achieved at current standard doses could be insufficient to ensure bacterial killing

CSF=cerebrospinal fluid. MIC=minimum inhibitory concentration. \*Based on calculated area under the curve (AUC)<sub>CSF</sub>/AUC<sub>plasma</sub> when possible, but data are limited for most antibiotics and AUC cannot be calculated on the basis of single CSF measurements. In these circumstances, CSF penetration is estimated from paired plasma and CSF measurements.

**Table 2: Estimates of CSF penetration of antibiotics used for the treatment of bacterial meningitis<sup>8,9</sup>**

	Antibiotic therapy
Gram-positive cocci in pairs	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)
Gram-negative cocci in pairs	Third-generation cephalosporin (either cefotaxime or ceftriaxone)
Gram-positive bacilli	Amoxicillin/ampicillin* or penicillin G*
Gram-positive cocci in chains	Amoxicillin/ampicillin or penicillin G*
Gram-negative bacilli	Third-generation cephalosporin

\*Consider the addition of an aminoglycoside.

**Table 3: Recommended antibiotics in patients with community-acquired meningitis by result of cerebrospinal fluid Gram stain**

penicillin and an increased risk of death or neurological sequelae in children with meningococcal meningitis. Therefore, patients with meningococcal meningitis should be treated empirically with a third-generation cephalosporin (cefotaxime or ceftriaxone) until results of

in-vitro susceptibility testing are available. High-level resistance to chloramphenicol (MIC  $\geq 64$   $\mu\text{g/mL}$ ) has been reported,<sup>26</sup> but the incidence is low in most countries.<sup>27</sup> Furthermore, ciprofloxacin resistance has been described in some regions of the USA,<sup>28</sup> and has affected recommendations for chemoprophylaxis. During meningococcal meningitis epidemics in resource-poor settings, one intramuscular injection of long-acting chloramphenicol is sufficient;<sup>27</sup> an injection of ceftriaxone is equally effective.<sup>29</sup>

#### *Listeria monocytogenes*

Amoxicillin, ampicillin, or penicillin G is the treatment of choice for *Listeria* meningitis.<sup>30</sup> Some authorities have recommended the addition of an aminoglycoside because of enhanced in-vitro killing and in-vivo synergy in animal models. No study has been done to compare amoxicillin or ampicillin alone versus amoxicillin or

ampicillin plus gentamicin, although retrospective clinical data suggest that the addition of gentamicin can reduce mortality.<sup>31</sup> By contrast, in a cohort of 118 patients with listeriosis, the aminoglycoside-treated group had increased rates of kidney injury and mortality.<sup>32</sup> Trimethoprim-sulfamethoxazole is an alternative treatment in patients who are allergic to or intolerant of penicillin. In a retrospective study,<sup>33</sup> treatment with trimethoprim-sulfamethoxazole plus ampicillin was associated with a lower antibiotic failure rate and fewer neurological sequelae than was the combination of ampicillin plus an aminoglycoside.

### *Streptococcus agalactiae*

The standard approach to the treatment of meningitis caused by group B streptococci is amoxicillin or ampicillin or penicillin G combined with an aminoglycoside.<sup>4</sup> Vancomycin and third-generation cephalosporins are alternatives. Some group B streptococci are less sensitive to penicillin (MIC 0.12–1.0 µg/mL) than others; the optimum regimen for these isolates is not clear and the efficacy of the third-generation cephalosporins in this setting has not been established.<sup>34</sup>

### *Haemophilus influenzae*

Since the emergence of β-lactamase-producing and chloramphenicol-resistant strains of *H influenzae*, third-generation cephalosporins have become standard treatment. Third-generation cephalosporins are more effective than second-generation cephalosporins (eg, cefuroxime)<sup>35</sup> and chloramphenicol, even in patients with *H influenzae* type b meningitis caused by chloramphenicol-sensitive strains.<sup>36</sup> The rates of isolation of β-lactamase-producing strains vary worldwide (15% in the UK, 26% in the USA, 31% in France, and 42% in Spain), with high rates (42%) for non-typeable strains in the USA.<sup>4</sup> Chloramphenicol resistance is also a concern in resource-poor settings, where the drug is often used as first-line therapy for patients with bacterial meningitis. In Japan, the prevalence of β-lactamase-negative ampicillin-resistant *H influenzae* meningitis has increased rapidly from 6% in 2000 to 35% in 2004; many of these strains are also resistant to ceftriaxone.<sup>37</sup>

### Aerobic Gram-negative bacilli

The emergence of multidrug-resistant Gram-negative bacilli is worrying, especially in patients with health-care-associated bacterial meningitis.<sup>9</sup> Resistance to the third-generation and fourth-generation cephalosporins, and carbapenems, has reduced the range of antibiotic options available. Outbreaks of meningitis caused by *Escherichia coli* strains producing extended-spectrum β-lactamases in neonatal wards can be difficult to control.<sup>38</sup> In patients with *Acinetobacter baumannii* meningitis, the most commonly used empirical antibiotic is meropenem with or without gentamicin or amikacin given either intraventricularly or intrathecally.<sup>9</sup> If the organism is resistant to carbapenems,

	Recommended therapy	Alternative therapies
<i>Streptococcus pneumoniae</i>		
Penicillin MIC ≤0.06 µg/mL	Penicillin G or amoxicillin/ampicillin	Cefotaxime, ceftriaxone, chloramphenicol
Penicillin MIC ≥0.12 µg/mL		
Cefotaxime or ceftriaxone MIC† <1.0 µg/mL	Cefotaxime or ceftriaxone	Cefepime, meropenem
Cefotaxime or ceftriaxone MIC† ≥1.0 µg/mL	Vancomycin plus either cefotaxime or ceftriaxone‡	Vancomycin plus moxifloxacin§
<i>Neisseria meningitidis</i>		
Penicillin MIC <0.1 µg/mL	Penicillin G or amoxicillin/ampicillin	Cefotaxime, ceftriaxone, chloramphenicol
Penicillin MIC ≥0.1 µg/mL	Cefotaxime or ceftriaxone	Cefepime, chloramphenicol, fluoroquinolone, meropenem
<i>Listeria monocytogenes</i>		
	Amoxicillin/ampicillin or penicillin G¶	Trimethoprim-sulfamethoxazole
<i>Streptococcus agalactiae</i>		
	Amoxicillin/ampicillin or penicillin G¶	Cefotaxime, ceftriaxone, vancomycin
<i>Haemophilus influenzae</i>		
β-lactamase negative	Amoxicillin/ampicillin	Cefotaxime, ceftriaxone, cefepime, chloramphenicol, aztreonam, fluoroquinolone
β-lactamase positive	Cefotaxime or ceftriaxone	Cefepime, chloramphenicol, aztreonam, fluoroquinolone
β-lactamase negative, ampicillin resistant	Meropenem	Fluoroquinolone
<i>Staphylococcus aureus</i>		
Meticillin sensitive	Nafcillin or oxacillin	Vancomycin, linezolid, daptomycin
Meticillin resistant	Vancomycin	Trimethoprim-sulfamethoxazole, linezolid, daptomycin
<i>Staphylococcus epidermidis</i>	Vancomycin	Linezolid
Enterobacteriaceae**		
	Cefotaxime or ceftriaxone	Aztreonam, fluoroquinolone, trimethoprim-sulfamethoxazole, meropenem, ampicillin
<i>Pseudomonas aeruginosa</i>	Ceftazidime or cefepime¶	Aztreonam, meropenem, ciprofloxacin¶
<i>Acinetobacter baumannii</i> **	Meropenem	Colistin (usually formulated as colistimethate sodium), polymyxin B††

MIC=minimum inhibitory concentration. \*In the absence of clinical data, recommendations for use of some agents are based on cerebrospinal fluid penetration and efficacy in experimental animal models of bacterial meningitis. †In-vitro activities of β-lactam antibiotic agents against *S pneumoniae* are predictable within drug classes, but the relation between penicillin and cefotaxime-ceftriaxone MICs is not linear. ‡Addition of rifampicin can be considered if the organism is susceptible, the expected clinical or bacteriological response is delayed, or the cefotaxime/ceftriaxone MIC of the pneumococcal isolate is >4.0 µg/mL. §No clinical data exist for use of this agent in patients with pneumococcal meningitis; recommendation is based on cerebrospinal fluid penetration and in-vitro activity against *S pneumoniae*. ¶Addition of an aminoglycoside should be considered; might need intraventricular or intrathecal administration in Gram-negative meningitis. ||Addition of rifampicin should be considered. \*\*Choice of a specific agent should be based on in-vitro susceptibility testing. ††Might also need to be administered by the intraventricular or intrathecal routes.

