Acute bacterial meningitis (ABM) is an important cause of morbidity and mortality in children but there are no published data on the treatment outcomes of ABM in Afghanistan.

Methods

We conducted a prospective observational cohort study over one year, February 2020 to January 2021 in a tertiary care hospital in Kandahar, Afghanistan. AMB was diagnosed clinically and on lumbar puncture findings. Binary logistic regression assessed factors for death.

Results

A total of 393 ABM children of mean age 4.8 years were recruited. Most were males [231 (58.8%)], living in rural areas [267 (67.9%)] and in households of >10 inhabitants [294 (74.8%)]. Only 96 (24.4%) had received against both Haemophilus influenzae type b (Hib) or pneumococcal (PCV) vaccines. Children were treated with combination of ceftriaxone and ampicillin and 169/321 (52.6%) received dexamethasone. Of the 321 children with a known outcome, 69 (21.5%) died. Death was significantly associated with: not receiving dexamethasone [adjusted odds ratio (AOR) 4.9 (95% CI 2.6–9.5, \( p < 0.001 \)], coma on admission [AOR 4.6 (1.2–9.5, \( p < 0.001 \)], no PCV [AOR 2.8 (1.2–6.6, \( p = 0.019 \)] or Hib vaccine [AOR 2.8 (1.2–6.6, \( p = 0.019 \)], and being male [AOR 2.7 (1.4–5.5, \( p = 0.005 \)].

Conclusions

ABM causes significant morbidity and mortality in Afghan children that may be improved by greater use of PCV and Hib vaccines. Adjunct dexamethasone should be evaluated formally in our setting.
Introduction

Acute bacterial meningitis (ABM) is a severe disease in children and is associated with mortality in 14.4% (5.3–26.2%) [1] and neurological sequelae in 16–50%; the main sequelae are hearing loss (11%), paresis (4%), seizures (4%), and mental retardation (4%) [2–5]. The pathophysiology of ABM involves inflammation of the blood brain barrier (BBB), loss of vascular autoregulation, increased intracranial pressure and cerebral oedema [6]; hydrocephalus may also occur due to impaired reabsorption of cerebrospinal fluid (CSF) by arachnoid villi and obstructed flow in the third or fourth ventricles [7–9]. All of these factors contribute to neuronal damage and neurological deficits [6].

Globally, in 1990, of the common causes of bacterial meningitis (Neisseria meningitidis, Haemophilus influenzae, Streptococcus pneumoniae) N. meningitidis was the leading cause of meningitis related mortality [10]. However, by 2016, previously less common pathogens like Listeria monocytogenes, Staphylococcus, Gram-negative bacteria, fungal and viral infections were the leading causes of deaths and incident cases, estimated at 318,400 (95% uncertainty interval 265,218–408,705) and 2.82 million (95% uncertainty interval 2.46–3.31), respectively [10]. This is most probably due to the introduction of PCV and Hib vaccines. The top ten countries for meningitis mortality were India, Nigeria, Ethiopia, Pakistan, Democratic Republic of the Congo, Uganda, Tanzania, Niger, Afghanistan, and China with the four non-African countries, India, Pakistan, Afghanistan, and China reporting 63,001; 16,335; 7,302 and 907 deaths, respectively [10].

Afghanistan has been suffering civil conflict for the last four decades and, together with natural disasters, has weakened its economic development [11], contributing to poor health infrastructure and poor health indices. Afghanistan’s public health challenges include poor control of infectious diseases, and limited safe water supply and waste disposal [12]. There is widespread childhood malnutrition and approximately 50% of children have anaemia and vitamin A deficiency [13]. Immunization coverage against routine childhood illnesses is very low with substantial differences between cities and rural areas [14]. The Afghanistan Expanded Program on Immunization (EPI) introduced Haemophilus influenzae type b (Hib) in 2009 and the 13-valent pneumococcal conjugate vaccine (PCV13) in 2013 [11]. However, a weak surveillance system precludes an estimation of illnesses or deaths prevented from these two bacterial infections. The schedules for Hib and PCV are 6, 10, and 14 weeks and two doses of measles vaccine are given at 9 and 18 months.

