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Review Article

Bacterial Meningitis in Childhood: Diagnosis, Management and Challenges in the Era of Conjugate Vaccines

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Abstract

Background: Bacterial meningitis remains a major cause of morbidity and mortality in childhood worldwide. Diagnosis of bacterial meningitis is challenging, as clinical and laboratory findings are not always present and often have limited diagnostic accuracy.

Aims: To summarize salient features on diagnosis and treatment of bacterial meningitis in children and identify challenges currently faced in the era of conjugate vaccines.

Methods: A MEDLINE search of English-language articles on bacterial meningitis in childhood published between 2000 and November 2017 was conducted.

Results: Although the incidence of bacterial meningitis has significantly decreased following the introduction of conjugate vaccines, new challenges have arisen, with change of serotype distribution and shift of the disease burden to neonatal and early infantile period.

Conclusions: Future perspectives have to turn on further development of conjugate vaccines, that should target all strains regardless of their capsule type, as well as focus on neonatal and maternal immunization.

Keywords: *Conjugate Vaccines; Diagnosis; Meningitis; Treatment*

Abbreviations

ABM: Acute Bacterial Meningitis; BBB: Blood Brain Barrier; CDC: Centre for Disease Control and Prevention; CRP: C-Reactive Protein; CSF: Cerebrospinal Fluid; CT: Computed Tomography; EFNS: European Federation of Neurological Societies; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; Hib: Haemophilus influenzae type b; IDSA: Infectious Diseases Society of America; NICE: National Institute for Health and Care Excellence; IPD: Invasive Pneumococcal Diseases; PCR: Polymerase Chain Reaction; PCV7: Heptavalent Pneumococcal Conjugate Vaccine; PCV10: 10-valent Pneumococcal Conjugate Vaccine; PCV13: 13-valent Pneumococcal Conjugate Vaccine; PRSP: Penicillin Resistant *S. pneumoniae*; SBA: Serum Bactericidal Antibody

Introduction

Acute bacterial meningitis (ABM) constitutes a life-threatening disease that requires early recognition and medical treatment. Despite the progress in antibiotics and vaccines, ABM still contributes to mortality and morbidity of the children worldwide.

The incidence of ABM is estimated 1-3 per 100,000 people annually in developed countries [1]. *Haemophilus influenzae* type b (Hib) was the major cause of paediatric meningitis, before the introduction of Hib vaccines [2]. *Streptococcus pneumoniae* and *Neisseria meningitis* are currently the leading causes of ABM in childhood, while group B *Streptococcus*, *Escherichia coli* and *Listeria monocytogenes* account for majority of ABM in neonates in the developed world [1].

Diagnosis

Given the fact that signs and symptoms of paediatric meningitis are non-specific, especially in the early stages of the infection, its diagnosis relies on cerebrospinal fluid (CSF) testing and culture. The classic signs and symptoms include fever, vomiting, altered mental status, anorexia, petechial rash, convulsions, headache and photophobia. In infants, bulging fontanelle, pale or marble skin, poor feeding and irritability may be the first signs and symptoms, whether in older children classic signs of neck stiffness, Kerning and Brudzinski are not always present. In the adult population, sensitivity of these signs is only 5% for both of them, while this is approximately 30% for nuchal rigidity [3]. Meningitis is confirmed with laboratory tests in only 11-30% of children with meningeal signs [4,5], while these signs can be absent in 20% of paediatric meningitis cases [6]. Cervical lymphadenitis and pleural irritation due to pneumonia may also provoke meningeal signs in the absence of meningitis [6].