**Table 4: Antibiotics for bacterial meningitis after microorganism identification and in-vitro susceptibility testing\***

colistin (usually formulated as colistimethate sodium) or polymyxin B should be given intravenously, and might be given by the intrathecal or intraventricular route. In one retrospective study of 51 patients with *Acinetobacter* meningitis,<sup>39</sup> all eight patients given a combination of intravenous and intrathecal colistin survived.

### *Staphylococcus aureus*

*S aureus* meningitis occurs mainly after neurosurgical procedures or placement of CSF shunts.<sup>9</sup> Treatment

should depend on the local prevalence of methicillin-resistant *S aureus*; antistaphylococcal penicillins are more effective than is vancomycin for the treatment of severe *S aureus* disease, but empirical vancomycin can be used until susceptibility testing results are ready.<sup>40</sup>

### Duration of antibiotic therapy

Antibiotics need enough time to kill all the bacteria and prevent disease recurrence, but the timescale of this process varies widely and depends on the causative bacteria, disease severity, and antimicrobial agent used. Uncomplicated meningococcal disease can be treated effectively with one intramuscular dose of ceftriaxone or oily chloramphenicol, both of which are recommended by WHO in African meningococcal meningitis epidemics.<sup>29,41</sup> WHO recommends at least 5 days of treatment in non-epidemic situations, in patients younger than 24 months, or if fever, coma, or convulsions last for longer than 24 h.<sup>41</sup> In a meta-analysis of five controlled trials investigating shorter (4–7 days) versus longer (7–14 days) antibiotic treatments for bacterial meningitis, investigators noted no difference in outcome.<sup>41,42</sup> In a controlled trial in 1027 children with bacterial meningitis caused by *S pneumoniae*, *H influenzae*, or *N meningitidis* in Bangladesh, Egypt, Malawi, Pakistan, and Vietnam, the investigators reported no differences in treatment failure or relapse between 5 days versus 10 days of ceftriaxone treatment.<sup>43</sup> Nevertheless, many authorities in high-income countries recommend at least 7 days of treatment for haemophilus and meningococcal meningitis, and 10–14 days of treatment for pneumococcal meningitis.<sup>3,6</sup>

### New antibiotics for meningitis

The increasing prevalence of meningitis caused by resistant bacteria has led to the consideration of new antimicrobial agents for therapy, although data describing their role are generally limited to extrapolations from experimental animal models and case reports. We will limit our discussion to agents that have been assessed in patients with bacterial meningitis.

#### Cefepime

The fourth-generation cephalosporin cefepime has broad-range activity and greater stability against  $\beta$ -lactamases, including those often produced by *Pseudomonas aeruginosa*, than have agents from the preceding generation (eg, ceftriaxone and cefotaxime). Findings from experimental meningitis models and some human studies suggested that cefepime could have better CSF activity than ceftriaxone, including against penicillin-resistant *S pneumoniae*;<sup>44,45</sup> however, in two controlled trials of 345 children with bacterial meningitis, the investigators reported that cefepime has similar efficacy to cefotaxime and ceftriaxone.<sup>44,45</sup> The Infectious Diseases Society of America (IDSA) guidelines recommend cefepime as a second-line agent in the treatment

of *H influenzae* meningitis, and either cefepime or ceftazidime as empirical first-line treatment in patients with post-neurosurgical meningitis.<sup>6</sup>

#### Carbapenems

Of the  $\beta$ -lactams, the carbapenems possess the broadest range of in-vitro activity against Gram-positive and Gram-negative bacteria. Results from studies in human beings suggest that meropenem has better CSF penetration than do imipenem and doripenem.<sup>8,46</sup> In four controlled trials of 448 children and 58 adults, meropenem had similar efficacy and safety to cefotaxime or ceftriaxone, making meropenem the carbapenem of choice in the treatment of bacterial meningitis.<sup>8</sup> The emergence of novel  $\beta$ -lactamases with direct carbapenem-hydrolysing activity has contributed to an increased prevalence of carbapenem-resistant Enterobacteriaceae.<sup>47</sup>

#### Fluoroquinolones

The fluoroquinolones gatifloxacin and moxifloxacin penetrate the CSF effectively and have greater in-vitro activity against Gram-positive bacteria than do their earlier counterparts (eg, ciprofloxacin). Findings from experimental meningitis models suggested their efficacy in *S pneumoniae* meningitis, including that caused by penicillin-resistant and cephalosporin-resistant strains.<sup>48,49</sup> Although one controlled trial suggested the fluoroquinolone trovafloxacin mesilate to be as effective as ceftriaxone, with or without the addition of vancomycin, for paediatric bacterial meningitis,<sup>50</sup> no clinical trials describe the use of gatifloxacin or moxifloxacin to treat bacterial meningitis in human beings. Trovafloxacin and gatifloxacin have been associated with serious hepatic toxicity and dysglycaemia, respectively, and were withdrawn from many markets.<sup>51</sup> The IDSA guidelines recommend moxifloxacin as an alternative to third-generation cephalosporins plus vancomycin for meningitis caused by *S pneumoniae* strains resistant to penicillin and third-generation cephalosporins,<sup>6</sup> although some experts recommend that this agent should not be used alone but rather should be combined with another drug (either vancomycin or a third-generation cephalosporin), because of the absence of clinical data supporting its use.

#### Daptomycin

Daptomycin is a cyclic lipopeptide with solely Gram-positive activity. Although it penetrates the CSF poorly, experimental models indicate that CSF bactericidal concentrations are achieved against most susceptible organisms, and daptomycin could have greater bactericidal activity than vancomycin against  $\beta$ -lactam-resistant bacteria.<sup>52</sup> Human data are limited to case reports that describe the successful use of daptomycin (6–12 mg/kg once daily), usually combined with rifampicin, for meningitis caused by methicillin-resistant *S aureus* and vancomycin-resistant *Enterococcus* spp.<sup>53,54</sup>

### Linezolid

Linezolid is an oxazolidinone that acts only on Gram-positive bacteria. It has never been assessed in a controlled trial in patients with bacterial meningitis, although some case reports have been published;<sup>55</sup> linezolid penetrates the CSF well and is associated with cure rates of about 90%. Clinical studies have reported variable CSF penetration; about 50% of patients given standard doses (600 mg every 12 h) might not achieve therapeutic CSF concentrations.<sup>56</sup> Higher doses and CSF concentration measurements might be needed to optimise linezolid therapy for bacterial meningitis.