There are no currently no published data on treatment outcomes of paediatric ABM in Afghanistan. We, therefore, set out to assess prospectively the outcome of ABM in children and determine factors associated with death.

Materials and methods

Study site

This study was conducted in the paediatric ward of Mirwais Regional Hospital (MRH), a tertiary care regional hospital located in Kandahar city, southwest Afghanistan. Diagnostic capacity is limited as there are no facilities for Gram staining, bacterial and cerebrospinal fluid (CSF) culture. Basic radiology is available.

Ethical considerations

Written informed consent was obtained from all the participants or guardians prior to the study. All guardians were assured of the voluntary nature of the study and that all patient data were confidential. The study was approved by the Kandahar University Ethics Committee.
For data collection, only patients’ initials and medical registration numbers were used. Prior to entering into the computer for analysis, the collected data were coded and de-identified.

**Study design and participants**

This hospital-based, prospective observational cohort study was conducted from February 2020–January 2021. Children were enrolled in the study if they from Kandahar province and were aged < 18 years with clinically suspected meningitis and had at least one of the following findings on examination of cerebrospinal fluid (CSF): (i) turbid appearance, (ii) leucocytosis $> 100$ cells/mm$^3$, and (iii) a leucocytosis of 10–100 cells/mm$^3$ with either an elevated protein level ($> 100$ mg/dl) or decreased glucose concentration ($< 40$ mg/dl) [15]).

Children were excluded from the study if they met any one of the exclusion criteria: (i) diagnosed with tuberculous meningitis (TBM), based on the definition by Marais et al [clinically suspected TBM plus a total diagnostic score of $\geq 10$ points (cerebral imaging unavailable) or $\geq 12$ points (cerebral imaging available) with at least 2 points from CSF or cerebral imaging criteria and exclusion of alternative diagnoses [16], (ii) clinically diagnosed viral meningitis: CSF analysis showing a lymphocytic predominance ($> 100$ cells/mm$^3$), protein $< 45$ mg/dl, and glucose $> 40$ mg/dl), (iii) had received any parenteral broad-spectrum antibiotics before admission.

**Management of children with suspected ABM**

All admitted children underwent a detailed history, physical examination and a lumbar puncture by our team of experienced paediatricians. Children with clinically diagnosed ABM were treated with combination of ceftriaxone (100 mg/kg/day) and ampicillin (150–200 mg/kg/day) for 10–14 days. Dexamethasone (0.6 mg/kg/day x 4 days) was administered to children aged $\geq 6$ weeks at the physician’s discretion. Children were discharged when afebrile and after completing their antibiotics. Follow up in the study was during the hospitalization days of the patients.

**Data collection & analysis**

Data were collected on standardised case report forms (CRFs) and included socio-demographic characteristics, symptoms, physical signs, routine laboratory findings and CSF results. Vaccination status of the younger children was assessed by looking at the vaccination cards (or recall if the card was left at home) while, for the older children, it was generally by recall of the parents or caretakers. If the caretakers were unsure, other family members were contacted by phone.

Data were double entered into Microsoft Excel, and checked for accuracy before analysis using SPSS version 22 (Chicago, IL, USA). Frequency and percentage were used to summarise categorical variables. Chi-square test [using crude odd ratio (COR)] was performed to assess the association between two categorical variables. All variables that were statistically significant ($p$-value $< 0.05$) in univariate analyses were assessed for independence in a binary logistic regression, using adjusted odds ratio (AOR), to determine the factors associated with death. Children with missing data for death were excluded from this analysis. A two-sided $p$-value of $< 0.05$ was considered statistically significant.