A lumbar puncture is necessary for the definitive diagnosis of bacterial meningitis. However, established criteria can identify the high-risk patients, that need antibiotic therapy even before a lumbar puncture is performed [4]. CSF examination is strongly recommended in suspicion of acute bacterial meningitis in children, in the absence of lumbar puncture contraindications (Table 1). Classic CSF findings in bacterial meningitis, as pleocytosis with neutrophilic predominance, low glucose and elevated protein levels (Table 2) are not always present, especially in neonates. In children and adults these criteria are met in ≥ 90% of the cases [7]. According to "Bacterial Meningitis Score", the possibility of bacterial meningitis in children with CSF pleocytosis is 0.1% in the absence of the following criteria: convulsions at the onset of symptoms, absolute neutrophil count in peripheral blood ≥ 10,000/microL and in CSF ≥ 1000/microL, positive CSF Gram stain and CSF protein ≥ 80 mg/dl [8]. CSF gram stain is a quick test for the identification of a bacterial infection and has a high specificity (99.9%), but variable sensitivity (67 - 94%) [9,10]. Thus, it can only be used to confirm a bacterial meningitis. CFS culture is an integral part of the diagnosis of bacterial meningitis and it is positive in 70 - 85% of the patients if they have not previously received antibiotics [11]. Polymerase Chain Reaction (PCR) is a sensitive technique for identifying the presence of bacterial DNA, especially in patients previously treated with antibiotics. Both National Institute for Health and Care Excellence (NICE) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend PCR in negative CSF culture samples [12,13]. Latex agglutination is a rapid method for the etiological diagnosis of bacterial meningitis, but it has a variable sensitivity rate (22% to 100%), which can be decreased after antibiotic treatment, dependent on the causative microorganism [14]. Thus, it can only be used in combination with other CSF markers. Cerebrospinal fluid (CSF) Gram stain and culture aside, the single most important CSF diagnostic parameter of ABM is the CSF lactic acid level, even with a negative CSF Gram stain [15]. While the usual CSF lactic acid level breakpoint is 2.2 mmol/L, for ABM a cutoff of 6 mmol/L is highly sensitive/specific and differentiates ABM from partially treated bacterial meningitis (PTBM), as well as aseptic acute meningitis/encephalitis [15,16].

Absolute (lumbar puncture is not to be recommended)
Signs of raised intracranial pressure
Local skin infection in needle track
Evidence of obstructive hydrocephalus, cerebral oedema or herniation in CT (or MR) scan of brain
Relative (appropriate therapeutic measures and/or investigations are indicated before lumbar puncture)
Sepsis or hypotension (systolic blood pressure < 100 mmHg, diastolic blood pressure < 60 mmHg): patients should be stabilized first
Coagulation disorder (disseminated intravascular coagulopathy, platelet count < 50 000/mm^3, therapeutic use of warfarin): appropriate correction first
Presence of focal neurological deficit, especially in suspicion of posterior fossa lesion[a]
Glasgow coma score of 8 or less*
Epileptic seizures*

Table 1: *Lumbar puncture contraindications in suspected acute bacterial meningitis [21].*

**In all these cases, CT (or MR) scan of brain should be the first step. Isolated single cranial nerve palsy without papilloedema does not necessarily contraindicate LP without brain imaging.*

CSF finding	Normal	Viral	Bacterial	Partially treated bacterial
White cell count (cells/mm^3)	< 5	< 1000	> 1000	> 1000
Neutrophils	0	24 - 40%	> 85 - 90%	> 80%
Protein (mg/dl)	< 40	Normal or < 100	> 100 - 200	60 - 100+
Glucose (mmol/l)	≥ 2,5	Normal	Undetectable-<2,2	< 2,2
CSF/blood glucose ratio	≥ 0,6	Normal	< 0,4	< 0,4
Gram stain positive	-	-	75 - 90%	55 - 70%
Culture positive	-	-	> 70-85%	< 85%

Table 2: *Lumbar puncture findings [17].*

Blood culture is necessary in suspected bacterial meningitis, especially when CSF culture is negative or not available [17] and should be taken before antibiotic treatment is commenced [7]. Among inflammatory markers, procalcitonin has a higher diagnostic accuracy than C Reactive Protein (CRP) in differentiating between bacterial and viral meningitis, with sensitivity of 96% and specificity of 89% [18]. However, they can both be elevated in other bacterial infections. "Clinical decision rules", which include clinical and laboratory variables [13] have also been described in order to discriminate bacterial and aseptic meningitis.

Regarding imaging, head Computed Tomography (CT) scan prior to lumbar puncture is not routinely recommended and should only be based on specific indications [19].