### Tigecycline

Tigecycline is a glycylglycyl antibiotic that is active against many Gram-positive and Gram-negative bacteria. Data about its use in bacterial meningitis are limited mainly to case reports describing tigecycline treatment for multidrug-resistant *Acinetobacter* meningitis,<sup>57</sup> some of which show that standard intravenous tigecycline doses produce subtherapeutic CSF concentrations.<sup>57,58</sup>

### Adjunctive dexamethasone therapy

Experimental animal models have shown that outcome from bacterial meningitis is related to the severity of inflammation in the subarachnoid space and could potentially be improved by modulation of the inflammatory response—eg, with dexamethasone.<sup>59</sup> Initial trials suggested that dexamethasone reduced the risk of hearing loss in children with *H influenzae* type b meningitis.<sup>60</sup> Additional data extended the likely benefit to children with *S pneumoniae* meningitis if dexamethasone was given with or before the first dose of an antibiotic agent.<sup>60</sup> However, subsequent randomised controlled trials in Malawian and South American children did not show a benefit of dexamethasone.<sup>61,62</sup> A Cochrane meta-analysis published in 2010<sup>60</sup> showed that adjunctive dexamethasone treatment did not reduce mortality in children with bacterial meningitis, but did decrease hearing loss from 20% in the control group to 15% in corticosteroid-treated children (risk ratio [RR] 0.74, 95% CI 0.62–0.89). None of the included studies investigated children younger than 1 month (neonatal meningitis), and one randomised, but not placebo-controlled, trial did not show a benefit of dexamethasone in neonates.<sup>63</sup>

For adults with community-acquired bacterial meningitis, the results of a European controlled trial showed that adjunctive dexamethasone, given before or with the first dose of antibiotic therapy, was associated with a reduced risk of unfavourable outcome (15% vs 25%; RR 0.59, 95% CI 0.37–0.94) and a reduction in mortality (7% vs 15%, 0.48, 0.24–0.96).<sup>64</sup> This beneficial effect was most obvious in adults with pneumococcal meningitis, in whom the mortality rate decreased from 34% to 14%. However, randomised controlled trials in Malawi and Vietnam did not show that dexamethasone benefited adult patients,<sup>65,66</sup>

although the Vietnam trial<sup>66</sup> did show that dexamethasone increased survival in patients with microbiologically confirmed bacterial meningitis.

Investigators of an individual patient data meta-analysis of trials published since 2000 attempted to explain the differences between individual trial results.<sup>67</sup> In this analysis of 2029 patients of all age groups from five trials, treatment with adjunctive dexamethasone did not significantly reduce mortality, neurological disability, or severe hearing loss in patients with bacterial meningitis. There were no significant treatment effects in any of the prespecified subgroups. A post-hoc analysis suggested that adjunctive dexamethasone treatment reduced the rate of hearing loss in survivors (odds ratio [OR] 0.77, 95% CI 0.60–0.99;  $p=0.04$ ). Adjunctive dexamethasone treatment was not associated with an increased risk of adverse events.

Guidelines recommend the use of adjunctive dexamethasone in patients with suspected or proven community-acquired bacterial meningitis, but only in high-income countries.<sup>68</sup> Dexamethasone treatment should be started with or before the first dose of antibiotics. It should be given for 4 days at a dose of 0.6 mg per kg of bodyweight intravenously every day for children, and 10 mg given intravenously every 6 h for adults. A controlled study of 118 children with bacterial meningitis showed 2-day and 4-day regimens of dexamethasone to be similarly effective.<sup>69</sup> However, this study was underpowered, with neurological sequelae or hearing loss occurring in 1.8% and 3.8% of patients in the 2-day and 4-day regimen groups, respectively. Dexamethasone should be stopped if the patient is discovered not to have bacterial meningitis or if the bacterium causing the meningitis is a species other than *H influenzae* or *S pneumoniae*, although some experts advise that adjunctive treatment should be continued irrespective of the causative bacterium.<sup>3</sup> A recent study showed that adjunctive dexamethasone is widely prescribed for Dutch patients with meningococcal meningitis and is not associated with harm.<sup>70</sup>

Adjunctive dexamethasone therapy has been implemented on a large scale for patients with pneumococcal meningitis in some settings. In a nationwide observational cohort study in the Netherlands,<sup>71</sup> the drug was given in 92% of meningitis episodes during 2006–09. This observational study reported a decrease in mortality from 30% to 20% after the introduction of adjunctive dexamethasone therapy (absolute risk difference 10%, 95% CI 4–17;  $p=0.001$ ).

Cognitive deficits occur often after bacterial meningitis,<sup>72</sup> and studies in animals have suggested that corticosteroids can aggravate learning deficiencies.<sup>59</sup> A follow-up of the European study in adults did not show differences in cognitive outcome between patients who received dexamethasone and those who received placebo.<sup>73</sup>

A potential rare complication of dexamethasone therapy in pneumococcal meningitis is delayed cerebral thrombosis, although a causal relation between this complication and dexamethasone is difficult to establish.<sup>74</sup> Delayed cerebral

thrombosis can occur 7–19 days after hospital admission in patients with excellent initial recovery.<sup>74</sup>

Studies published so far do not address two important questions: is dexamethasone effective after the first antibiotic dose; and is dexamethasone effective in patients with septic shock? In experimental pneumococcal meningitis, CSF bacterial concentrations at the start of treatment seemed to be a more important factor affecting the antimicrobial-induced inflammatory response than the time when dexamethasone therapy was started.<sup>75</sup> An individual patient data meta-analysis showed that dexamethasone reduced hearing loss, irrespective of whether the drug was given before or after antibiotics.<sup>67</sup> In patients with bacterial meningitis and severe sepsis or septic shock, the survival benefit in patients with pneumococcal meningitis who were given adjunctive dexamethasone outweighed the risks associated with high-dose steroids.<sup>71,76</sup>

### Other adjunctive therapies

Glycerol is a hyperosmolar agent that has been used to decrease intracranial pressure. Although glycerol had no beneficial effect in experimental meningitis models,<sup>59</sup> a randomised clinical trial in Finland suggested that this drug might protect against sequelae in children with bacterial meningitis.<sup>77</sup> A randomised controlled trial of 654 children with bacterial meningitis in several South American countries showed a significant decrease in sequelae.<sup>62</sup> However, a randomised controlled trial of 265 Malawian adults with bacterial meningitis showed that adjuvant glycerol was harmful and increased mortality.<sup>78</sup> In children, the evidence is insufficient to justify routine glycerol treatment, but a randomised controlled trial of this topic is ongoing in Malawi (NCT00619203).

Despite some reported beneficial effects of monitoring and lowering of intracranial pressure in patients with bacterial meningitis,<sup>79</sup> when and how it should be undertaken is unclear.<sup>80</sup> Randomised studies of various strategies to lower intracranial pressure have not been done. Nevertheless, in patients with impending cerebral herniation, monitoring of intracranial pressure and use of osmotic diuretics to lower intracranial pressure could be considered, but outcomes are generally poor in this critically ill group of patients.<sup>80</sup>

Antipyretic treatments are often administered in severely ill patients, but their effect on outcome is uncertain. In a randomised controlled trial of 723 children with bacterial meningitis in Luanda, Angola, treatment with paracetamol for the first 48 h did not increase survival.<sup>16</sup> Active cooling leading to hypothermia has beneficial effects in animals with pneumococcal meningitis.<sup>59</sup> The results of a randomised clinical trial of moderate hypothermia in patients with severe bacterial meningitis are eagerly awaited (NCT00774631).

Patients with bacterial meningitis should be monitored carefully. Seizures occur frequently and the high

associated mortality rate means that the threshold at which anticonvulsant therapy is started should be low.<sup>81</sup> Blood glucose concentrations need to be monitored and normoglycaemia achieved.<sup>82</sup> The goal of fluid management should be to maintain a normovolaemic state; even in patients with severe hyponatraemia, fluid maintenance therapy should be used, rather than fluid restriction.<sup>3</sup> Monitoring of kidney function is also important, especially in patients who develop septic shock and in those with pre-existing kidney disease. Repeat CSF analysis should only be done in patients whose condition has not responded clinically after 48 h of appropriate antimicrobial therapy.