**Results**

Of the total of 718 patients were admitted with meningitis, 158 patients had TB meningitis, 121 encephalitis, 27 had received prehospital intravenous ceftriaxone, and 19 guardians
declined participation in the study. This left 393 patients who were enrolled in the study. Their mean age was 4.8 years [with 192 (48.8%) under age 5] and males accounted for just under 60% (Table 1). Some two thirds were rural dwellers, more than half [222 (56.5%)] came from families whose monthly income was <2,500 Afghanis (<30 USD), while 294 (74.8%) were living in households of >10 inhabitants. Only 96 (24.4%) children had been vaccinated for both Hib and PCV and only 94 (23.9%) had received the measles vaccine.

Main reported symptoms in the children included headache and seizures; while main signs were fever (body temperature of ≥38°C), irritability, neck stiffness, Kernig sign, and coma. Evidence of concurrent infections were present in 250 (63.6%) of these patients, mainly tonsillitis/pharyngitis, pneumonia, and otitis media (Table 2).

The blood and CSF findings are shown in Table 3. The median CSF total white cell count was 110 cells/mm³ with a range of 5 to 12,400 cells/mm³; all children had a raised total protein but only 75.6% of children had a neutrophilic predominance.

All the patients were treated with combination of ceftriaxone and ampicillin, 169 (52.6%) received dexamethasone and the mean hospital stay was ~2 weeks. Among these children, 72 were discharged by their parents against medical advice and they could not be followed up. Most of the 72 patients were in critical situation, so possibly their parents thought they were dying. Consequently, a total of 321 children had a known outcome. Of these, 69 (21.5%) died and 96 (29.9%) had neurological sequelae, mostly focal muscle weakness and spasticity (Table 4).

Bivariate analysis identified coma on admission, no adjunctive dexamethasone therapy, no PCV or Hib vaccination, male gender and a purpuric/petechial rash as factors for death (Table 5); all except petechial rash were identified as independent variables for death in the logistic regression model (Table 6).

Discussion

In this hospital-based, prospective observational cohort study, we have shown that a fifth of children with clinically diagnosed ABM died and a little under a third had neurological sequelae. The key risk factors we identified were coma on admission, not receiving dexamethasone, being male and lack of vaccination (PCV, Hib) against two common causes of meningitis whilst a purpuric/petechial rash was suggestive. The majority of our children were young (half < 5y), from poor families living in overcrowded conditions in rural areas.

The in-hospital case fatality was 21.5% in our study. The fact that 72 of the children were critical ill when brought home by their parents means that the mortality rate may have been much higher than the stated 21.5%. If all of these died, the mortality would have actually been 35.9%. Our death rate is higher compared to studies conducted in children from wealthier countries like Kosovo, 2.6% (age one month–16 years) [17], Iceland, 4.4% (age ≤18.5y) [18], South Korea, 9.5% (age ≤18y) [19], and Iran, 10% (5m–10y) [20]. One comparable study from India reported a 16% death rate in children aged one month–five years [21]. Higher mortality rates have been reported from Malawi, 28.7% (<15 years) [22], Nepal, 33.3% (<15y) [23], Angola, 33% (2m–12y) [24], and Pakistan, 34% (<5 y) [25]. The differences in mortality rates observed in different studies are due to several reasons, including type of study, age spectrum of the children, definition of ABM, culture, and socio-economic, nutritional status and HIV status. Broader factors that are likely to be related to our high mortality include the fragile health system, a health infrastructure lacking basic facilities like microbiological diagnosis and intensive care for critically ill patients, the weak referral link between primary care and tertiary centres, and the lack of health education.
| Variable                                      | Number (Percentage) (N = 393) |
|----------------------------------------------|-------------------------------|
| Age (years), mean (SD)                       | 4.8 (3.5)                     |
| Age (years)                                  |                               |
| <1                                           | 76 (19.3)                     |
| 1–5                                          | 116 (29.5)                    |
| 5–12                                         | 122 (31.1)                    |
| >12                                          | 79 (20.1)                     |
| Gender                                       |                               |
| Male                                         | 231 (58.8)                    |
| Female                                       | 162 (41.2)                    |
| Number of siblings, mean (SD)                | 6 (3)                         |
| Place of living                              |                               |
| Urban                                        | 126 (32.1)                    |
| Rural                                        | 267 (67.9)                    |
| Father’s literacy level                      |                               |
| Illiterate                                   | 264 (67.2)                    |
| Literate                                     | 129 (32.8)                    |
| Primary                                      | 102                           |
| Secondary                                    | 12                            |
| Bachelor                                     | 15                            |
| Father’s occupation                          |                               |
| Self-employed                                | 177 (45.0)                    |
| Non-government employee                      | 168 (42.8)                    |
| Government employee                          | 24 (6.1)                      |
| Unemployed                                    | 24 (6.1)                      |
| Family monthly income (in Afghanis)          |                               |
| <2,500 (<30 USD)                             | 222 (56.5)                    |
| 2,500–20,000 (30–250 USD)                    | 159 (40.5)                    |
| >20,000 (>250 USD)                           | 12 (3.0)                      |
| Number of people living in the same house    |                               |
| <5                                           | 3 (0.8)                       |
| 5–10                                         | 96 (24.4)                     |
| >10                                          | 294 (74.8)                    |
| Exclusive breastfeeding a                     | 378 (96.2)                    |
| PCV and Hib vaccination                      | 98 (24.9)                     |