Treatment

Antibiotic treatment

The significant role of early antibiotic therapy in ABM is well known, as any delay in the initiation of antibiotics has been associated with poor outcomes [20]. According to EFNS (European Federation of Neurological Societies) guidelines, pre-hospital antibiotic treatment is recommended in strong suspicion of generalized infection by *N. meningitidis* and in other suspected cases of ABM, if the patient is expected to reach the hospital in more than 90 minutes. Hospital antibiotic therapy, on the other hand, is recommended within the 1st hour after admission and not > 3 hours after the contact with a health service [21,22]. In any case, blood cultures need to be collected before the first dose of antibiotic therapy [21]. Empirical antibiotic treatment should be based on the patient's age, clinical signs and symptoms, as well as the local epidemiology of bacterial resistance. Infectious Diseases Society of America (IDSA) recommends empiric treatment with vancomycin plus ceftriaxone or cefotaxime in infants and children with possible bacterial meningitis, whereas ESCMID recommendations suggest ceftriaxone or cefotaxime for the same age group when bacterial resistance to these antibiotics is not expected, and addition of vancomycin or rifampicin in cases of higher risk for resistant *S. pneumoniae* strains [7,11]. Neonates < 1 month old with suspected bacterial meningitis should be treated with ampicillin plus cefotaxime or an aminoglycoside according to IDSA. ESCMID recommends amoxicillin or ampicillin or penicillin plus cefotaxime. Alternatively, amoxicillin or ampicillin plus an aminoglycoside can be used for neonates [7,11]. Based on the different antimicrobial sensitivity, the recommendations for the empiric treatment in neonates, infants and children differ between USA and Europe [7,11].

After identification of the pathogen, antibiotic therapy can be modified according to the susceptibility patterns. For acute meningitis due to penicillin-sensitive *Streptococcus pneumoniae*, penicillin or ampicillin/amoxicillin for 10 - 14 days is acceptable, although not preferable for most clinicians in a developed world setting due to the frequency of required administration - 4 hourly for penicillin in meningitis. Cefotaxime or ceftriaxone are recommended for strains of *S. pneumonia* that are penicillin-resistant and 3rd generation susceptible [7]. In case of reduced susceptibility of *Streptococcus pneumoniae,* ceftriaxone or cefotaxime should be combined with either vancomycin or rifampicin [7]. Bacterial meningitis by *Neisseria meningitides* can be treated with penicillin/amoxicillin/ampicillin if it is penicillin

susceptible (MIC < 0.1 μg/mL), and with cefotaxime/ceftriaxone in case of resistant microorganisms to penicillin (MIC > 0.1 μg/mL). The duration is 7 days in both cases [23]. Therapeutic options for *Haemophilus influenzae* type B meningitis include ceftriaxone or cefotaxime for 7 to 14 days, while Listerial meningitis requires ampicillin or amoxicillin for 21 days, in combination with gentamicin for the first 7 to 10days [21]. In case of staphylococcal meningitis, antibiotic therapy should last for at least 14 days and should include flucloxacillin, nafcillin or oxacillin for methicillin sensitive bacteria, vancomycin for resistant to methicillin and linezolid for vancomycin-resistant *Staphylococcus aureus* [7]. For Gram negative Enterobacteriaceae, cefotaxime, ceftriaxone or meropenem are recommended for 21 to 28 days, whereas bacterial meningitis without identification of the responsible microbial strains should be treated for at least 10 to 14 days [21]. In patients with known history of severe beta-lactam allergy, vancomycin can be administered as the alternative for pneumococcal or staphylococcal meningitis, chloramphenicol for meningococcal and cotrimoxazole for listerial meningitis [21]. Meropenem can be used for the empiric therapy of inpatients with community-acquired bacterial meningitis that are allergic to penicillin or for hospital-acquired bacterial meningitis combined with vancomycin [24]. Linezolid acts only in Gram positive bacteria, has been used for multi-resistant microorganisms and should only be used after resistance tests recommend it [24]. Ceftaroline and ceftobiprole are new cephalosporins, which are supposed to act against MRSA staphylococcus and multiresistant pneumonococcus [24]. There is not enough clinical experience with these new agents yet apart from a report for successful treatment of post-surgery MRSA meningitis with ceftaroline [25].

A critical element in order to achieve a successful treatment in children with bacterial meningitis is to administer the most susceptible antibiotic against the causing agent and in the correct dosage, achieving therapeutic concentrations in the CSF (Table 5) [7]. Antibiotic penetration into CSF depends on the antibiotic's molecular size, lipid solubility and degree of blood brain barrier (BBB) permeability [15]. The best index of BBB penetrability is CSF albumin, i.e., the higher the CSF albumin, the greater BBB penetrability [15]. This is clinically relevant since some pneumococcal strains may be penicillin resistant *S. pneumoniae* (PRSP), and are often empirically treated with "high dose" vancomycin. In spite of the "high dose" vancomycin, CSF penetration is not assured as only ~15% of vancomycin simultaneous serum levels penetrate the CSF in the presence of inflammation, i.e. ABM and < 1% penetrates the BBB in the absence of inflammation. Therefore, increasing the dose of an inflammation dependent antibiotic, e.g., vancomycin, is likely to be ineffective in the case of PRSP ABM. In contrast, "meningeal doses" of third generation cephalosporins or meropenem penetrate the CSF if PRSP is administered in therapeutic concentrations [15].