### Novel therapeutic approaches

Investigators have used experimental meningitis models to study whether outcomes can be improved by modulation of damage caused by reactive oxygen species, or by inhibition of caspase or other mediators in the inflammatory, coagulant, or complement cascades.<sup>59</sup> Because bacteriolytic antibiotic regimens temporarily increase the release of bacterial components, investigators have used animal studies to explore the role of non-bacteriolytic antibiotics in the treatment of bacterial meningitis.<sup>59</sup> In a genetic association study in patients with bacterial meningitis,<sup>83</sup> investigators reported that a common non-synonymous single nucleotide polymorphism in the gene for complement component 5 (C5) was associated with unfavourable clinical outcome. Consistent with these human data, C5a receptor-deficient mice with pneumococcal meningitis had decreased brain damage, and adjuvant treatment with C5-specific monoclonal antibodies prevented death in all wild-type mice with pneumococcal meningitis.<sup>83</sup>

### Conclusions and future challenges

Two main therapeutic strategies exist to improve the outcome of patients with bacterial meningitis: optimisation of antimicrobial killing with antibiotics, and reduction of the inflammatory response in the subarachnoid space with adjunctive agents such as dexamethasone. Optimisation of the antibiotic effect depends on active antibiotic therapy being started early in infection, usually before the causative bacterium and its antibiotic susceptibility are known. Determination of which antibiotic agent will be most effective is becoming ever more difficult in the face of increasingly drug-resistant bacteria. Clinical data for new antibiotics for bacterial meningitis have not kept pace with the rise of resistance, and controlled trials exploring the role of these agents are urgently needed. Dexamethasone is the only accepted adjunctive therapy for the treatment of patients with bacterial meningitis, but it has shown obvious efficacy only in high-income countries. A greater understanding of disease pathogenesis and pathophysiology could explain why dexamethasone treatment benefits some patients with bacterial meningitis, but not others, and could help to identify new adjunctive

therapeutic strategies. In the near future, controlled trials are needed to assess treatment modalities such as induction of hypothermia, intracranial pressure management, and specific monoclonal antibodies. However, the greatest effect on the burden of illness due to bacterial meningitis is likely to be achieved through widespread use of vaccinations.

#### Contributors

All authors contributed to writing and editing of the review, and all authors approved the final version.

#### Conflicts of interest

We declare that we have no conflicts of interest.

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## Bacterial Meningitis 3

### Effect of vaccines on bacterial meningitis worldwide

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Three bacteria—*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*—account for most acute bacterial meningitis. Measurement of the effect of protein-polysaccharide conjugate vaccines is most reliable for *H influenzae* meningitis because one serotype and one age group account for more than 90% of cases and the incidence has been best measured in high-income countries where these vaccines have been used longest. Pneumococcal and meningococcal meningitis are caused by diverse serotypes and have a wide age distribution; measurement of their incidence is complicated by epidemics and scarcity of surveillance, especially in low-income countries. Near elimination of *H influenzae* meningitis has been documented after vaccine introduction. Despite greater than 90% reductions in disease attributable to vaccine serotypes, all-age pneumococcal meningitis has decreased by around 25%, with little data from low-income settings. Near elimination of serogroup C meningococcal meningitis has been documented in several high-income countries, boding well for the effect of a new serogroup A meningococcal conjugate vaccine in the African meningitis belt.

#### Introduction

Primary prevention of meningitis is paramount, since death and long-term disabling sequelae are substantial in all settings, especially those with least access to health care.<sup>1</sup> Low-income and middle-income countries account for 98% of the estimated 5·6 million disability-adjusted life years attributed to meningitis globally and bacterial meningitis ranks among the top ten causes of death in children younger than 14 years in high-income countries.<sup>2</sup> Several vaccines are relevant to prevention of bacterial meningitis worldwide, such as BCG vaccine for the prevention of tuberculous meningitis, but in this review, we focus on the three most common causes of acute bacterial meningitis: *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*. We compare patterns of meningitis attributable to these three pathogens, key issues for measurement of disease burden and vaccine effect, and the future role of vaccines in prevention of acute bacterial meningitis.

#### Causative bacteria before vaccine availability

*H influenzae*, *S pneumoniae*, and *N meningitidis* are the predominant causes of bacterial meningitis, but their relative contribution differs over time, by location, and by age group. Before vaccines became available, *H influenzae* was the most common cause of bacterial meningitis in the USA, followed by *S pneumoniae*,<sup>3</sup> whereas in Europe *N meningitidis* was most common in the UK,<sup>4</sup> and *H influenzae* in Scandinavia.<sup>5</sup> In high-income countries, *Streptococcus agalactiae* and *Listeria monocytogenes* were other substantial causes.<sup>4,6</sup> In Africa, epidemics of meningococcal disease occur in a well defined region—the meningitis belt.<sup>7</sup> In this region, even in interepidemic periods, incidence of all-cause bacterial meningitis was 15 times greater than that in the USA in 1986.<sup>3,8</sup> Both within<sup>8</sup> and outside<sup>9</sup> meningitis-belt countries, infants had the highest incidence of bacterial meningitis, predominantly caused by *H influenzae*.<sup>9</sup> Other important

causes of meningitis in low-income countries are Enterobacteriaceae (especially non-typhoidal salmonella species) in children in sub-Saharan Africa,<sup>8,10</sup> and *Streptococcus suis* in adults in southeast Asia.<sup>11</sup>

*H influenzae*, *S pneumoniae*, and *N meningitidis* have several similarities and differences (table 1). Similarities with important implications for vaccine development include being largely or entirely human pathogens, possession of a polysaccharide capsule that is the main determinant of virulence, and that capsular types associated with meningitis are only a small subset of those that colonise the nasopharynx. Important differences include the proportion of disease accounted for by one serotype and propensity to cause outbreaks.

In the case of *H influenzae*, before immunisation one capsular serotype (*H influenzae* type b—Hib) caused almost all cases and the age-range of cases was largely limited to children younger than 5 years.<sup>3,4,8</sup> Outbreak potential is greatest for *N meningitidis*, which has caused regular epidemics in sub-Saharan Africa.<sup>7</sup> These epidemics are attributable mainly to serogroup A meningococci, but outbreaks attributable to serogroup C and, in the past 10 years, serogroups W135 and X have been

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See [Comment](#) page 1623

This is the third in a [Series](#) of three papers about bacterial meningitis

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#### Search strategy and selection criteria

We searched the Cochrane Library (The Cochrane Library 2011, issue 1), Medline (1966 to March, 2012), and Embase (1974 to March, 2012). We used the search terms “bacterial meningitis” or “meningitis” or “meningococcal disease” or “*Neisseria meningitidis*” or “pneumococcal disease” or “*Streptococcus pneumoniae*” or “*Haemophilus influenzae*” or “*Haemophilus* infections” in combination with the terms “vaccination” or “vaccines” or “prevention” or “epidemiology” or “surveillance”. We largely selected publications from the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references than can be included in this review. We modified our reference list on the basis of comments from peer reviewers.

	<i>Haemophilus influenzae</i>	<i>Streptococcus pneumoniae</i>	<i>Neisseria meningitidis</i>
Cell wall	Gram negative	Gram positive	Gram negative
Capsular types	6 capsular types (a–f) Capsular type b in >90% Other capsular types can cause meningitis, especially type a; unencapsulated rarely	>90 capsular types Prominent serotype variation; by region, time period, and invasive potential Wide distribution of serotypes with high incidence	12 serogroups Most disease due to 6 serogroups (A, B, C, W135, X, Y) Unencapsulated meningococci predominate in carriage
Laboratory detection	Fastidious, requires specific culture media Specialised laboratory facilities required for capsular typing	Fastidious, requires specific culture media Specialised laboratory facilities required for serotyping	Fastidious, requires specific media and very rapid processing Molecular methods have greatly enhanced detection
Colonisation vs disease	Carriage 3–5% in high-income countries, 2 to 3 times higher in settings with high incidence of invasive disease	Carriage increases steeply in early infancy in low-income settings, later increase elsewhere Up to 90% of infants <2 years are carriers; serotypes differ from those causing disease	Carriage varies from 8% to 25% Short carriage duration before invasive disease well documented
Case severity	Meningitis more severe than other focal infections; in low-income countries pneumonia accounts for more severe infections than meningitis	Meningitis more severe than other focal infections	Sepsis and hypotension more severe than meningitis
Meningitis as a proportion of invasive disease	50%; higher where blood cultures not taken or unavailable	10%; higher where blood cultures not taken or unavailable and lower in adults	Higher in epidemic settings and with serogroup A
Age distribution	90% <5 years Age distribution shifted towards infants in high-incidence settings	Highest incidence <2 years and >75 years Age distribution shifted towards infants in high-incidence settings	Peaks in infants and adolescents Age distribution varies by serogroup and in epidemics
Epidemic potential	Intrahousehold transmission, no community epidemics	Epidemics in closed settings (high-income countries); community outbreaks in Africa—predominantly type 1	Epidemics documented with all serogroups, especially serogroup A, also W135 and B