* Feeding infants only breast milk during the first 6 months of life.

Hib, *Haemophilus influenzae* type b; PCV, pneumococcal vaccine; kg, SD, standard deviation; USD, United States Dollar.

https://doi.org/10.1371/journal.pone.0265487.t001
Table 2. Clinical features on admission in the 393 ABM patients.

| Symptom/Sign                  | Number (Percentage) |
|-------------------------------|---------------------|
|                               | (N = 393)           |
| Fever                         | 363 (92.4)          |
| Vomiting                      | 321 (81.7)          |
| Headache (N = 301)            | 240 (79.7)          |
| Anorexia                      | 312 (79.4)          |
| Irritability                  | 297 (75.6)          |
| Neck stiffness                | 231 (58.8)          |
| Coma a                        | 56 (14.2)           |
| Seizures b                    | 372 (94.7)          |
| Kernig's sign                 | 186 (47.3)          |
| Brudzinski's sign             | 15 (3.8)            |
| Bulging fontanelle            | 18 (4.6)            |
| Purpuric/petechial rash       | 21 (5.3)            |
| Concurrent infections (N = 250) c | 250 (63.6)        |
| Tonsillitis/Pharyngitis       | 108 (43.2)          |
| Pneumonia                     | 72 (28.8)           |
| Otitis media                  | 36 (14.4)           |
| Measles                       | 12 (4.8)            |
| Others                        | 22 (8.8)            |

a Coma is defined as Glasgow Coma Scale (GCS) of ≤8.
b Seizures observed on admission as well as history of seizures during 48 hours before hospitalisation.
c Among these 250 patients, 247 (98.8%) had single infections and 3 (1.2%) had double infections.

https://doi.org/10.1371/journal.pone.0265487.t002

Table 3. Full blood count and CSF findings in 393 ABM children.

