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Recent interventions in treating bacterial meningitis

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Abstract

Bacterial meningitis (BM) affects the central nervous system (CNS) and is a significant long-term sequela for 50% of survivors globally. Resource-poor areas have a higher prevalence of acute bacterial meningitis than resource-rich ones. The pathogenesis of BM involves intricate pathways linked to bacterial survival and proliferation in the circulation, increased blood-brain barrier (BBB) permeability, oxidative stress, and an overactive inflammatory response in the central nervous system (CNS). Drug-resistant bacteria make treating meningitis more challenging, as the morbidity rate for BM is still very high. There has been promising progress in neurology recently for drug supplements that effectively prevent and treat BM. There have been hopeful advancements in neurology recently for medication supplements that effectively prevent and cure BM. Numerous *in vivo* and *in vitro* researches have gone into detail on how drugs affect BM and its important mechanism. However, prevention of BM at community and individual levels is vital and can be achieved via various strategies. Some of the strategies are particular hygiene protocols, isolation, social distancing, quite smoking, immunoglobulin treatments and many other methods. Yet, vaccinations still remain the best stratagem against the risk of bacterial meningitis and several other severe infections at the level of the community.

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Introduction

Acute bacterial meningitis proves a fatal infectious disease where a substantial change in its epidemiology has been reported since the conjugate vaccines were approved (Van de Beek *et al.*, 2004; Thigpen *et al.*, 2011; van de Beek *et al.*, 2021). Nonetheless, a huge toll is inflicted by this disease even in countries with high income and results in considerable mortality as well as morbidity (Brouwer *et al.,* 2010; Thigpen *et al.,* 2011). Early administering of antibiotics leads to saving lives, but the emergence of the bacteria that is resistant to multiple drugs on a global scale serves to prove a threat to the easily accessible and available antibiotics. In the following section, numerous strategies of the treatment that are available will be discussed including drawing attention to the advancements made in antibiotic as well as adjunctive therapy.

Initial empirical antibiotics

If due for any reason, the lumbar puncture is delayed, for example, if there is a need for an additional diagnostic test like a CT scan following the blood culturing, empirical antibiotic therapy must be started at the earliest opportunity (Tunkel *et al.,* 2004). It is critical that antibiotic therapy must be started even when bacterial meningitis evaluation is underway because delayed treatment has been linked to an increase in rates of mortality as well as morbidity (Tunkel *et al.*, 2004).

Administering empirical antibiotics in the patients present with bacterial meningitis should have its base on the age of the patient, local epidemiology, particular underlying conditions being present or absent, or the risk factors (Brouwer *et al.,* 2010; Tunkel *et al.,* 2004). In the geographical regions where strains of the *Streptococcus pneumoniae* (pneumococcal) show resistance against cephalosporins as well as penicillin, patients who are more than 1 month present with bacterial meningitis that is acquired from the community should be administered with 3rd generation cephalosporin (ceftriaxone or cefotaxime) in conjunction with vancomycin (McGill *et al.,* 2016; van de Beek *et al.,* 2016). The decision regarding the use of vancomycin is based on the resistance rate against the third-generation cephalosporins. Areas showing the lower prevalence of the *S. pneumoniae* which is resistant to the cephalosporins (<1% resistance), using a 3rd generation cephalosporin (ceftriaxone or cefotaxime) normally proves enough as the empirical therapy.

Moreover, vancomycin is not best from an economic point of view as it is expensive and it is not usually available in countries with low income (Scarborough and Thwaites, 2008). In conditions such as these, alternative agents are used, like anti-pneumococcal fluoroquinolone (such as moxifloxacin) as well as rifampicin, even though there is a scarcity of clinical data which supports the use of these drugs. Rifampicin is comparatively cheaper, shows good penetration into the CSF, normally is active in-vitro against pneumococcal strains that are resistant to ceftriaxone and is available widely (Brouwer *et al.,* 2010; Nau *et al.,* 2010).

Optimisation of the delivery and effectiveness of antibiotics

Two major therapeutic challenges are faced in bacterial meningitis; the first is delivery optimization and the second one is antibiotic effectiveness. For a successful treatment to take place, it is essential that the antibiotic penetrates across the BBB and it depends upon the degree of the disruption caused to the integrity of the barriers resulting due to inflammation, as well as the ability to bind the protein, interaction of antibiotic with the efflux pump, charge, size and lipophilicity (Andes and Craig, 1999; Nau *et al.,* 2010). Nonetheless, the concentration of the antibiotic in the CSF, along with a bactericidal activity to the bacteria causing the disease, also impacts the clinical Efficacy (Nau *et al.,* 2010).

Antibiotics for specific organisms

Upon the identification of the bacterial pathogen via CSF gram stain, and sometimes after doing the isolated and the *in-vitro* susceptibility testing, modifications can be brought up into the antibiotic therapy so optimal results can be obtained.

Streptococcus pneumoniae

Pneumococcal meningitis treatment has observed changes since strains showing diminished susceptibility to penicillin have emerged. In some regions of the USA, reduction in the susceptibility has a range that goes from 25% to greater than 50% (Appelbaum, 2002) and an increase was observed in the Asian region from 2012-2017, where it went from 16.0% in the time between 2008 to 2009 to 28.1% (Kim *et al.,* 2020). Resistance to penicillin proves as a marker indicating the diminished susceptibility to the other antibiotics as well, which might lead to failure of the treatment in patients present with pneumococcal meningitis (Klugman *et al.*, 2008; Erdem *et al.,* 2014).

In the areas where there is resistance against cephalosporin, pneumococcal meningitis empirical therapy must include administration of the vancomycin in conjunction with ceftriaxone or the cefotaxime even though the susceptibility test results conducted in-vitro are still pending. Even though pneumococcal meningitis rates have observed a decrease from the time of heptavalent pneumococcal conjugate vaccine getting introduced, these vaccines fail to cover meningitis resulting due to some serotypes and also the resistant strains, increasing the number such patients (Oligbu *et al.,* 2019).

Administering the vancomycin in the appropriate doses is crucial so that appropriate concentrations in the CSF can be achieved because using adjunctive dexamethasone concomitantly might lead to a reduction in the penetration of vancomycin into the CSF.

Even though data on rifampin effectiveness is rarely found regarding pneumococcal meningitis patients, some authorities make use of this agent along with the 3rd generation cephalosporins, sometimes in conjunction with vancomycin or sometimes without it, for the treatment of pneumococcal meningitis that is resulted due to strains which probably show high resistance to the cephalosporins or the penicillin (Brouwer *et al.,* 2010).

Neisseria meningitidis

The ongoing recommendation for the treatment of meningococcal meningitis is using ampicillin, penicillin G, or amoxicillin (Tunkel *et al.,* 2004; Van de Beek *et al.,* 2006 Brouwer *et al.,* 2010). Nonetheless, strains of the meningococci showing reduced ability toward penicillin have been isolated in numerous countries (Zouheir *et al.,* 2019 ; Rostamian *et al.,* 2022). In one of the studies (Cubells *et al.*, 1997), it was recorded by the investigators that there exists a relationship between the increase in the neurological sequelae or the risk of death in patients present with meningococcal meningitis and a reduction in the susceptibility to the penicillin. Thus, treatment of meningococcal meningitis patients should be started empirically using 3rd generation cephalosporins (ceftriaxone or cefotaxime) until in-vitro susceptibility test results become available (Nadel, 2016). There have been reports of a higher level of resistance against chloramphenicol (MIC ≥64 µg/mL) (Galimand *et al.,* 1998), but until now, most countries show a lower incidence (Rostamian *et al.,* 2022). Moreover, resistance against ciprofloxacin has also been reported in some parts of the USA (Wu *et al.,* 2009), and showed its effects on chemoprophylaxis recommendations. During epidemics of the meningococcal meningitis in settings where the resources are poor, it is sufficient to administer a single IM injection of the long-acting chloramphenicol (Stephens *et al.,* 2007); or a single injection of the ceftriaxone works equally efficiently (Nathan *et al.,* 2005).