	IV Dosages
Neonates	**Age < 1 week**
	Cefotaxime 50 mg/kg x 3
	Ampicillin/amoxicillin 50 mg/kg x 3
	Gentamicin 2.5 mg/kg x 2
	Age 1 - 4 weeks
	Ampicillin 50 mg/kg x 4
	Cefotaxime 50 mg/kg x 3-4
	Gentamicin 2.5 mg/kg x 3
	Tobramycin 2.5 mg/kg x 3
	Amikacin 10 mg/kg x 3
Infants/children	Vancomycin 10 - 15 mg/kg x4, goal serum trough concentrations of 15 - 20 μg/mL
	Rifampicin 10 mg/kg x 2, max 600 mg/day
	Cefotaxime 75 mg/kg x 3-4
	Ceftriaxone 50 mg/kg x 2, max 2 g x 2

Table 3: *ESCMID recommendations for antibiotic dosages in bacterial meningitis.*

Steroids

Although the use of dexamethasone in acute bacterial meningitis is supposed to affect the blood brain barrier causing reduced concentration of hydrophilic antibiotics in CSF, such as vancomycin [24] it has been used for its benefit in reducing hearing and neurological complications without decreasing mortality [26]. Dexamethasone can moderate the harmful response caused by the proinflammatory mediators that are produced when antibiotics interact with bacteria [27]. It has also been proposed that glucocorticoids acting with Toll-like receptors promote anti-inflammatory and immunosuppressive response [28]. Treatment with dexamethasone should be started ideally before or with the first dose of antibiotics [11] while the European guidelines suggest that a delay of up to 4 hours after the initiation of antibiotic therapy is acceptable [7]. Regarding the duration of dexamethasone therapy, European guidelines recommend a total duration of 4 days in case of pneumococcal and Hib meningitis in children [7,21] whereas American guidelines recommend the use of dexamethasone for 2 - 4 days in children with Hib meningitis. There are not clear recommendations for pneumococcal infection [11].

Other adjunctive therapies

The use of osmotic agents, such as mannitol or hypertonic saline, has been proposed to reduce intracranial pressure, but they are not recommended for children with bacterial meningitis as there are not sufficient data to prove favorable outcome. On the other hand, glycerol and therapeutic hypothermia should not be used in bacterial meningitis, as increased mortality has been associated with their use [7].

The impact of conjugate vaccines

Conjugate vaccines, comprising a conjugate between an antigenic protein and a polysaccharide, have been developed against a variety of bacterial species to overcome the issues associated with the T cell-independent immunological characteristics of pure polysaccharide antigens [29]. In particular, a conjugate vaccine, depending on T cell dependent response, is expected to have benefits over a polysaccharide vaccine, in terms of booster response, immunological memory and generally improved immune responses, due to the T cell-dependent characteristics of the immune response. Thus, immunological memory is established and herd immunity effect is enhanced with the use of conjugate vaccines [30]. Conjugate vaccines have been developed against the main causes of paediatric meningitis in the past; pneumococcal, meningococcal serotypes and Hib.

Streptococcus pneumonia

The heptavalent pneumococcal conjugate vaccine (PCV7) has dramatically reduced the incidence of pneumococcal diseases, not only in vaccinated children but also in unvaccinated individuals of all ages, by inducing herd immunity [31]. Since its introduction in the USA in 2000, the US Center for Disease Control and Prevention (CDC) has reported up to about 90% reduction of the incidence of invasive pneumococcal diseases (IPDs), in young children [32]. Notably, impact dynamics of pneumococcal meningitis and other IPDs are not identical [33]. Specifically, meningitis affects more often younger children than other IPDs, and frequently was less reduced compared with other IPDs, possibly because children were often too young to be vaccinated and serotype distribution was different [33]. These young infants are dependent on indirect (herd) protection, and thus, delayed vaccine impact in this population could be expected [33]. Apart from the reduction in the incidence of pneumococcal meningitis, reduction in antibiotic resistance in vaccine serotypes and carriage of vaccine serotypes and antibiotic-resistant serotypes have also been observed in several developed countries after the introduction of PCV7 [29].