| Variable                        | Mean (SD)     | Range       |
|---------------------------------|---------------|-------------|
| Full blood count                |               |             |
| Haemoglobin (g/dl)              | 10.0 (2.1)    | 3.7–14.2    |
| Total leukocyte count (cells/mm³) | 13,399 (7,862) | 1,700–35,000 |
| Neutrophils (%)                 | 64.4 (19.2)   | 11.8–96.1   |
| Neutrophilia, N (%)             | 296 (75.4)    |             |
| Lymphocytes (%)                 | 28.7 (16.0)   | 2.3–66.0    |
| Platelets (cells/mm³)           | 321,350 (170,242) | 16,000–738,000 |
| CSF findings                    |               |             |
| Appearance                      |               |             |
| Clear                           | 194           | 49.4        |
| Turbid                          | 184           | 46.8        |
| Bloody                          | 15            | 3.8         |
| Total white blood cells (cells/mm³), median (IQR) | 110 (95–128) | 5–12,400 |
| Neutrophils (%), median (IQR)   | 70.8 (51.7–88.9) |             |
| Neutrophilia (>50%), N (%)      | 297 (75.6)    |             |
| Mononuclear cells (%), median (IQR) | 29.2 (11.1–48.3) |         |
| Protein (mg/dl), mean (SD)      | 182 (49)      | 101–305     |
| Glucose (mg/dl), mean (SD)      | 57.6 (23.8)   | 8.0–111.0   |

CSF, cerebrospinal fluid; IQR, interquartile range; SD, standard deviation. Categorical data are N (%).

https://doi.org/10.1371/journal.pone.0265487.t003
Many of our children had not received Hib and PCV vaccines, a public health failure. In Brazil, the introduction of pneumococcal and meningococcal vaccines in the childhood immunization programme was associated with a 50% nationwide decline in meningitis deaths in children aged 2-4y (1.46 to 0.72/100,000) and those < 2y (6.99 to 3.45/100,000) [26] and another Brazilian study showed that, in the under 2s, the pneumococcal vaccine reduced the incidence rates of pneumococcal meningitis by ~60% (6.01 to 2.49 cases/100,000) and deaths by 75% (1.85 to 0.47/100,000) [27]. Over the past three decades in the Netherlands, H. influenzae meningitis has declined from 1.57 to 0.14 per 100,000 population following the introduction of the Hib vaccine [28]. Clearly, PCV and Hib vaccines represent an excellent cost-effective strategy and, in high burden areas, will have incremental effects in reducing the burden of ABM [29].

Although a number of clinical trials have been conducted, adjuvant dexamethasone in the treatment of paediatric ABM still remains controversial. Mortality in our study was significantly lower in children who received adjunctive dexamethasone treatment but our study was not a randomised trial with matched groups. Most studies from high-income countries have demonstrated higher survival rates and improved overall outcomes following dexamethasone in the treatment of bacterial meningitis [30], such as studies from USA (all were children) [31, 32], France (all were children) [33], and Europe (all were adults) [34]. By contrast, several studies from low- and middle-income countries have not shown a clear benefit of dexamethasone [30], such as studies from Malawi (all were children with 24% HIV positive) [35], India (all were children with HIV status unknown) [36], Egypt (all were children HIV status unknown) [37], and Mozambique (HIV status unknown) [38]. A study from India reported that dexamethasone significantly reduced fatality in neonates [39]. Reasons for not using dexamethasone include anxiety regarding underlying HIV and the association of a higher mortality in patients with suspected ABM [40].

Surprisingly, in our study, a high percentage (25%) of mononuclear predominance was observed in CSF analysis. One of the possibilities could be that some of these patients were actually tuberculous meningitis.
### Table 5. Chi-square test of the factors associated with mortality in ABM patients.