Haemophilus influenzae

From the time of the rise of strains of *H. influenzae* that are resistant to chloramphenicol and produce β-lactamase, using third-generation cephalosporins has become the standard mode of treatment. Enhanced efficacy is shown by the 3rd generation cephalosporins compared to the second generation cephalosporins like cefuroxime (Schaad *et al.,* 1990) as well as chloramphenicol, even for the patients present with the *H. influenzae* type b meningitis resulted by the strains sensitive to the chloramphenicol (Peltola *et al.,* 1989). In the cases

where Hib meningitis is suspected, antibiotics like ampicillin-sulbactam, azithromycin, ceftriaxone, fluoroquinolones, ceftazidime and cefotaxime are administered via the parenteral route in the course of one week (Tristram *et al.,* 2007; Bradley, 2002). Antibiotics that are usually avoided are ampicillin because of the production of the beta-lactamase that is mediated by plasma and results in resistance (Bradley, 2002; Tristram *et al.,* 2007), cefuroxime is avoided because of delayed sterilization (Schaad *et al.,* 1990), and chloramphenicol is avoided due to strenuous monitoring of the level of the drug as it has numerous side effects like idiosyncratic aplastic anaemia as well as the toxicity of the bone marrow (Barnhill *et al.,* 2012). Furthermore, an increase in the resistance of bacteria against the chloramphenicol in the *H. influenzae* suggests that there is a need for an alternate antibiotic treatment for meningitis presently (Duke *et al.,* 2003; Mengistu *et al.,* 2011; Swann *et al.*, 2014).

Aerobic Gram-negative bacilli

The emergence of gram-negative bacilli that is resistant to multiple drugs it's worrisome. Particularly in the patients who present with bacterial meningitis that is associated with health care (Andes and Craig, 1999). development of resistance against third-generation as well as fourth-generation cephalosporins (Sandulescu, 2016), and the carbapenems have caused reduction in the range of available antibiotic options. Meningitis outbreaks resulting due to the strains of *E. coli* that produce ESBL in the neonatal wards might prove hard to control (Moissenet *et al.,* 2010; Stapleton *et al.,* 2016). If resistance against carbapenems is shown by the organism, polymyxin B or colistin which is normally formulated as the colistimethate sodium must be administered IV, or it could be administered via intraventricular or intrathecal route (Jiménez-Mejías *et al.,* 2002; Gupta *et al.*, 2009).

Staphylococcus aureus

Meningitis by *S. aureus* has resulted following CSF shunts placement or neurosurgical procedures (Andes and Craig, 1999). The basis of the treatment is on the localized prevalence of the *S. aureus* strains resistant to methicillin; vancomycin proves less effective than using anti-staphylococcal penicillins for treating severe cases of *S. aureus* disease. Nonetheless, empirical vancomycin could be administered until results for susceptibility testing become available (DeLeo *et al.,* 2010).

K. pneumoniae

K. pneumoniae is among the commonest pathogens which show resistance to multiple drugs as well as the carbapenems in healthcare settings (Podschun and Ullmann, 1998; World Health Organization, 2015 ; Sugden *et al.,* 2016 ; Sherry and Howden, 2018) . For the past few decades, mostly used antibiotic options for *K. pneumoniae* which is resistant to carbapenem, have been represented by polymyxins. Indeed the use of the polymyxin E (colistin) is considered the last choice antibiotic agent against infections caused by MDR *K. pneumoniae*, proving to be the antibacterial compound that achieved adequate levels in the serum as well as MIC (Arnold *et al.,* 2011).

Thus, recently reported isolates of *K. pneumoniae* that are resistant to colistin raise concern as it limits further antimicrobial options as well as the higher rate of mortality related to such infections (Capone *et al.,* 2013). Regimens given in combination for the Enterobacteriaceae that involves carbapenems with 8mg/l MICs or less for the carbapenems (given in dual combination along with the colistin, or high dosage of tigecycline or the aminoglycosides or sometimes triple combinations) prove to have therapeutic advantages over the monotherapy, in Enterobacteriaceae where the MICs are higher compared to what is mentioned above. Combination of three or sometimes two antibiotics including tigecycline in high dosage, Fosfomycin, colistin and aminoglycosides are related to decrease in mortality (Rafailidis and Falagas, 2014 ; Lin *et al.*, 2018). Primarily, isolate's antibiotic susceptibility profile, pharmacokinetics (PK) properties, pharmacodynamics (PD) properties, potentially occurring adverse events and the infection site determines their usage.

New antibiotics for meningitis

The increase in the meningitis prevalence that resulted due to the resistant bacteria led to consideration of new therapeutic antimicrobial agents, even though data that describes their role is scarce and is limited to the extrapolations from animal models used for experimentation along with the case reports. This discussion is limited to the agents of which the assessment has been done in patients with bacterial meningitis.

Cefepime

Cefepime is a fourth-generation Cephalosporin having a broad activity range as well as showing greater stability when it comes to β-lactamases, and those agents that *Pseudomonas aeruginosa* produce compared to having agents from a former generation, for example, cefotaxime and the ceftriaxone. Results obtained from experimental models of meningitis, as well as some studies conducted on humans, indicated cefepime has better activity in the CSF compared to ceftriaxone even against *S. pneumonia* that is resistant to penicillin (Lodise Jr *et al.,* 2007; Miranda and Tunkel, 2009); nonetheless, in the two control trials consisting of 345 children present with bacterial meningitis it was noted by the investigators that cefepime demonstrated same efficacy as demonstrated by ceftriaxone and the cefotaxime (Lodise Jr *et al.,* 2007; Miranda and Tunkel, 2009). It is recommended by guidelines from The Infectious Diseases Society of America (IDSA) to use cefepime as second-line agent for the treatment of meningitis caused by *H. influenzae*, while ceftazidime or cefepime should have opted as an empirical first-time treatment for the patients present with the post-neurosurgical meningitis (Tunkel *et al.*, 2004).

Carbapenems

When it comes to beta-lactams, the most extensive range of activity in vitro against both the Gram-negative and the gram-positive bacteria is shown by the carbapenems. Studies that included human beings indicate meropenem do have better penetration in the CSF compared to doripenem and imipenem (Nau *et al.*, 2010;Nalda *et al.*, 2012). In the four controlled trials consisting of 448 children as well as 58 adults, it was shown that meropenem demonstrated efficacy as well as safety similar to that of ceftriaxone and cefotaxime, illustrating meropenem as the best carbapenem candidate for bacterial meningitis treatment (Nau *et al.,* 2010). Novel beta-lactamases emergence, which shows direct activity for hydrolyzation of carbapenems has a significant contribution to increasing the prevalence of Enterobacteriaceae that are resistant to carbapenems (Gupta *et al.,* 2011).

Fluoroquinolones

Moxifloxacin and gatifloxacin are two fluoroquinolones that effectively penetrate CSF and show increased activity in vitro for ground-positive bacteria compared to their predecessors, for example, ciprofloxacin. Results obtained from experimental models of meningitis indicate them to be effective for meningitis caused by *S. pneumoniae*, as well as meningitis caused by strains that are resistant to penicillin as well as cephalosporin (Lutsar *et al.,* 1998; Østergaard *et al.,* 1998). Even though it was suggested by one controlled trial that trovafloxacin mesylate, which is a fluoroquinolone, that it has similar efficacy as shown by ceftriaxone in both cases, i.e., without adding the vancomycin or adding it, for treatment of bacterial meningitis in the pediatric patients (Sáez-Llorens *et al.,* 2002), there is the absence of clinical trials which underline using the moxifloxacin or the gatifloxacin in the humans for the treatment of bacterial meningitis.