However, since the availability of PCV7, increased infections caused by non-PCV7 serotypes were reported by several groups and in particular a rise mainly in the serotypes 19A, 7F, 6A, and 6Cwas observed globally [34]. To overcome this problem, new vaccines covering more serotypes including the emerging serotypes have been developed. The 13-valent pneumococcal conjugate vaccine (PCV13), which was licensed to replace PVC7 in 2010, currently covers the most serotypes, including 7 PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) and six additional serotypes 1, 3, 5, 6A, 7F, and 19A causing bacterial meningitis. The carrier protein used in PCV13 remains the same as that in PCV7. Thus, all the capsular polysaccharides of the 13 serotypes included in PCV13 were conjugated with the nontoxic mutant of diphtheria toxin CRM 197.

Today, a few years after the PCV13 applications in the immunization schedule in young children, global evaluation studies on the effectiveness of PCV13 against meningitis and other Invasive Pneumococcal Diseases (IPD) have demonstrated that PCV13 introduction has significantly reduced the incidence of IPD in both vaccinated children and unvaccinated population compared to the previous PCV7 applications, and the results were independent of countries or the scheme of PCV13 administration [31]. The impact of PCV13 in the US showed a decrease of serotype cases from 54% in 2007 - 2009 to 27% in 2011 - 2013 [35]. The non-PCV13 serotype cases estimated 73% and the minimum inhibitory concentration of ceftriaxone ≥1 μg/mL declined (13% to 3%) from 2007 - 2009 to 2011 - 2013 [35]. However, no significant results were found in the hospital course or outcome, except the greater percentage of patients with subdural empyema and hemiparesis [35]. Although, the colonization with non-PCV13 serotypes appears increased, the rate of overall colonization remained unchanged [36].

The incidence of IPD by vaccine types has been reported to increase quickly in unimmunized people as vaccine coverage fell under the borderline from which herd immunity is achieved (65 - 70%) [35]. Unlike PCV7 introduction, the incidence rate of non-PCV13-type IPD was not significantly elevated after PCV13 introduction, while colonization of nasopharynx has been replaced by non-PCV13 serotypes, which are supposed to be less "invasive" [37].

The *S. pneumoniae* has a remarkable level of plasticity and heterogeneity, in terms of genomics. This is due to the processes of selection and recombination that play a critical role in the emergence of multi-resistant strains and the serotype replacement, which leads to change of serotype distribution, most frequent in serotypes before the vaccine implementation. We thus expect that the long-term use of multi-valent conjugate vaccines will contribute to serotype replacement, unless the formulation could contain all capsular types. Another way to solve this problem of serotype replacement would be to develop new types of vaccines, that will target any pneumococcal strain regardless of its capsule type [38].

Neisseria meningitidis

N. meningitidis is classified into serogroups based on the composition of the bacterial capsular polysaccharide. Overall 13 serotypes of the meningococcus have been isolated, with only five of them associated with invasive disease (A, B, C, Y, X and W135) [39]. Four of the disease-causing serogroups (A, C, Y, and W) can be effectively prevented with available quadrivalent capsular polysaccharide protein conjugate vaccines; however, capsular polysaccharide conjugate vaccines are not effective against meningococcal serogroup B (MenB) and there is no vaccine available for serogroup X.

After the implementation of MenC vaccination program, disease incidence and mortality by serogroup C have dramatically declined and this effect has been reported in both vaccinated and unvaccinated children [40,41].

However, the challenges of MenC and the rest of the conjugate meningococcal vaccines consist of the duration of protection provided and the need of repeated booster doses to provide continuing protection [42]. In the UK, the study of MenC conjugate vaccine revealed that it is immunogenic in children under 2 years, with 98% of children generating human serum bactericidal antibody assay (SBA) titres. At the age of 12 months, the SBA titres decrease to 75%, but re-challenge with a polysaccharide MenC vaccine induce a significant immune response [38]. Although MenC vaccine has been reported to be immunogenic in infants, SBA titres are not adequate in the majority of infants prior to the booster dose [40].