| Variable | Total | Survived | Died | COR | 95% CI | P-value |
|----------|-------|----------|------|-----|--------|---------|
| **N = 321** | **N = 252** | **N = 69** | | | | |
| Age (years) | 0.4–1.1 | 0.076 | | | | |
| <5 | 156 (48.6) | 129 (82.7) | 27 (17.3) | 0.6 | | |
| ≥5 | 165 (51.4) | 123 (74.5) | 42 (25.5) | 1 | | |
| Gender | 1.3–4.2 | 0.004 | | | | |
| Male | 189 (58.9) | 138 (73.0) | 51 (27.0) | 2.3 | | |
| Female | 132 (41.1) | 114 (86.4) | 18 (13.6) | 1 | | |
| PCV and Hib vaccination | 1.4–6.7 | 0.004 | | | | |
| Yes | 80 (24.9) | 72 (90.0) | 8 (10.0) | 1 | | |
| No | 241 (75.1) | 180 (74.7) | 61 (25.3) | 3.0 | | |
| Place of living | 0.7–2.2 | 0.424 | | | | |
| Urban | 99 (30.8) | 75 (75.8) | 24 (24.2) | 1.3 | | |
| Rural | 222 (69.2) | 177 (79.7) | 45 (20.3) | 1 | | |
| Vomiting | 0.4–1.5 | 0.464 | | | | |
| Yes | 261 (81.3) | 207 (79.3) | 54 (20.7) | 0.8 | | |
| No | 60 (18.7) | 45 (75.0) | 15 (25.0) | 1 | | |
| Headache (N = 295) | 0.7–3.7 | 0.290 | | | | |
| Yes | 240 (82.4) | 195 (81.2) | 45 (18.8) | 1.5 | | |
| No | 55 (17.6) | 48 (87.3) | 7 (12.7) | 1 | | |
| Anorexia | 0.3–1.1 | 0.127 | | | | |
| Yes | 258 (80.4) | 207 (80.2) | 51 (19.8) | 0.6 | | |
| No | 63 (19.6) | 45 (71.4) | 18 (28.6) | 1 | | |
| Irritability | 0.2–0.8 | 0.005 | | | | |
| Yes | 72 (22.4) | 48 (66.7) | 24 (33.3) | 1 | | |
| No | 249 (77.6) | 204 (81.9) | 45 (18.1) | 0.4 | | |
| Neck stiffness | 0.5–1.5 | 0.576 | | | | |
| Yes | 177 (55.1) | 141 (79.7) | 36 (20.3) | 0.9 | | |
| No | 144 (44.9) | 111 (77.1) | 33 (22.9) | 1 | | |
| Coma on admission | 1.5–10.6 | 0.002 | | | | |
| Yes | 18 (5.6) | 9 (50.0) | 9 (50.0) | 4.0 | | |
| No | 303 (94.4) | 243 (80.2) | 60 (19.8) | 1 | | |
| Kernig sign | 0.7–1.9 | 0.702 | | | | |
| Yes | 147 (45.8) | 114 (77.6) | 33 (22.4) | 1.1 | | |
| No | 174 (54.2) | 138 (79.3) | 36 (20.7) | 1 | | |
| Purpuric/petechial rash | 0.5–1.5 | 0.638 | | | | |
| Yes | 181 (56.7) | 164 (77.7) | 47 (22.3) | 1 | | |
| No | 110 (34.3) | 88 (80.0) | 22 (20.0) | 0.9 | | |
| Concurrent infections | 2.5–8.5 | <0.001 | | | | |
| Yes | 169 (52.6) | 152 (89.9) | 17 (10.1) | 1 | | |
| No | 152 (47.4) | 100 (65.8) | 52 (34.2) | 4.6 | | |

COR, Crude odds ratio; CSF, Cerebrospinal Fluid; Hib, *Haemophilus influenzae* type b; PCV, Pneumococcal Vaccine.

https://doi.org/10.1371/journal.pone.0265487.t005
Limitations

Although the main strength of our study was its prospective design in a real-life setting of a country ravaged by war and lacking significant resources, it had several limitations. We did not have essential microbiological diagnostics so none of our patients had a CSF Gram stain and bacteriologically proven meningitis. Just under a fifth of our patients discharged themselves before an outcome was known; therefore, our morbidity and mortality rates could be higher than reported. Although this was a single centre study conducted in a resourced limited referral hospital, our findings are probably applicable to most settings in Afghanistan and comparable settings in our region where HIV prevalence is low. Finally, we only assessed complications/sequelae at discharge and so cannot estimate long term morbidity and mortality and the effect on cognitive development and school performance.