An association between the use of gatifloxacin and trovafloxacin has been made with dysglycaemia as well as severe hepatic toxicity, respectively, and they were removed from numerous markets (Park-Wyllie *et al.*, 2006). it is recommended by the guidelines from IDSA that moxifloxacin be used as an alternative for 3rd generation of cephalosporins including vancomycin, for the treatment of meningitis resulting from the strains of *S. pneumoniae* that show resistance against 3rd generation cephalosporins as well as penicillin (Tunkel *et al.,* 2004), even though it is recommended by some of the experts do not use

this agent alone but in combination with some other drug like a 3rd generation cephalosporin or vancomycin due to clinical data being absent which supports using it.

Daptomycin

Daptomycin is essentially a cyclic lipopeptide and only shows activity against Gram-positive bacteria. Even though its penetration into the CSF is poor, it is shown by experimental models that the bactericidal concentrations in the CSF are achieved for the organisms that are most susceptible and that daptomycin might be elicited better bactericidal activity against bacteria that are resistant to β-lactam compared to the vancomycin (Egermann *et al.*, 2009). There is limited human data available in the form of case reports which demonstrate using daptomycin successfully (6–12 mg/kg per day) normally in combination with the rifampicin for the treatment of meningitis resulting from *S. aureus* that is resistant to meticillin and the Enterococcus spp. which is resistant to vancomycin (Lee *et al.*, 2008;Le *et al.*, 2010;).

Linezolid

Linezolid is oxazolidinone which shows activity only against Gram-positive bacteria. Its assessment has never been carried out in controlled trials for bacterial meningitis patients, but there are some published case reports (Ntziora and Falagas, 2007); penetration into the CSF is achieved by the linezolid and is related to successful treatment rates of nearly 90%. Variable penetration into the CSF has been described by clinical studies; nearly 50% of the patients who are provided with a standard dosage (600mg twice in 24 h) might fail to achieve therapeutic concentrations in the CSF (Yogev *et al.,* 2010). There is a need for the measurement of concentration in the CSF and the higher doses so that linezolid therapy for bacterial meningitis can be optimized.

Tigecycline

Tigecycline shows activity against numerous gram-negative bacteria along with numerous gram-positive bacteria and is glycycline antibiotic. There is limited data available regarding their use in the management of bacterial meningitis and is confined to the case reports which describe using tigecycline treatment for meningitis caused by Acinetobacter that is resistant to multiple drugs (Kim *et al.,* 2009), and some of them demonstrate standard IV doses of tigecycline leading to the production of subtherapeutic concentrations in the CSF (Kim *et al.,* 2009; Ray *et al.,* 2010).

Adjunctive Therapy (Dexamethasone and Rifampin)

Rationale for using the adjunctive dexamethasone is the reduction of inflammatory responses in subarachnoid space that is resulted due to bacterial components getting released in response to the bactericidal therapy, which serves as a precursor to neurological complications related to the inflammation (van de Beek *et al.,*2016 ; Hasbun, 2019). It has been demonstrated that adjunctive dexamethasone when used in adults suffering with pneumococcal meningitis, lowers mortality as well as decreases loss of hearing in children suffering from Hib meningitis (Tunkel *et al.,* 2004; Hasbun, 2019). It is recommended by guidelines from the IDSA that adjunctive dexamethasone is used in adults where meningitis is proven or even suspected to occur due to *S. pneumoniae* and in infants, excluding the neonates, as well as children present with meningitis resulting from the Hib (Hasbun, 2019). The suggested regimen dosage for dexamethasone is 0.15 mg/kg administered 4 times per day at equal intervals for the duration of 2 days to 4 days, where the first dosage is administered 10 min to 20 min prior to the first antibacterial therapy dosage or at a similar time of it (van de Beek *et al.,* 2016 ; Hasbun, 2019). If it is revealed by the testing that there is another pathogen is involved, or it ruled out that it is bacterial meningitis, discontinuation of the dexamethasone should be done, as there is no data that supports using it to gain an advantage for treating other pathogens (Hasbun, 2019). Moreover, it is advised that dexamethasone be not administered in patients who are already receiving antibacterial therapy because it is highly unlikely that improved outcomes will be attained (Hasbun, 2019).

If the administration of dexamethasone is done in patients where pneumococcal meningitis is suspected, some of the experts prefer adding rifampin to the empirical vancomycin antimicrobial regimen along with 3rd generation cephalosporin, making it a part of the initial regimen or when the susceptibility test results are pending. For *S. pneumoniae* isolates that show resistance against a cephalosporin (described as MIC >2 mcg/mL), rifampin might be added or continued if already added before as it incurs synergetic effects with the ceftriaxone against *S. pneumoniae* which shows resistance against cephalosporin (Costerus *et al.,* 2017; Hasbun, 2019).

Vaccine-based prevention

Bacterial meningitis falls into the category of diseases that are preventable due to the availability of vaccines against the commonest of the pathogens that cause this disease (McIntyre *et al.,* 2012). Vaccines that were derived from *S. pneumoniae, N. meningitidis*, and *Hib* polysaccharide capsules were introduced first many decades ago. They lead to the generation of immune responses that are T-independent, and cause no induction of immunological memory; other than that, and they also do not prove immunogenic in infants, rendering them not suitable to be implemented in the universal programmes for the immunization of infants. The development of vaccines based on the conjugate of polysaccharide and protein against the Hib in the 1980s bypassed poor responses in infancy to plain polysaccharides via evocation of the immune responses that were T-cell dependent, class-switching of the immunoglobin as well as immunological memory was also acquired. Since that time, it has become possible to use anti-meningitis vaccines on a wider scale (Hargreaves *et al.*, 1996; Peltola, 2000).

Polysaccharide vaccines

Polysaccharides are antigens that are not dependent on the T-cell, meaning that there is no presentation to the T-cell in conjunction with the MHC-II molecules, which in turn prevents memory B cells from developing (Kelly *et al.*, 2004; Plotkin *et al.,* 2008). Subsequently, following a vaccination concentration of the antibody sees a rapid decline in children of young age, and no further anamnestic response is observed to further doses of the polysaccharide with little or no observable effect on the oropharyngeal or nasopharyngeal carriage (Plotkin *et al.,* 2008). Efficacy against meningitis by polysaccharide vaccines has been best demonstrated for the A serogroup meningococcal disease, but protection declined following 3 years of administration, also being poor in the children younger than 2 years of age (Patel and Lee, 2005; Stephens *et al.*, 2007). Likewise, pneumococcal vaccine responses against most of the serotypes is found to be reduced in children aged 2 years. Talking about the adults, such vaccines prove effective against the invasive pneumococcal disease which can be attributed to the serotypes of the vaccines, and also against meningitis is implicated, but there is a lack of available data (Moberley *et al.,* 2013). Minute effect of the vaccine constructed from the Hib polysaccharide on the disease, particularly meningitis, was noted when this vaccine was in routine use in the USA among children who were older than 2 years despite of the fact efficacy was documented (Wenger *et al.,* 1991), might be due to the small number of cases of Hib meningitis in the people of this age (McIntyre *et al.,* 2012).

Conjugate vaccines

Conjugate vaccines are dependent on T-cell, which allow the memory B-cell to develop, subsequently leading to anamnestic responses and their effect on the carriage is one of the most important factors of them (Kelly *et al.,* 2004; Plotkin *et al.,* 2008).