**Table 1: Microbiological and epidemiological characteristics of *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* as causes of acute bacterial meningitis**

documented.<sup>12</sup> In high-income countries, population-level long-lasting outbreaks of serogroup A meningococcal disease are largely historical, but in the past 30 years serogroup B outbreaks have occurred in Norway and New Zealand.<sup>12,13</sup> Hib can spread within households and day-care centres, but has not been associated with epidemics.<sup>14</sup> Outbreaks of pneumococcal infection are described in closed settings usually caused by epidemic serotypes 1, 5, and 12F.<sup>15</sup> Community-level epidemics due to *S pneumoniae* also occur, especially in the meningitis belt, where serotype 1 meningitis can be as prevalent as *N meningitidis* in interepidemic periods.<sup>16</sup> In addition to high amplitude and short-lived (weeks to months) outbreaks, more undulating variability in frequency of meningococcal and pneumococcal serotypes occurs over longer periods.<sup>13,17</sup>

### Measurement of disease burden before and after vaccination programmes

Disease burden from bacterial meningitis includes the sum of cases, deaths, and disability in survivors and is a function of age-specific incidence, access to effective treatment, pathogen virulence, and host immune responses. Such responses are related both to age and immune status, which can be compromised by disorders such as HIV infection,<sup>18</sup> and, for pneumococcal meningitis, by sickle-cell disease.<sup>19</sup> Optimum measurement of disease burden requires identification of all cases in a defined population. Identification entails access of cases

to hospital care, well defined criteria for doing lumbar puncture, appropriate handling of specimens, and access to appropriate laboratory techniques, all of which are scarce in low-income and middle-income settings.<sup>20</sup> Measures of meningitis burden in all but the most highly resourced settings should therefore be deemed minimal estimates. For low-income and middle-income countries, minimum estimates of incidence have been summarised by the global burden of disease study,<sup>2</sup> and by specific studies of pneumococcal and Hib disease,<sup>21,22</sup> which included meningitis as a separate category. Global patterns of meningococcal disease are more diverse than for *H influenzae* and *S pneumoniae*, because of its greater epidemic potential.<sup>12,13,23</sup> Additionally, measurement of the disease burden specific to meningococcal meningitis is problematic because distinctions between meningitis and bacteraemia might be blurred. In all settings, meningococcal sepsis has a higher case fatality than does meningitis.<sup>13</sup> Among survivors, meningococcal meningitis has lower risk of sequelae than *H influenzae* meningitis, which is in turn lower than *S pneumoniae* meningitis.<sup>1</sup> For meningitis as a syndromic diagnosis, 164 000 deaths in children aged 1–59 months were estimated to have occurred worldwide in 2008.<sup>24</sup>

Table 2 shows key summary disease-burden measurements for acute bacterial meningitis (cases, deaths, and prevalence of sequelae among survivors) in children younger than 5 years by organism in high-income and

low-income countries.<sup>1,12,21–23</sup> For Hib, ascertainment is fairly uniform for all invasive disease including meningitis in high-income countries, although less so for other *H influenzae* serotypes because appropriate laboratory methods are sometimes lacking. For *S pneumoniae*, even in high-income countries, ascertainment of non-meningitic invasive disease varies substantially,<sup>15,25</sup> but ascertainment of meningitis has been more consistent.<sup>17,25</sup> Molecular methods for diagnosis have increased case ascertainment and might also help to establish serotype distribution.<sup>26</sup> During epidemics, the burden of meningococcal disease in the African meningitis belt greatly exceeds that for *H influenzae* or pneumococcal meningitis in other low-income countries. Outside epidemic situations, the incidence of cases attributable to Hib or pneumococcal meningitis in low-income countries exceeds that in high-income settings by a factor of three, with six times more deaths. The increased probability of severe sequelae in survivors of pneumococcal meningitis adds to its overall disease burden.

In the setting of a vaccine trial, disease estimates can be enhanced by the so-called vaccine probe design. This technique measures the vaccine-preventable fraction of meningitis defined by syndromic surveillance, whereby cases identified in individuals randomised to receive vaccine are subtracted from those randomised to receive placebo. In a hamlet-randomised study of Hib vaccine on the island of Lombok, Indonesia,<sup>27</sup> because of increased sensitivity of the vaccine probe approach, the estimated incidence of Hib meningitis was revised from 16 per 100 000 (95% CI 1–31) on the basis of microbiologically confirmed cases alone to 158 per 100 000 (42–273). The Lombok trial estimates are consistent with those from populations in Africa with high quality surveillance and laboratory methods and low use of antibiotics before specimen collection,<sup>28</sup> and with data from indigenous populations that share many epidemiological characteristics and risk factors with low-income countries.<sup>29,30</sup> Researchers have attempted to quantify pathogen-specific meningitis burden at the country level on the basis of a systematic review of incidence and case-fatality rate, with data assessed according to quality metrics and, when adequate, included in a model that adjusted for access to care, HIV prevalence, and Hib vaccine use.<sup>21,22,24</sup> Figure 1 shows the estimated number of Hib and pneumococcal meningitis deaths in the ten countries with the greatest absolute number of such deaths in 2000, on the basis of global burden of disease studies.<sup>21,22</sup>

### Mechanisms of protective immunity

The absence of type-specific opsonising antibody is the most important determinant of susceptibility to bloodstream invasion and meningitis;<sup>31–33</sup> non-capsular factors are also important determinants of virulence, although their role in pathogenesis is less clearly understood.<sup>31–33</sup> Genetic factors are likewise important determinants of susceptibility to pneumococcal and meningococcal

infection.<sup>34</sup> The first vaccines used the polysaccharide capsule alone as an immunising agent. This approach was enhanced by conjugation of polysaccharide antigens to various protein carriers.<sup>35</sup>

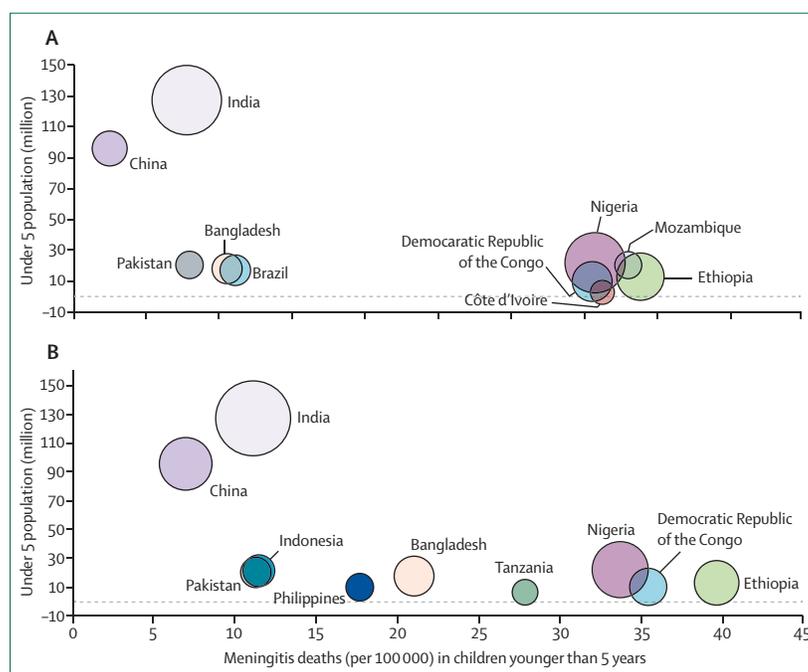
### Polysaccharide vaccines

Polysaccharides are T-cell-independent antigens that cannot be presented to T cells in conjunction with MHC class II molecules, preventing development of memory

	<i>Haemophilus influenzae</i> type b <sup>22</sup>	<i>Streptococcus pneumoniae</i> <sup>21</sup>	<i>Neisseria meningitidis</i> <sup>12,23</sup>
<b>Cases</b>			
Highest incidence region (Africa)	46 (31–52)	38 (11–48)	>100 (endemic)* >1000 (epidemic)*
Lowest incidence region (Europe)	16 (12–22)	6 (5–9)	1–2 (endemic)† 2–10 (epidemic)†
<b>Deaths</b>			
Highest mortality region (Africa)*	31 (20–35)	28 (7–36)	..
Lowest mortality region (Europe)†	4 (3–6)	3 (1–7)	..
<b>Morbidity</b>			
Proportion of survivors with major long-term sequelae <sup>1</sup>	9.5% (7.1–15.3)	24.7% (16.2–35.3)	7.2% (4.3–11.2)

Data are n per 100 000 population per year (95% CI) unless otherwise specified. Mean proportion of survivors with major long-term sequelae for all organisms combined in the highest incidence regions is 25% (95% CI 19–32), and in the lowest incidence regions is 9% (7–12).<sup>1</sup> \*African meningitis belt. †Low incidence regions for invasive meningococcal disease—Europe, USA, and Australia.