Conclusion

Presumed ABM in our setting was associated with high rates of morbidity and mortality. Increasing PCV and Hib vaccine coverage is likely to have a profound and positive effect on meningitis in Afghanistan. We found a beneficial effect of dexamethasone and this should be further investigated in countries in south Asia despite the discouraging data from Africa.

Supporting information

S1 Fig.  
(TIF)

S1 Data.  
(SAV)

Acknowledgments

We present our highest and sincere thanks to the authorities of Faculty of Medicine, Kandahar University and Kandahar Directorate of Public Health. We are also very thankful of the staff members (clinicians, nurses, lab technicians) of the hospital and all of our study participants.

Author Contributions

Conceptualization: Bilal Ahmad Rahimi, Niamatullah Ishaq, Ghulam Mohayuddin Mudaser, Walter R. Taylor.

Data curation: Bilal Ahmad Rahimi.

Formal analysis: Bilal Ahmad Rahimi.
**Investigation:** Bilal Ahmad Rahimi, Niamatullah Ishaq, Ghulam Mohayuddin Mudaser.

**Methodology:** Bilal Ahmad Rahimi, Ghulam Mohayuddin Mudaser, Walter R. Taylor.

**Project administration:** Bilal Ahmad Rahimi, Walter R. Taylor.

**Resources:** Niamatullah Ishaq.

**Software:** Bilal Ahmad Rahimi.

**Supervision:** Bilal Ahmad Rahimi.

**Validation:** Bilal Ahmad Rahimi.

**Visualization:** Bilal Ahmad Rahimi.

**Writing – original draft:** Bilal Ahmad Rahimi.

**Writing – review & editing:** Niamatullah Ishaq, Ghulam Mohayuddin Mudaser, Walter R. Taylor.

**References**

1. Lukšić I, Mulić R, Falcoiner R, Orban M, Sidhu S, Rudan I. Estimating global and regional morbidity from acute bacterial meningitis in children: assessment of the evidence. Croat Med J. 2013; 54: 510. https://doi.org/10.3325/cmj.2013.54.510 PMID: 24382845

2. Nigrovic LE, Kuppermann N, Malley R. Children with bacterial meningitis presenting to the emergency department during the pneumococcal conjugate vaccine era. Acad Emerg Med. 2008; 15: 522–528. https://doi.org/10.1111/j.1553-2712.2008.00117.x PMID: 18616437

3. Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, et al. Bacterial Meningitis in the United States, 1998–2007. N Engl J Med. 2011; 364: 2016–2025. https://doi.org/10.1056/NEJMoa1005384 PMID: 21612470

4. Edmond K, Clark A, Korcazi VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: A systematic review and meta-analysis. The Lancet Infectious Diseases. Lancet Infect Dis; 2010. pp. 317–328. https://doi.org/10.1016/S1473-3099(10)70048-7 PMID: 20417414

5. Chandran A, Herbert H, Misurski D, Santosham M. Long-term sequelae of childhood bacterial meningitis: An underappreciated problem. Pediatr Infect Dis J. 2011; 30: 3–6. https://doi.org/10.1097/INF.0b013e3181ef25f7 PMID: 20683377

6. Lepage P, Dan B. Infantine and childhood bacterial meningitis. Handbook of Clinical Neurology. Elsevier B.V.; 2013. pp. 1115–1125. https://doi.org/10.1016/B978-0-444-52910-7.00031-3 PMID: 23622319

7. Scheld WM, Dacey RG, Winn HR, Welsh JE, Jane JA, Sande MA. Cerebrospinal fluid outflow resistance in rabbits with experimental meningitis: Alterations with penicillin and methylprednisolone. J Clin Invest. 1980; 66: 243–253. https://doi.org/10.1172/JCI109850 PMID: 6995482

8. Mactier H, Galea P, McWilliam R. Acute obstructive hydrocephalus complicating bacterial meningitis in childhood. Br Med J. 1998; 316: 1887–1889. https://doi.org/10.1136/bmj.316.7148.1887 PMID: 9632412