Hib conjugate vaccines

The very first conjugate vaccine that was commercially available was constructed against Hib (Chandran *et al.*, 2005). Manufacturers made use of the different proteins (the outer membrane protein of *N. meningitidis* serogroup B [OMP], mutant diphtheria toxin [CRM] conjugated to Hib polysaccharide [PRP], diphtheria toxoid [D], and tetanus toxoid [TT]) (Kelly *et al.*, 2004;Chandran *et al.,* 2005). The vaccine constructed from PRP-OMP showed antibody response after delivery of the first

dosage proving a crucial advantage in the settings where there was the occurrence of Hib in the early phases of life. Other conjugates of Hib (PRP-CRM, PRP-D, and PRP-T) needed two or sometimes three doses of vaccines to achieve such an antibody response (Capeding *et al.,* 1998; Chandran *et al.,* 2005). Pneumococcal and Hib conjugate vaccines are provided to infants in a series of three to four doses (McIntyre *et al.,* 2012), but children of an older age need fewer doses. This vaccine has proved useful in causing a reduction of Hib infection incidence in the childhood population that was susceptible (van de Beek *et al.,* 2016).

Pneumococcal conjugate vaccines

The first conjugate vaccine constructed against pneumococcal infection was PCV which, as a protein carrier, made use of CRM and in 2000, it was licensed as well as recommended in the USA to be used routinely. All the seven serotypes that were commonest and caused invasive disease (18C, 23F, 4, 9V, 19F, 6B, 14) were included in that. Some other vaccines where conjugates were 13, 11, 10 or 9 (serotypes included were 19A, 5, 1, 3, 7F, 6A) have been researched, with 13-valent products and 10-valent products acquiring licensure. The immunogenicity of these products varies by the serotype, consequent administration of the vaccine, population under study, and number of doses (Käyhty *et al.,* 2008). Some of the policies for the national immunization have a recommendation that pneumococcal vaccines in adults be done as they are present at a higher risk of pneumococcal infection owing to their immunocompromised makeup, chronic ailments like sickle cell anemia, or older age (Adriani *et al.,* 2013). The 13-valent vaccine constructs caused prevention of the invasive pneumococcal disease as well as pneumonia resulting from the serotypes that were covered in a mass clinical trial conducted on a population belonging to the elderly age group (Bonten *et al.,* 2015). Since 1983, a 23-valent polysaccharide vaccine against pneumococcal infection has been available and is recommended for people of adult age, even though there is availability and licensure of the 13-valent conjugate vaccine for adults as well as the recommendation for its usage in adults equal to or greater than 65 years of age in the USA (Kobayashi *et al.,* 2015).

Meningococcal vaccines

There are 12 known serotypes of the meningococci, but vaccines are available only against W, B, A, Y and C, either in the single targeting serotype versions (B, A or C) or in the form of multiple (A/C/Y/W, A/C or A/C/Y) targeting serotypes (Ladhani *et al.,* 2016). Vaccine conjugate containing serotype C polysaccharide in combination with the CRM was the first ever conjugate vaccine against meningococci; consequently, TT conjugates as well as serotype Y, W135, and A conjugates have already been developed (Khatami and Pollard, 2010). The use of the conjugate vaccine is done routinely for the prevention of diseases, whereas for controlling epidemics or outbreaks, both polysaccharides and conjugate versions of the vaccines are used. Vaccination of the individuals higher at risk (like, those present with complement deficiencies or asplenia) is a common practice, but there are variations when it comes to the universal policies for the vaccination among the countries. In the UK, since 1998, there has been the implementation of the serotype C vaccine in the regions of Wales and England, but in 2015 serotype B vaccination was implemented. In this programme, there was routine administration of both serotype C and B vaccines in the infants, whereas all the teenagers received a booster dosage of A/C/Y/W conjugate vaccine construct (Ladhani *et al.,* 2016). In the USA, the overall rate of meningococcal disease is low in the general population but a bit higher in both young adults and adolescents, the recommendation has been given regarding the administration of the 4-valent W, A, C and B serotype targeting vaccine in the children aged 11-12 years whereas a booster dosage be administered at 16 years; a less-restrictive recommendation for serotype B vaccine usage has been proposed in a recently given policy, stating that use of the vaccine might be done for the individuals with ages between 16 to 23 years in whom the risk of the meningococcal disease is high (MacNeil *et al.,* 2015). MenAfriVac (Serum Institute of India Pvt. Ltd,

Pune, India), a monovalent construct of serotype A conjugate vaccine particularly developed from an economic point of view to be used in settings where there is low income. It was introduced first time in Burkina Faso in 2010. There is a recommendation of the WHO that MenAfriVac has a target range for individuals aged from 1 to 29 years in all the countries coming under the meningitis belt, as well as establishing routine programmes for the vaccination for children aged 9 to 18 months (Meningococcal, 2015). Early obtained reports on control of serotype A vaccines are very promising (Daugla *et al*., 2014).

Trials of vaccine efficacy

The interplay between the immunogenicity of the vaccine and the epidemiology of the disease was highlighted by trials of the first two developed Hib conjugate vaccines, which made use of PRP-D in settings that differed very much. In Finland, Efficacy showed by the PRP-D was 94% (CI 83 lower 95%) (Eskola *et al.,* 1990), whereas in the state of Alaska, USA, where the incidence of Hib was higher and the peak of it was observed in the initial 6 months compared to the second year of life, the efficacy of the vaccine was noted to be 35% (−233%) (Ward *et al.,* 1990). A contrasting observation was made when researchers made an assessment of the PRP-OMP in the infants of Navajo in who occurrence of Hib disease was predominant in the initial few months (Coulehan *et al.,* 1984), similar to the Alaska Native infant population as well as the aboriginal infant population of Australia, and Efficacy was noted to be 95% (72%) after administration of two doses as well as protective following one dose (CI for one individual dose 45% lower 95%) (Santosham *et al.,* 1991).

Trails of the 7-valent PCV with the schedule of four doses were carried out in the state of California, USA (Black *et al.,* 2000), as well as also in infants of the Navajo population (O'Brien *et al.,* 2003), where there is a greater diversity of the serotypes as well as higher incidence compared to the general infant population of the USA. It was shown by these trials that there was higher efficacy of 94% against the serotypes of the vaccine (Black *et al.,* 2000) and 83% (O'Brien *et al.,* 2003), respectively.

Trials of the 9-valent vaccine administered in the schedule of 3 primary doses at 6 weeks, 10 weeks and 14 weeks of the being born as per the recommendations of the Expanded Programme on Immunization in the regions of Gambia and South Africa demonstrated similar results of efficacy against the serotypes of the vaccine, with the exception of children infected with HIV. Efficacy against all of the serotypes of meningitis or sepsis in the trials conducted was less compared to what was noted in the studies conducted in the USA due to the higher baseline incidence of the disease by non-vaccine serotypes (Klugman *et al*., 2003; Cutts *et al*., 2005). In spite of these findings, The Gambia has high mortality rates and administration of the vaccine caused 16% (CI 3-28 95%) reduction in the all-cause mortality (Cutts *et al.,* 2005).

None of the conjugate vaccines against the meningococcal have been subjected to test in the randomized control trials with the disease endpoints as it was not thought justified in the context that immunological correlates of the protection can predict the effectiveness of the vaccine reliably (Khatami and Pollard, 2010). Efficacy of the vaccine against meningitis caused by the meningococci is, thus, deduced from the studies conducted on the effectiveness following the licensure, where observed results of multiple studies showed a significant effect of the vaccine (Campbell *et al*., 2009; Galloway *et al.,* 2009; Plotkin *et al*., 2009; Miller *et al*., 2011; Halperin *et al.,* 2012; Kaaijk *et al.,* 2012).

Chemoprophylaxis

In various situations, antimicrobial chemoprophylaxis is indicated to prevent infection spread from patients with meningitis involving *H. influenzae* or *N. meningitidis* (Cohn *et al*., 2013; Briere *et al*., 2014).