**Table 2: Estimates of global disease burden for meningitis attributable to *Haemophilus influenzae* type b, *Streptococcus pneumoniae* (children younger than 5 years), and *Neisseria meningitidis* (all ages), by organism and region**



**Figure 1: Estimated number of Hib and pneumococcal meningitis deaths in children aged 1–59 months, in 2000<sup>21,22</sup>** Bubble size indicates number of *Haemophilus influenzae* type b (Hib, A) or pneumococcal (B) meningitis deaths.

B cells.<sup>31,35</sup> Consequently, after vaccination antibody concentrations wane rapidly in young children, there is no anamnestic response to later doses of the polysaccharide, and little or no effect on nasopharyngeal or oropharyngeal carriage.<sup>35</sup> Effectiveness of polysaccharide vaccines against meningitis has been shown most convincingly for serogroup A meningococcal disease, but protection waned after 3 years, and was poor among children younger than 2 years.<sup>13,36</sup> Similarly, antibody responses to most serotypes after pneumococcal polysaccharide vaccines are poor in children younger than 2 years. In adults, these vaccines are efficacious against invasive pneumococcal disease attributable to vaccine serotypes, and by implication also meningitis, but no specific data are available.<sup>37</sup> Little effect of Hib polysaccharide vaccine on disease, especially meningitis, was recorded during routine use of this vaccine in US children older than 24 months despite documented efficacy,<sup>38</sup> probably because of the small proportion of Hib meningitis cases in this age group.

### Conjugate vaccines

Conjugate vaccines are T-cell-dependent, allowing development of memory B cells, and consequent anamnestic responses and, importantly, they affect carriage.<sup>31,35</sup> The first commercially viable conjugate vaccine was produced against Hib.<sup>14</sup> Manufacturers used different proteins (diphtheria toxoid [D], the outer membrane protein of *N meningitidis* serogroup B [OMP], tetanus toxoid [TT], or mutant diphtheria toxin [CRM] conjugated to Hib polysaccharide [PRP]).<sup>14,31</sup> One vaccine, PRP-OMP, was associated with antibody response after one dose, an important advantage for settings where Hib disease occurred very early in life. Other Hib conjugates (PRP-T, PRP-CRM, and PRP-D) required two or three doses to achieve such antibody response.<sup>14,39</sup> The first pneumococcal conjugate vaccine (PCV), which used CRM as the protein carrier, was first licensed and recommended for routine use in the USA in 2000. It included seven of the most common serotypes causing invasive disease (4, 6B, 9V, 14, 18C, 19F, 23F). Other vaccines with nine, ten, 11, or 13 conjugates (including serotypes 1, 3, 5, 6A, 7F, 19A) have been studied, with the ten-valent and 13-valent products reaching licensure. For these products, immunogenicity varies by serotype, number of doses, concomitant vaccine administration, and population studied.<sup>40</sup> Trials with both immunogenicity and clinical outcome measures have allowed development of antibody correlates of protection deemed sufficient for licensure without efficacy trials.<sup>41</sup>

The first meningococcal conjugate vaccine to become available used the serogroup C polysaccharide conjugated to CRM; subsequently TT conjugates and serogroup A, W135, and Y conjugates have been developed.<sup>42</sup> Epidemiological studies have shown a well defined threshold for serogroup C serum bactericidal activity, which correlates with protection against serogroup C invasive disease; all meningococcal C conjugates met this threshold.<sup>42</sup> A

monovalent serogroup A meningococcal conjugate vaccine has been developed specifically for use in the meningitis belt, with immunogenicity studies showing that it is significantly better than polysaccharide A vaccine after one or two doses in children and young adults.<sup>43</sup>

### Efficacy trials

The interplay between vaccine immunogenicity and disease epidemiology was underlined by the first two Hib conjugate vaccine clinical trials, which used PRP-D in very different settings. In Finland, PRP-D had an efficacy of 94% (lower 95% CI 83%),<sup>44</sup> whereas in Alaska, USA, where Hib incidence was much higher and peaked in the first 6 months rather than the second year of life, vaccine efficacy was 35% (–233%).<sup>45</sup> By contrast, when researchers assessed PRP-OMP in Navajo infants, among whom Hib disease occurred predominantly in the first few months of life,<sup>29</sup> as in Alaska Native and Australian Aboriginal infants, efficacy was 95% (72%) after two doses and protective after one dose (lower 95% CI for one dose 45%).<sup>46</sup>

Trials of a seven-valent PCV with a four-dose schedule were done in California, USA,<sup>47</sup> and also in Navajo infants<sup>48</sup> who have higher incidence and greater serotype diversity of invasive pneumococcal disease than do infants in the general US population. These trials showed high efficacy against vaccine serotype invasive pneumococcal disease of 94%<sup>47</sup> and 83%,<sup>48</sup> respectively. Trials of a nine-valent vaccine given in a three-dose primary schedule at 6, 10, and 14 weeks of age according to Expanded Programme on Immunization recommendations in South Africa and The Gambia showed similar efficacy against vaccine serotypes, except in HIV-infected children.<sup>49,50</sup> The efficacy against all serotype meningitis or sepsis in these trials was less than recorded in US studies, because of higher baseline incidence of non-vaccine serotype disease.<sup>49,50</sup> Despite this finding, in the high mortality setting of The Gambia, vaccination resulted in a 16% (95% CI 3–28) reduction in all-cause mortality.<sup>50</sup>

None of the meningococcal conjugate vaccines have been tested in randomised controlled trials with disease endpoints, because these were not thought justified in the context of immunological correlates of protection that reliably predict vaccine effectiveness.<sup>42</sup> Efficacy against meningococcal meningitis is, therefore, inferred from post-licensure studies of effectiveness.

### Post-licensure studies

More data are available for the effect of Hib vaccines when delivered through routine immunisation programmes than for either pneumococcal or meningococcal vaccines. First, in high-income countries, routine use of Hib vaccine preceded that of pneumococcal or meningococcal vaccines and the background rate of Hib meningitis was high.<sup>45</sup> Second, the proportion of invasive *H influenzae* disease caused by the vaccine serotype (ie, serotype b) was 90–95% and concentrated in one age group.