The quadrivalent conjugate vaccine MenACW135Y uses the natural mutant of the diphtheria toxin and aluminum phosphate as an adjuvant, providing better immune response than the monovalent MenC conjugate vaccine. In the UK and Canada, infants immunized at 2, 3 and 4 months, were found to have 92% increased or equal SBA titres. At 12 months a challenge with MenACW135Y offers significant antibody response indicating the induction of immune memory [40].

Although *N. meningitidis* is found worldwide and meningococcal outbreaks can occur anywhere in the world, the highest incidence occurs in the "meningitis belt" of sub-Saharan Africa [41]. Meningococcal disease is hyperendemic in this region, and periodic epidemics

during the dry season (December - June) reach up to 1,000 cases per 100,000 population. Historically, outbreaks in the meningitis belt were primarily due to serogroup A and this led to the introduction of a new conjugate vaccine against group A serotype (MenAfriVac) in the African meningitis belt in 2010. MenA conjugate vaccine is more immunogenic than the previously mentioned conjugate meningococcal vaccines as it eliminates the carriage of group A meningococcus throughout vaccinated and unvaccinated individuals [41]. However, with the introduction of MenAfriVac in this region, recent meningococcal outbreaks have primarily been due to serogroups C and W, although serogroup X outbreaks are also reported.

Haemophilus influenzae type b

Conjugate vaccine against *H. influenzae* type b (Hib) is safe and efficacious and its introduction against Hib appeared significantly effective in preventing Hib meningitis [43,44]. This could be attributed not only to the direct protection of the vaccine, but also to the lower carriage of Hib in the nasopharynx of children, offering herd immunity [45].

However, nowadays, more than two decades after the implementation of the Hib conjugate vaccine, the epidemiology of invasive *H. influenzae* disease has changed substantially with most invasive diseases now caused by non-b serotypes and non-typeable (i.e. non-encapsulated) strains [46]. The PCV10, used before the introduction of PCV13, is conjugated to *Haemophilus influenza* protein-D and showed some protection against infections caused by those Hib serotypes [47]. With more countries implementing Hib conjugate vaccines, it will be timely to set up better surveillance network to document any changing epidemiology that may occur upon introduction of vaccines targeting infections with multiple antigenic variants.

Conjugate vaccines and neonates

The first days of life are prone to infections due to the unique nature of the neonatal immune system, which is a direct consequence of the challenging immunological adaptation during the transitional period from intra- to extrauterine life. The World Health Organization estimates that 45% of deaths among children under the age of 5 years occur during the newborn period [48]. The group B *Streptococcus,* for instance, the main pathogen for neonatal meningitis, was reported as the leading cause of meningitis in USA, after the induction the PCV in paediatric populations, with 86% of cases in infants younger than 3 months [49]. The interest for conjugate vaccines has now been focused on neonatal vaccination, which could potentially provide early protection for newborns and infants, narrowing the critical period of vulnerability intrinsic to routine vaccination schedules that start later in life.

Two recent trials, for instance, have examined neonatal vaccination with the PCV7, as pneumococcus remains a significant pathogen in newborns and in early infancy, particularly in sub-Saharan Africa [50]. In both studies, the safety profile was reassuring and good responses to the vaccine administered at birth were documented [50]. However, there was no evidence of hampering potential long-term protection or inducing immune tolerance [51]. A variety of approaches have been proposed to overcome the inherent regulatory constraints of the newborn innate and adaptive immune system, including alternative routes of delivery, novel vaccine configurations, improved innate receptor agonists and optimized antigen-adjuvant combinations [50,51].

Maternal immunization could be an alternative choice for infant protection, as prevention of severe infections has been proposed without adverse effects [50]. Further clinical trials are currently underway or being planned to examine both maternal and neonatal pneumococcal-conjugate vaccination in low-income settings [52]. In order to develop improved neonatal vaccines, better and more applicable research models will be required; this would enable the accurate assessment of both vaccine immunogenicity and safety [51].

Conclusions

Despite the introduction of new antibiotic agents and new types of vaccines, bacterial meningitis remains a major cause of morbidity and mortality in childhood worldwide. Although the incidence of bacterial meningitis has significantly decreased following the introduction of conjugate vaccines, new challenges have arisen, with change of serotype distribution and shift of the disease burden to the neonatal and early infantile period. Thus, new conjugate vaccines are needed that would target all strains regardless of their capsule type. Moreover, research should focus on maternal and neonatal immunization, targeting the age with the main burden of the disease at the moment.

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