There is an indication for chemoprophylaxis for infection caused by *N. meningitidis* where there is a close contact, described as at ≥3 feet distance (close

proximity) and for greater than 8 hours (prolonged contact), or for any person getting exposed to the oral secretions of the patient in seven days prior to the onset of symptoms. Therefore, meningococcal chemoprophylaxis might be used for the contact of child-care, household members, or anyone getting directly exposed to the oral secretions of the patients through activities for example mouth to mouth resuscitation, kissing, management of the endotracheal tube or endotracheal intubation. For *N. meningitidis,* the chemoprophylaxis should be administered at the earliest possible and within 24 hrs., ideally after identifying the index patient. Administration of prophylaxis is not recommended after 14 days of exposure as it has been observed not to pose any benefit after 14 days (Cohn *et al.*, 2013). Regarding *H. influenzae* type b chemoprophylaxis, it is recommended for all contacts of household in households with partially vaccinated individuals who are younger than 4 years of age, for any household contact who is immunocompromised and younger than 18 years of age (regardless of immunization status) and for all child-care providers and attendees when there are children whose vaccination is not completed yet and there are 2 or greater than 2 cases of invasive infection reported to have occurred in previous 60 days (Briere *et al.,* 2014).

Prevention of bacterial meningitis

Preventing infectious diseases at the level of individual people or level community is achievable via different methods. Mainly, a reduction in the risk of acquiring bacterial meningitis can be achieved either by minimizing the occurrence of the pathogens responsible for it or by boosting the defense mechanism of that particular individual against that specific disease.

The task of diminishing the bacterial occurrence responsible for meningitis within the community is hard. Chiefly, such bacteria sometimes are part of the normal bacterial flora of humans, or their colonization takes place without resulting in infection (Mace, 2008; Kim, 2010;). Three of the most commonly found bacteria that cause meningitis are *N. meningitidis, S. pneumoniae,* and *H. influenzae*, whereas all of these bacteria show colonization of the upper respiratory tract (URT) epithelium (Grief, 2013). Even though there is the possibility of eliminating it by the use of antibiotics in case of local outbreaks inside restricted groups, this option becomes useless at the level of community, while also being not an option when it comes to the treatment of *H. Influenzae* or *S. pneumoniae* (Cuevas and Hart, 1993; Fraser *et al.,* 2005). Vaccination is the only viable option when it comes to reducing occurrence at the level of the community. Meningococcal vaccination has been demonstrated to cause a reduction by 18% to 100% when talking about nasopharyngeal carriage and swift serotype replacement has been seen in nasopharyngeal carriage upon pneumococcal vaccine administration in the children who got vaccinated compared to their siblings who did not get vaccinated (Vergison, 2008; Balmer *et al.,* 2018).

Providing hindrance in the way of transmission is usually a preventive measure of importance for the reduction of infectious diseases that are contagious. Some of the strategies are particular hygiene protocols, isolation, social distancing, and many others (Rashid *et al.,* 2015; Smith *et al.*, 2015; Baseler *et al.,* 2017). This proves viable in larger gatherings where there is a higher risk of meningococcal meningitis outbreaks. Nonetheless, there is usually no deployment of such strategies because these pathogens have widespread colonization inside the community (Mace, 2008; Kim, 2010; Grief, 2013; Yezli *et al.*, 2018).

Lastly, the option that remains is strengthening the defense of individuals to fight off the infections. Despondently, strengthening the physical barriers can be done only by repair of the defects that occur rarely and cause leakage of the cerebrospinal fluid (Wang *et al.,* 2005; Daudia *et al.,* 2007; Phang *et al.*, 2016; Englhard *et al.,* 2018; Wang *et al.,* 2019) and there is no way the leads to the improvement of the blood-brain barrier (Dando *et al.*, 2014; Serlin *et al.,* 2015; Mazurek *et al.*, 2017). Thus, the only strategy that

remains feasible in such conditions is that the immune system should be strengthened. In an isolated event, this is achievable via starting immunoglobulin treatments in the child who is primarily immunodeficient or by optimization of the illnesses that were pre-existing in children who are secondary immunodeficient (Yusuf *et al.,* 1999; Chinen and Shearer, 2010; Goldacre *et al.,* 2014; Sankar *et al.,* 2015; Amaya-Uribe *et al.,* 2019). It is important that determinants of health, like reduction in the rate of smoking in patients or increasing breastfeeding in infants to strengthen immunity, be addressed at the level of the community. But, infant vaccinations still remain the best stratagem against the risk of bacterial meningitis and several other severe infections at the level of community (Doherty *et al.,* 2016).

References

Adriani KS, Brouwer MC, Van der Ende A, Van de Beek D. 2013. Bacterial meningitis in adults after splenectomy and hyposplenic states. Paper presented at the Mayo Clinic proceedings.

Amaya-Uribe L, Rojas M, Azizi G, Anaya JM, Gershwin ME. 2019. Primary immunodeficiency and autoimmunity: a comprehensive review. Journal of autoimmunity **99,** 52-72.

Andes DR, Craig WA. 1999. Pharmacokinetics and pharmacodynamics of antibiotics in meningitis. Infectious disease clinics of North America **13(3),** 595-618.
https://doi.org/10.1016/S0891-5520(05)70096-9

Arnold RS, Thom KA, Sharma S, Phillips M, Kristie Johnson J, Morgan DJ. 201. Emergence of Klebsiella pneumoniae carbapenemase-producing bacteria. Southern medical journal **104(1),** 40-45.
https://doi.org/10.1097/SMJ.0b013e3181fd7d5a

Balmer P, Burman C, Serra L, York LJ. 2018. Impact of meningococcal vaccination on carriage and disease transmission: a review of the literature. Human vaccines and immunotherapeutics **14(5),** 1118-1130.

Barnhill AE, Brewer MT, Carlson SA. 2012. Adverse Effects of Antimicrobials via Predictable or Idiosyncratic Inhibition of Host Mitochondrial Components. Antimicrobial agents and chemotherapy **56(8),** 4046-4051.
https://doi.org/10.1128/AAC.00678-12

Baseler L, Chertow DS, Johnson KM, Feldmann H, Morens DM. 2017. The pathogenesis of Ebola virus disease. Annual Review of Pathology: Mechanisms of Disease **12,** 387-418.

Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, Siber G. 2000. efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. The Pediatric infectious disease journal **19(3),** 187-195.

Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, Verheij TJ. 2015. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. New England Journal of Medicine **372(12),** 1114-1125.

Bradley JS. 2002. Management of community-acquired pediatric pneumonia in an era of increasing antibiotic resistance and conjugate vaccines. The Pediatric infectious disease journal **21(6),** 592-598.

Brouwer MC, Tunkel AR, Van de Beek D. 2010. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clinical microbiology reviews **23(3),** 467-492.

Campbell H, Borrow R, Salisbury D, Miller E. 2009. Meningococcal C conjugate vaccine: the experience in England and Wales. Vaccine, **27**, B20-B29.

Capeding MRZ, Nohynek H, Käyhty H, Pascual LG, Sunico ES, Tamundong AA, Ruutu P. 1998. Antibody responses of three Haemophilus influenzae type b conjugate vaccines after one, two and three doses in Filipino children. Vaccine **16(9-10),** 1004-1008.

Capone A, Giannella M, Fortini D, Giordano, A, Meledandri M, Ballardini M, Petrosillo N. 2013. High rate of colistin resistance among patients

with carbapenem-resistant Klebsiella pneumoniae infection accounts for an excess of mortality. Clinical Microbiology and Infection **19(1),** E23-E30. https://doi.org/10.1111/1469-0691.12070

Chandran A, Watt JP, Santosham M. 2005. Prevention of Haemophilus influenzae type b disease: past success and future challenges. Expert review of vaccines **4(6),** 819-827.

Chinen J, Shearer WT. 2010. Secondary immunodeficiencies, including HIV infection. Journal of Allergy and Clinical Immunology **125(2),** S195-S203.