### High-income countries

Conjugate Hib vaccines were introduced into routine use first in the USA, from 1987 at 18 months of age and from 1991 at 2 months of age, with most high-income countries following during the 1990s; these vaccines have proved highly effective in all settings.<sup>51</sup> The first conjugate pneumococcal vaccine, containing conjugates of the seven most common serotypes in the USA, was introduced into routine practice in 2000. Figure 2 shows changes in incidence estimates for bacterial meningitis from surveillance of more than 10 million people in the USA after the introduction of conjugate vaccines against invasive Hib disease (after 1986) and invasive pneumococcal disease due to seven serotypes (after 1998).<sup>3,6,52</sup>

The reduction in all-age incidence of *H influenzae* meningitis shown in figure 2—more than 97% in the 20 years from 1986 to 2007—shows the profound population-wide effect of Hib vaccines in the USA.<sup>3,6,52</sup> Furthermore, the proportion of *H influenzae* meningitis cases due to serotype b decreased sequentially from 95%, to 33%, to 9%.<sup>3,6,52</sup> Among high-income countries, two exceptions to the near elimination of *H influenzae* meningitis arose. In the UK, a rebound in Hib disease occurred in the 1990s. This recurrence was attributed to waning of herd effects generated by an initial catch-up campaign among children younger than 5 years, low PRP antibody concentrations after use of a Hib-acellular-pertussis combined vaccine, and an accelerated primary dose schedule with no booster dose.<sup>53</sup> This rebound of Hib disease resolved with the introduction of a booster dose in the second year of life and a temporary catch-up campaign in children aged 2–4 years.<sup>54</sup> In Alaska, USA,<sup>55</sup> with a historically high incidence of Hib disease, an increase in *H influenzae* meningitis occurred after replacement of PRP-OMP with PRP-CRM vaccine.<sup>55</sup> This occurrence was presumed to result from an insufficient antibody response after the first or second dose of PRP-CRM, combined with persistent circulation of Hib within the community despite a routine Hib vaccine programme.<sup>14,55</sup>

Definitive data for the effect of a seven-valent pneumococcal conjugate vaccine on meningitis have emerged from large populations in the USA<sup>52</sup> and England and Wales.<sup>56</sup> All-age incidence of pneumococcal meningitis of any serotype in the USA remained stable before introduction of pneumococcal conjugate vaccines from 1998, but by 2006–07 a 26% (95% CI 23–29) reduction had occurred (figure 2).<sup>52</sup> The decrease in pneumococcal meningitis is closer to that recorded for Hib meningitis when only vaccine serotypes or the age group with the highest incidence of pneumococcal meningitis is considered. Specifically, all-age incidence of vaccine-serotype meningitis decreased by 92% (91–93) and incidence of pneumococcal meningitis in children younger than 2 years attributable to any serotype by 62% (58–66), despite an increase in the all-age incidence of meningitis due to non-vaccine serotypes of

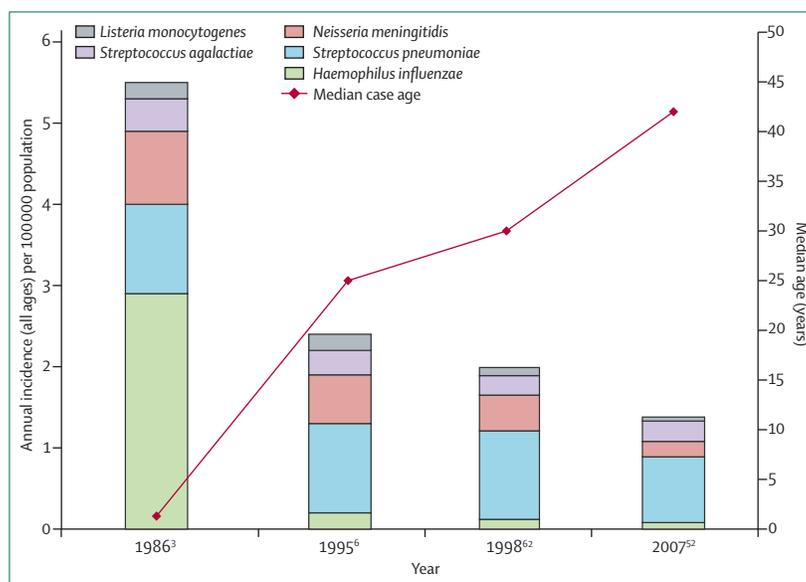


Figure 2: Prevalence of bacterial meningitis in the USA attributable to *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Streptococcus agalactiae*, and *Listeria monocytogenes*, 1986–2007.<sup>3,6,52</sup>

61% (54–69) and in children younger than 5 years of 92% (68–119).<sup>52</sup> Similarly, in England and Wales, an overall reduction of 44% (11–54) in pneumococcal meningitis was recorded in children younger than 5 years after introduction of a seven-valent pneumococcal conjugate vaccine, despite an increase in non-vaccine serotypes of 77% (27–247).<sup>55</sup> In the USA and England and Wales, these reductions occurred in the context of the seven serotypes in the vaccine, accounting for almost 80% of pneumococcal meningitis before vaccine introduction.<sup>52,56</sup>

Variability in the incidence of meningococcal disease in the absence of vaccination, both overall and by serogroup, complicates assessment of vaccine effect. For example, in the USA, meningococcal meningitis steadily decreased in the absence of specific interventions including immunisation (figure 2).<sup>3,6,52</sup> However, several countries with recent increases in the incidence of serogroup C meningococcal disease have shown substantial reductions in serogroup C disease after large-scale vaccination campaigns with meningococcal C conjugate vaccines.<sup>23,57,58</sup> Figure 3 shows the near disappearance of *N meningitidis* serogroup C disease in England and Wales and the Netherlands after such campaigns, with reductions of more than 98% in targeted age groups and of more than 90% in age groups not included.<sup>56,58</sup> In New Zealand, a strain-specific group B vaccine, based on the outer membrane vesicle protein, was given in a broad population campaign, with special focus on Maori Pacific Island populations with the greatest disease burden.<sup>59</sup> Results of observational studies showed a significant vaccine effect that persisted after adjustment for precampaign downward trends.<sup>60</sup>

**Low-income countries**

Data from several high-incidence settings in Africa show rapid, pronounced decreases in both culture-proven Hib meningitis and all presumptive bacterial meningitis in the short term.<sup>61</sup> However, in South Africa, 10 years after routine vaccination, an increasing trend in Hib meningitis has been reported, mainly in children with HIV infection.<sup>62</sup> In The Gambia, after near elimination of invasive Hib disease in 2002,<sup>63</sup> an increase in the

incidence of Hib meningitis occurred in 2005–06, 5 years after vaccine introduction.<sup>64</sup> However, this increase was not sustained (Howie S, Medical Research Council unit, The Gambia, personal communication), even though a booster dose is not given routinely, as in South Africa. Although such reports need a long time series to document changes in incidence, in view of much reduced case numbers, monitoring of longer-term trends is important in settings without a scheduled booster, because of the UK experience.<sup>53</sup>

As yet, little information exists about the longer term effect of routine immunisation with pneumococcal conjugate vaccines in low-income settings, but detailed community-based surveillance is underway in Kenya, South Africa, and The Gambia.<sup>65</sup> Figure 4 shows the countries with routine *H influenzae* type b and pneumococcal conjugate vaccine programmes at the end of 2012, which viewed with figure 1 shows the great future potential for reduction in meningitis attributable to these organisms. At the end of 2010, the whole population of Burkina Faso aged 1–29 years was immunised with a serogroup A meningococcal conjugate vaccine, with a very low incidence of serogroup A meningococcal disease during the next meningitis season.<sup>66</sup> However, a longer period of surveillance will be needed to determine the effect of this vaccine at the community level as it is rolled out progressively across the African meningitis belt.<sup>66</sup>

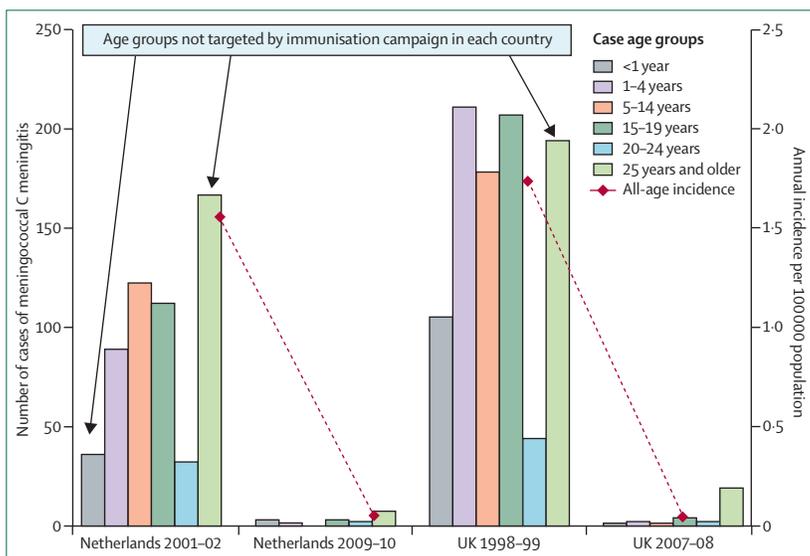


Figure 3: Case numbers by age group and all-age incidence of invasive *Neisseria meningitidis* serogroup C disease in England and Wales<sup>56</sup> and the Netherlands<sup>59</sup> before and after conjugate meningococcal C immunisation campaigns