Costerus JM, Brouwer MC, Bijlsma MW, and van de Beek D. 2017. Community-acquired bacterial meningitis. *Current Opinion in Infectious* Diseases **30(1),** 135-141.

Coulehan JL, Michaels RH, Hallowell C, Schults R, Welty TK, Kuo J. 1984. Epidemiology of Haemophilus influenzae type B disease among Navajo Indians. Public health reports **99(4),** 404.

Cuevas L, Hart C. 1993. Chemoprophylaxis of bacterial meningitis. Journal of Antimicrobial Chemotherapy **31**(suppl_B), 79-91.

Cutts F, Zaman S, Enwere Gy, Jaffar S, Levine O, Okoko J, Leach A. 2005. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. The lancet **365(9465),** 1139-1146.

Daudia A, Biswas D, Jones NS. 2007. Risk of meningitis with cerebrospinal fluid rhinorrhea. Annals of Otology, Rhinology and Laryngology, **116(12),** 902-905.

Daugla D, Gami J, Gamougam K, Naibei N, Mbainadji L, Narbé M, Coldiron M. 2014. Effect of a serogroup A meningococcal conjugate vaccine (PsA–TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. The lancet **383(9911),** 40-47.

DeLeo FR, Otto M, Kreiswirth BN, Chambers, HF. 2010. Community-associated meticillin-resistant Staphylococcus aureus. The Lancet, **375(9725),** 1557-1568. https://doi.org/10.1016/S0140-6736(09)61999-1

Doherty M, Buchy P, Standaert B, Giaquinto, C, Prado-Cohrs D. 2016. Vaccine impact: Benefits for human health. Vaccine **34(52),** 6707-6714.

Duke T, Michael A, Mokela D, Wal T, Reeder J. 2003. Chloramphenicol or ceftriaxone, or both, as treatment for meningitis in developing countries? Archives of Disease in Childhood **88(6),** 536-539. https://doi.org/10.1136/adc.88.6.536

Egermann U, Stanga Z, Ramin A, Acosta F, Stucki A, Gerber P, Cottagnoud P. 2009. Combination of daptomycin plus ceftriaxone is more active than vancomycin plus ceftriaxone in experimental meningitis after addition of dexamethasone. Antimicrobial agents and chemotherapy **53(7),** 3030-3033.

Englhard AS, Volgger V, Leunig A, Meßmer C. S, Ledderose GJ. 2018. Spontaneous nasal cerebrospinal fluid leaks: management of 24 patients over 11 years. European Archives of Oto-rhino-laryngology **275(10),** 2487-2494.

Erdem H, Elaldi N, Öztoprak N, Sengoz G, AKO, Kaya S, Pekok AU. 2014. Mortality indicators in pneumococcal meningitis: therapeutic implications. International Journal of Infectious Diseases **19,** 13-19.

Eskola J, Käyhty H, Takala AK, Peltola H, Rönnberg PR, Kela E, Mäkelä PH. 1990. A randomized, prospective field trial of a conjugate vaccine in the protection of infants and young children against invasive Haemophilus influenzae type b disease. New England Journal of Medicine, **323(20),** 1381-1387.

Fraser A, Gafter-Gvili A, Paul M, Leibovici L. 2005. Prophylactic use of antibiotics for prevention of meningococcal infections: systematic review and meta-analysis of randomised trials. European Journal of Clinical Microbiology and Infectious Diseases, **24(3),** 172-181.

Galimand M, Gerbaud G, Guibourdenche M, Riou JY, Courvalin P. 1998. High-level chloramphenicol resistance in Neisseria meningitidis. New England Journal of Medicine **339(13),** 868-874.

Galloway Y, Stehr-Green P, McNicholas A, O'Hallahan J. 2009. Use of an observational cohort study to estimate the effectiveness of the New Zealand group B meningococcal vaccine in children aged under 5 years. International journal of epidemiology **38(2),** 413-418.

Goldacre M, Wotton C, Maisonneuve J. 2014. Maternal and perinatal factors associated with subsequent meningococcal, Haemophilus or enteroviral meningitis in children: database study. Epidemiology and Infection **142(2),** 371-378.

Grief SN. 2013. Upper respiratory infections. Primary Care: Clinics in Office Practice **40(3),** 757-770.

Gupta N, Limbago BM, Patel JB, Kallen AJ. 2011. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clinical infectious diseases **53(1),** 60-67.

Gupta S, Govil, D, Kakar PN, Prakash O, Arora D, Das S, Malhotra A. 2009. Colistin and polymyxin B: a re-emergence. Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine **13(2),** 49-53. https://doi.org/10.4103/0972-5229.56048

Halperin SA, Bettinger JA, Greenwood B, Harrison LH, Jelfs J, Ladhani SN, Sáfadi MA. 2012. The changing and dynamic epidemiology of meningococcal disease. Vaccine **30,** B26-B36.

Hargreaves RM, Slack MP, Howard AJ, Anderson E, Ramsay ME. 1996. Changing patterns of invasive Haemophilus influenzae disease in England and Wales after introduction of the Hib vaccination programme. bmj, **312(7024),** 160-161

Hasbun R. 2019. Update and advances in community acquired bacterial meningitis. Current Opinion in Infectious Diseases **32(3),** 233-238.

Jiménez-Mejías M, Pichardo-Guerrero C, Márquez-Rivas F, Martín-Lozano D, Prados T, Pachón J. 2002. Cerebrospinal Fluid Penetration and Pharmacokinetic/Pharmacodynamic Parameters of Intravenously Administered Colistin in a Case of Multidrug-Resistant Acinetobacter baumannii Meningitis. European Journal of Clinical Microbiology and Infectious Diseases **21(3),** 212-214. https://doi.org/10.1007/s10096-001-0680-2

Kaaijk P, Van der Ende A, Berbers G, Van den Dobbelsteen GP, Rots NY. 2012. Is a single dose of meningococcal serogroup C conjugate vaccine sufficient for protection? Experience from the Netherlands. BMC Infectious Diseases **12(1),** 1-6.

Käyhty H, Lockhart S, Schuerman L. 2008. Immunogenicity and reactogenicity of pneumococcal conjugate vaccines in infants and children. Pneumococcal Vaccines: The Impact of Conjugate Vaccines 227-243.

Kelly DF, Moxon ER, Pollard AJ. 2004. Haemophilus influenzae type b conjugate vaccines. Immunology **113(2),** 163-174.

Khatami A, Pollard AJ. 2010. The epidemiology of meningococcal disease and the impact of vaccines. Expert review of vaccines **9(3),** 285-298.

Kim BN, Peleg A Y, Lodise TP, Lipman J, Li J, Nation R, Paterson DL. 2009. Management of meningitis due to antibiotic-resistant Acinetobacter species. The Lancet infectious diseases **9(4),** 245-255.

Kim SH, Chung DR, Song JH, Baek JY, Thamlikitkul V, Wang H, Tan SH. 2020. Changes in serotype distribution and antimicrobial resistance of Streptococcus pneumoniae isolates from adult patients in Asia: emergence of drug-resistant non-vaccine serotypes. Vaccine **38(38),** 6065-6073.

Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. 2003. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. New England Journal of Medicine **349(14),** 1341-1348.

Klugman KP, Walsh AL, Phiri A, Molyneux, E. M. 2008. Mortality in penicillin-resistant pneumococcal meningitis. The Pediatric infectious disease journal **27(7),** 671-672.

Kobayashi M, Bennett NM, Gierke R, Almendares O, Moore MR, Whitney CG, Pilishvili T. 2015. Intervals between PCV13 and PPSV23 vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report **64(34),** 944-947.

Ladhani SN, Ramsay M, Borrow R, Riordan A, Watson JM, Pollard AJ. 2016. Enter B and W: two new meningococcal vaccine programmes launched. Archives of disease in childhood **101(1),** 91-95.

Le J, Bookstaver PB, Rudisill CN, Hashem M. G, Iqbal R, James CL, Sakoulas G. 2010. Treatment of meningitis caused by vancomycin-resistant Enterococcus faecium: high-dose and combination daptomycin therapy. Annals of Pharmacotherapy **44(12),** 2001-2006.

Lee DH, Palermo B, Chowdhury M. 2008. Successful treatment of methicillin-resistant Staphylococcus aureus meningitis with daptomycin. Clinical infectious diseases **47(4),** 588-590.

LinYT, Su CF, Chuang C, Lin JC, Lu, PL, Huang CT, Fung CP. 2018. Appropriate Treatment for Bloodstream Infections Due to Carbapenem-Resistant Klebsiella pneumoniae and Escherichia coli: A Nationwide Multicenter Study in Taiwan. Open Forum Infectious Diseases **6(2).**
https://doi.org/10.1093/ofid/ofy336

Lodise Jr, TP, Nau R, Kinzig M, Jones R. N, Drusano G, Sörgel F. 2007. Comparison of the probability of target attainment between ceftriaxone and cefepime in the cerebrospinal fluid and serum against Streptococcus pneumoniae. Diagnostic Microbiology and Infectious Disease **58(4),** 445-452.

Lutsar I, Friedland IR, Wubbel L, McCoig CC, Jafri HS, Ng W, McCracken Jr GH. 1998. Pharmacodynamics of gatifloxacin in cerebrospinal fluid in experimental cephalosporin-resistant pneumococcal meningitis. Antimicrobial agents and chemotherapy **42(10),** 2650-2655.

Mace SE. 2008. Acute bacterial meningitis. Emergency medicine clinics of North America **26(2),** 281-317.

MacNeil JR, Rubin L, Folaranmi T, Ortega-Sanchez IR, Patel M, Martin SW. 2015. Use of serogroup B meningococcal vaccines in adolescents and young adults: recommendations of the Advisory Committee on Immunization Practices, 2015. Morbidity and Mortality Weekly Report **64(41),** 1171-1176.

McGill F, Heyderman R, Michael B, Defres S, Beeching N, Borrow R, Kaczmarski E. 2016. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. Journal of Infection **72(4),** 405-438.

McIntyre PB, O'Brien KL, Greenwood B, Van De Beek D. 2012. Effect of vaccines on bacterial meningitis worldwide. The lancet **380(9854),** 1703-1711.

Mengistu M, Asrat D, Woldeamanuel Y, Mengistu G. 2011. Bacterial and fungal meningitis and antimicrobial susceptibility pattern in Tikur Anbessa University Hospital, Addis Ababa, Ethiopia. Ethiopian medical journal **49(4),** 349-359.

Meningococcal A. 2015. WHO position paper on Meningococcal A conjugate vaccine: updated guidance, February 2015.

Miller E, Andrews NJ, Waight PA, Slack MP, George RC. 2011. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. The Lancet infectious diseases **11(10),** 760-768.

Miranda J, Tunkel AR. 2009. Strategies and new developments in the management of bacterial meningitis. Infectious Disease Clinics **23(4),** 925-943.

Moberley S, Holden J, Tatham DP, Andrews, RM. 2013. Vaccines for preventing pneumococcal infection in adults. Cochrane Database of Systematic Reviews **(1).**

Moissenet D, Salauze B, Clermont O, Bingen E, Arlet G, Denamur E, Vu-Thien H. 2010. Meningitis Caused by Escherichia coli Producing TEM-52 Extended-Spectrum and#x3b2;-Lactamase within an Extensive Outbreak in a Neonatal Ward: Epidemiological Investigation and Characterization of the Strain. Journal of clinical microbiology **48(7),** 2459-2463. https://doi.org/10.1128/JCM.00529-10

Nadel S. 2016. Treatment of Meningococcal Disease. J Adolesc Health, **59**(2 Suppl), S21-28. https://doi.org/10.1016/j.jadohealth.2016.04.013

Nalda-Molina R, Dokoumetzidis A, Charkoftaki G, Dimaraki E, Margetis K, Archontaki H, Vryonis E. 2012. Pharmacokinetics of doripenem in CSF of patients with non-inflamed meninges. Journal of Antimicrobial Chemotherapy **67(7),** 1722-1729.

Nathan N, Borel T, Djibo A, Evans D, Djibo S, Corty J, Guerin P. 2005. Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: a randomised non-inferiority study. The Lancet **366(9482),** 308-313.

Nau R, Sorgel F, Eiffert H. 2010. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clinical microbiology reviews **23(4),** 858-883.

Nau R, Sorgel F, Eiffert H. 2010. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clinical microbiology reviews **23(4),** 858-883.

Ntziora F, Falagas ME. 2007. Linezolid for the treatment of patients with central nervous system infection. Annals of Pharmacotherapy **41(2),** 296-308.

O'Brien KL, Moulton LH, Reid R, Weatherholtz R, Oski J, Brown L, Hackell J. (2003). Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. The lancet **362(9381),** 355-361.

Oligbu G, Collins S, Djennad A, Sheppard CL, Fry NK, Andrews NJ, Ladhani SN. 2019. Effect of pneumococcal conjugate vaccines on pneumococcal meningitis, England and Wales, July 1, 2000–June 30, 2016. Emerging infectious diseases **25(9),** 1708.

Østergaard C, Klitmøller Sørensen T, Dahl Knudsen J, Frimodt-Møller N. 1998. Evaluation of moxifloxacin, a new 8-methoxyquinolone, for treatment of meningitis caused by a penicillinresistant pneumococcus in rabbits. Antimicrobial agents and chemotherapy **42(7),** 1706-1712.

Park-Wyllie LY, Juurlink DN, Kopp A, Shah B. R, Stukel TA, Stumpo C, Mamdani MM. 2006. Outpatient gatifloxacin therapy and dysglycemia in older adults. New England Journal of Medicine, **354(13),** 1352-1361.

Patel M, Lee CK. 2005. Polysaccharide vaccines for preventing serogroup A meningococcal meningitis. Cochrane Database of Systematic Reviews (1).

Peltola H. 2000. Worldwide Haemophilus influenzae type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. Clinical microbiology reviews **13(2),** 302-317.

Peltola H, Anttila M, Renkonen OV, Group FS. 1989. Randomised comparison of chloramphenicol, ampicillin, cefotaxime, and ceftriaxone for childhood bacterial meningitis. The Lancet **333(8650),** 1281-1287.

Phang SY, Whitehouse K, Lee L, Khalil H, McArdle P, Whitfield PC. 2016. Management of CSF leak in base of skull fractures in adults. British journal of neurosurgery **30(6),** 596-604.

Plotkin S, Lennon D, Jackson C, Wong S, Horsfall M, Stewart J, Reid S. 2009. Fast tracking the vaccine licensure process to control an epidemic of serogroup B meningococcal disease in New Zealand. Clinical Infectious Diseases **49(4),** 597-605.

Plotkin S, Orenstein W, Offit P. 2008. Vaccines, 5th edn Philadelphia. PA: Saunders.[Google Scholar].

Podschun R, Ullmann U. 1998. Klebsiella spp. as Nosocomial Pathogens: Epidemiology, Taxonomy, Typing Methods, and Pathogenicity Factors. Clinical microbiology reviews **11(4),** 589-603.
https://doi.org/10.1128/CMR.11.4.589

Rafailidis PI, Falagas ME. 2014. Options for treating carbapenem-resistant Enterobacteriaceae. Current Opinion in Infectious Diseases **27(6),** 479-483.
https://doi.org/10.1097/qco.0000000000000109

Rashid H, Ridda I, King C, Begun M, Tekin H, Wood JG, Booy R. 2015. Evidence compendium and advice on social distancing and other related measures for response to an influenza pandemic. Paediatric respiratory reviews **16(2),** 119-126.