**Herd protection and serotype replacement**

For Hib, in low-incidence populations, a small but appreciable proportion of cases has occurred in individuals older than 5 years; indirect protection in this population has

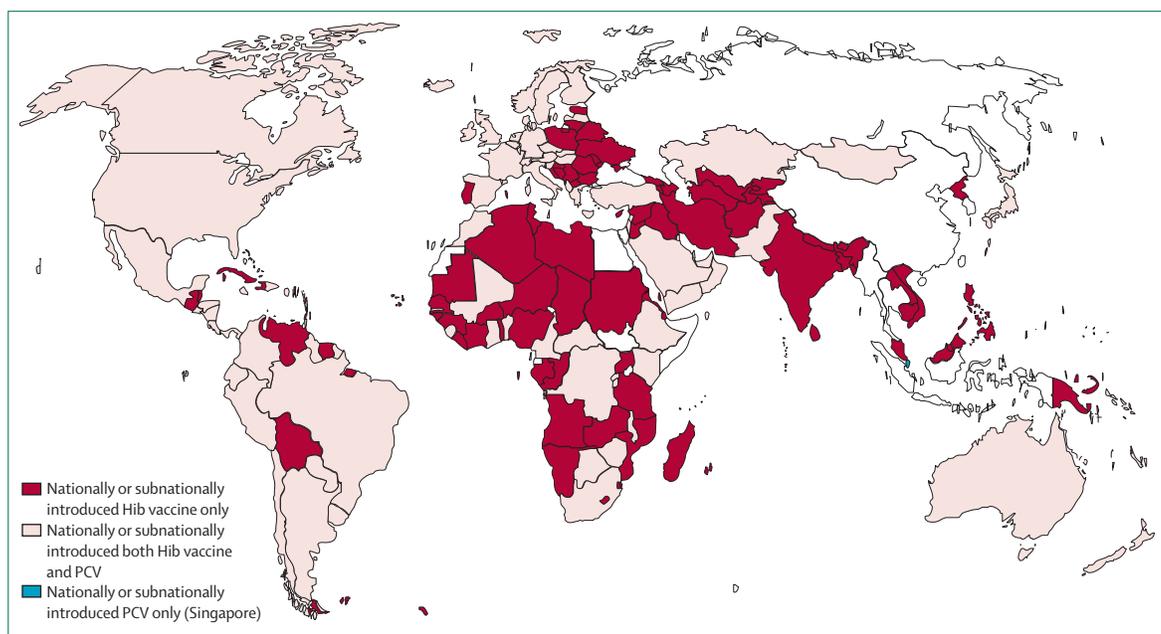


Figure 4: Countries with routine *Haemophilus influenzae* type b (Hib) and pneumococcal conjugate vaccine (PCV) programmes by October, 2012. Reproduced from IVAC, Johns Hopkins Bloomberg School of Public Health. Vaccine Information Management System (VIMS), October, 2012.

been documented in both the UK and Alaska, USA.<sup>53,67</sup> Although increases in non-b serotypes causing invasive disease have been documented (usually non-encapsulated strains and type f) after Hib immunisation in low-incidence populations,<sup>68</sup> the pronounced decrease in type b and its predominance as a cause of *H influenzae* meningitis mean that total *H influenzae* invasive disease and meningitis remain much lower than before vaccination. No increase in the incidence of non-serotype-b *H influenzae* disease was recorded in a multicountry European study.<sup>69</sup> Increases in serotype a have been recorded in some regions of the USA,<sup>70</sup> but are often short-lived, as in Brazil.<sup>71</sup> *H influenzae* type a is an important pathogen in some Native American populations.<sup>72</sup> However, occurrence of non-serotype-b *H influenzae* disease as short, highly localised clusters can result in spurious conclusions when only short periods of observation are reported.

In the case of pneumococcus, indirect protection against vaccine serotype strains has been identified in almost all study settings after introduction of seven-valent PCV. Serotype replacement, in vaccinated and unvaccinated age groups, might offset some of these indirect effects but caution is needed in drawing conclusions from individual study site reports because of the inherent challenges in disentangling the effect of study design from biological effects.<sup>73</sup> More data from sites that vary in characteristics such as epidemiological setting, time since vaccine introduction, and introduction with or without a catch-up schedule are needed to understand more clearly the drivers of herd and replacement effects.<sup>73</sup> Non-vaccine serotypes vary in invasiveness and geographical differences in their prevalence will also be an important determinant of the effect of PCVs on overall pneumococcal disease burden.<sup>74</sup> A systematic review of serotype replacement for WHO reported preliminary findings in 2011.<sup>75</sup>

When population-wide campaigns have been done with serogroup C meningococcal conjugate vaccines, herd effects have been identified in older children and adults,<sup>23</sup> adding substantially to the population health effect of such campaigns. However, meningococci are equipped to avoid the host immune response by interchange of genetic material,<sup>32</sup> and so there is concern that meningococci, and pneumococci, might show serotype replacement in response to conjugate vaccination, especially in high-incidence, high-transmission settings.

### Best use of existing vaccines

In high-incidence settings, commencing conjugate pneumococcal vaccination at birth has been considered in view of the very early onset of pneumococcal disease, and shown to be immunogenic and not associated with later immune tolerance.<sup>76</sup> The issue of how to best use three doses of PCV has been the subject of review.<sup>77</sup> Both three-dose primary schedules and two-dose primary schedules with a booster were acceptable, with decisions depending on the programmatic and epidemiological characteristics of the setting where the vaccine was used.

A crucial issue is the duration of protection provided by vaccination and whether this depends on induction of immunological memory or the antibody concentration at the time of exposure. Major controversy about the need for additional booster doses has arisen in the context of conjugate meningococcal vaccines, for which a clear correlate of protection is available, the serum bactericidal titre.<sup>32,42</sup> Evidence suggests that serogroup C antibody concentrations decline rapidly in children given their first dose at 12 months.<sup>78</sup> Up to now, very few vaccine failures have been identified among children who have received their first dose after 12 months, although this might be attributable to persisting herd protection. In the rare instances of conjugate vaccine failure, functional T-cell immune deficits and immunoglobulin deficiency have been identified.<sup>79-81</sup>

In developing countries, the Expanded Programme on Immunization schedule is accelerated but, in practice, second and third doses are often delayed,<sup>63</sup> which could result in greater persistence of immunity. Schedules with a booster dose late in the first year or early in the second year of life need to be assessed for cost-effectiveness and feasibility of delivery in low-income countries, but are now regarded as routine in high-income countries.

### Future challenges

In view of the challenges of several changing serotypes, intense interest surrounds development of protein vaccines with broad and ideally universal coverage for both meningococcal and pneumococcal disease. For meningococcal B disease, broad coverage is essential,<sup>32</sup> and a multicomponent meningococcal B protein vaccine candidate is immunogenic in infants<sup>82</sup> and adolescents,<sup>83</sup> as assessed by a novel proxy measure of bactericidal activity. Pneumococcal protein vaccines have long been of interest for their potential to obtain equivalent efficacy to polysaccharide conjugates without serotype replacement,<sup>84</sup> but no candidates have so far reached phase 3 clinical trials.

Widespread introduction of conjugate vaccines, especially where disease burden is greatest, will have incremental effects on the global burden of acute bacterial meningitis, but important challenges remain. These include delivery of potent vaccines to difficult-to-access populations at risk; appropriately designed and done studies of effect, which require adequate surveillance to be in place many years before vaccine introduction; and development and testing of improved vaccines.

#### Contributors

All authors contributed to writing and editing of the review. All authors approved the final version.

#### Conflicts of interest

KLO'B has received research grant support from Pfizer and has served on pneumococcal vaccine expert advisory boards for Pfizer, GlaxoSmithKline, Sanofi Pasteur, and Merck. The other authors declare that they have no conflicts of interest.

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