Ray L, Levasseur K, Nicolau DP, Scheetz MH. 2010. Cerebral spinal fluid penetration of tigecycline in a patient with Acinetobacter baumannii cerebritis. Annals of Pharmacotherapy **44(3),** 582-586.

Rostamian M, Lorestani RC, Jafari S, Mansouri R, Rezaeian S, Ghadiri K, Akya A. (2022). A systematic review and meta-analysis on the antibiotic resistance of Neisseria meningitidis in the last 20 years in the world. Indian Journal of Medical Microbiology.

Sáez-Llorens X, McCoig C, Feris JM, VargasS. L, Klugman KP, Hussey GD, Bradley J. 2002. Quinolone treatment for pediatric bacterial meningitis: a comparative study of trovafloxacin and ceftriaxone with or without vancomycin. The Pediatric infectious disease journal **21(1),** 14-22.

Sandulescu O. 2016. Global distribution of antimicrobial resistance in E. coli. Journal of Contemporary Clinical Practice **2,** 69+.

Sankar MJ, Sinha B, Chowdhury R, Bhandari, N, Taneja S, Martines J, Bahl R. 2015. Optimal breastfeeding practices and infant and child mortality: a systematic review and meta-analysis. Acta Paediatrica **104,** 3-13.

Santosham M, Wolff M, Reid R, Hohenboken M, Bateman M, Goepp J, Newcomer W. 1991. The Efficacy in Navajo infants of a conjugate vaccine consisting of Haemophilus influenzae type b polysaccharide and Neisseria meningitidis outer-membrane protein complex. New England Journal of Medicine **324(25),** 1767-1772.

Scarborough M, Thwaites GE. 2008. The diagnosis and management of acute bacterial meningitis in resource-poor settings. The Lancet Neurology **7(7),** 637-648.

Schaad UB, Suter S, Gianella-Borradori A, Pfenninger J, Auckenthaler R, Bernath O, Wedgwood J. 1990. A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. New England Journal of Medicine **322(3),** 141-147.

Sherry N, Howden B. 2018. Emerging Gram negative resistance to last-line antimicrobial agents fosfomycin, colistin and ceftazidime-avibactam – epidemiology, laboratory detection and treatment implications. Expert review of anti-infective therapy, **16(4),** 289-306.
https://doi.org/10.1080/14787210.2018.1453807

Smith SM, Sonego S, Wallen GR, Waterer G, Cheng AC, Thompson P. 2015. Use of non-pharmaceutical interventions to reduce the transmission of influenza in adults: A systematic review. Respirology **20(6),** 896-903.

Stapleton PJ, Murphy M, McCallion N, Brennan M, Cunney R, Drew RJ. 2016. Outbreaks of extended spectrum beta-lactamase-producing Enterobacteriaceae in neonatal intensive care units: a systematic review. Archives of Disease in

Childhood - Fetal and Neonatal Edition **101(1),** 72-78.
https://doi.org/10.1136/archdischild-2015-308707

Stephens DS, Greenwood B, Brandtzaeg P. (2007). Epidemic meningitis, meningococcaemia, and Neisseria meningitidis. The Lancet **369(9580),** 2196-2210.

Stephens DS, Greenwood B, Brandtzaeg P. 2007. Epidemic meningitis, meningococcaemia, and Neisseria meningitidis. The lancet **369(9580),** 2196-2210.

Sugden R, Kelly R, Davies S. 2016. Combatting antimicrobial resistance globally. Nature Microbiology **1(10),** 16187.
https://doi.org/10.1038/nmicrobiol.2016.187

Swann O, Everett DB, Furyk JS, Harrison E M, Msukwa MT, Heyderman RS, Molyneux EM. 2014. Bacterial meningitis in Malawian infants <2 months of age: etiology and susceptibility to World Health Organization first-line antibiotics. The Pediatric infectious disease journal **33(6),** 560-565.
https://doi.org/10.1097/INF.0000000000000210

Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, Bennett NM. (2011). Bacterial meningitis in the United States, 1998–2007. New England Journal of Medicine, **364(21),** 2016-2025.

Tristram S, Jacobs MR, Appelbaum PC. (2007). Antimicrobial Resistance in Haemophilus influenzae. Clinical microbiology reviews **20(2),** 368-389.
https://doi.org/10.1128/CMR.00040-06

Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, Whitley RJ. 2004. Practice guidelines for the management of bacterial meningitis. Clinical infectious diseases **39(9),** 1267-1284.

Van de Beek D, Brouwer MC, Koedel U, Wall, EC. 2021. Community-acquired bacterial meningitis. The Lancet **398(10306),** 1171-1183.

Van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. 2012. Advances in treatment of bacterial meningitis. The Lancet **380(9854),** 1693-1702.
https://doi.org/10.1016/S0140-6736(12)61186-6

Van de Beek D, Brouwer M, Hasbun R, Koedel U, Whitney CG, Wijdicks E. 2016. Community-acquired bacterial meningitis. Nature reviews Disease primers **2(1),** 16074.
https://doi.org/10.1038/nrdp.2016.74

Van de Beek D, De Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. 2004. Clinical features and prognostic factors in adults with bacterial meningitis. New England Journal of Medicine **351(18),** 1849-1859.

Van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. 2006. Community-acquired bacterial meningitis in adults. New England Journal of Medicine **354(1),** 44-53.

Vergison A. 2008. Microbiology of otitis media: a moving target. Vaccine **26,** G5-G10.

Wang B, Dai WJ, Cheng XT, Liuyang WY, Yuan YS, Dai CF, Chen B. 2019. Cerebrospinal fluid otorrhea secondary to congenital inner ear dysplasia: diagnosis and management of 18 cases. Journal of Zhejiang University-SCIENCE B, **20(2),** 156-163.

Wang H, Kuo M, Huang S. 2005. Diagnostic approach to recurrent bacterial meningitis in children. Chang Gung Medical Journal **28(7),** 441.

Ward J, Brenneman G, Letson G, Heyward W, Group AHIVS. 1990. Limited efficacy of a Haemophilus influenzae type b conjugate vaccine in Alaska native infants. New England Journal of Medicine **323(20),** 1393-1401.

Wenger J, Pierce R, Deaver K, Broome C, Plikaytis B, Facklam R, Group, HIVES. 1991. Efficacy of Haemophilus influenzae type b polysaccharide-diphtheria toxoid conjugate vaccine in US children aged 18-59 months. The lancet, **338(8764),** 395-398.

World Health Organization. 2015. Global action plan on antimicrobial resistance. WHO, Geneva, Switzerland.

Wu HM, Harcourt BH, Hatcher CP, Wei SC, Novak RT, Wang X, Rainbow J. 2009. Emergence of ciprofloxacin-resistant Neisseria meningitidis in North America. New England Journal of Medicine **360(9),** 886-892.

Yezli S, Gautret P, Assiri AM, Gessner BD, Alotaibi B. 2018. Prevention of meningococcal disease at mass gatherings: lessons from the Hajj and Umrah. Vaccine **36(31),** 4603-4609.

Yogev R, Damle B, Levy G, Nachman S. 2010. Pharmacokinetics and distribution of linezolid in cerebrospinal fluid in children and adolescents. The Pediatric infectious disease journal **29(9),** 827-830.

Yusuf HR, Rochat RW, Baughman WS., Gargiullo PM, Perkins BA, Bran tley MD, Stephens DS. 1999. Maternal cigarette smoking and invasive meningococcal disease: a cohort study among young children in metropolitan Atlanta, 1989-1996. American journal of public health **89(5),** 712-717.

Zouheir Y, Atany T, Boudebouch N. 2019. Emergence and spread of resistant N. meningitidis implicated in invasive meningococcal diseases during the past decade (2008–2017). J Antibiot (Tokyo), **72(3),** 185-188.