9. Soemirien Kasanmoentaib E, Brouwer MC, Van Der Ende A, Van De Beek D. Hydrocephalus in adults with community-acquired bacterial meningitis. Neurology. 2010; 75: 918–923. https://doi.org/10.1212/WNL.0b013e3181f11e10 PMID: 20820003

10. GBD 2016 Meningitis Collaborators. Global, regional, and national burden of meningitis, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018; 17: 1061–1082. https://doi.org/10.1016/S1474-4422(18)30387-9 PMID: 30597391

11. Wagner AL, Mubarak MY, Johnson LE, Porth JM, Yousif JE, Boulton ML. Trends of vaccine-preventable diseases in Afghanistan from the Disease Early Warning System, 2009–2015. PLoS One. 2017; 12: e0176677–undefined. https://doi.org/10.1371/journal.pone.0176677 PMID: 28570694

12. Mubarak MY, Wagner AL, Asami M, Carlson BF, Boulton ML. Hygienic practices and diarrheal illness among persons living in at-risk settings in Kabul, Afghanistan: A cross-sectional study. BMC Infect Dis. 2016; 16: 1–9. https://doi.org/10.1186/s12879-015-1330-6 PMID: 26729246

13. Varkey S, Higgins-Steele A, Mashal T, Hamid BA, Bhutta ZA. Afghanistan in transition: Call for investment in nutrition. The Lancet Global Health. Elsevier Ltd; 2015. pp. e13–e14. https://doi.org/10.1016/S2214-109X(14)70362-6 PMID: 25539958
14. Hemati S, Takano T, Kizuki M, Mashal T. Health-care provision factors associated with child immunization coverage in a city centre and a rural area in Kabul, Afghanistan. Vaccine. 2009; 27: 2823–2829. https://doi.org/10.1016/j.vaccine.2009.02.097 PMID: 19428893

15. World Health Organization. WHO-recommended standards for surveillance of selected vaccine-preventable diseases. Geneva: 2003. https://www.vhp.org/files/html/meetings_and_publications/VHPB_Meetings/Kyiv2004/backgrounddocuments/1EWHOrecommendidstandardsforsurveillance.pdf

16. Marais S, Thwaites G, Schoeman J, Török M, Misra U, Prasad K, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis. 2010; 10: 803–812. https://doi.org/10.1016/S1473-3099(10)70138-9 PMID: 20822958

17. Namani S, Milenković Z, Koci B. A prospective study of risk factors for neurological complications in childhood bacterial meningitis. J Pediatr (Rio J). 2013; 89: 256–262. https://doi.org/10.1016/j.jped.2012.10.001 PMID: 23664199

18. Snaebjarnardottir K, Erlendsdottir H, Reynisson IK, Kristinsson K, Hallardottir S, Hardardottir H, et al. Bacterial meningitis in children in Iceland, 1975–2010: A nationwide epidemiological study. Scand J Infect Dis. 2013; 45: 819–824. https://doi.org/10.3109/00365548.2013.817680 PMID: 23968225

19. Cho HK, Lee H, Kang JH, Kim KN, Kim DS, Kim YK, et al. The causative organisms of bacterial meningitis in Korean children in 1996–2005. J Korean Med Sci. 2010; 25: 895–899. https://doi.org/10.3346/jkms.2010.25.6.895 PMID: 20514311

20. Mahmoudi S, Zandi H, Pourakbari B, Haghi Ashtiani MT, Mamishi S. Acute bacterial meningitis among children admitted into an Iranian referral children’s hospital. Jpn J Infect Dis. 2013; 66: 503–506. https://doi.org/10.1288/jjaccd.24270138

21. Mohanty N, Biswas TK, Satapathy S, Meher SK, Patro D. Etioclinical profile and outcome of acute bacterial meningitis in post neo natal u-5 children: a study from tertiary care center of coastal Odisha, India. Int J Res Med Sci. 2017; 5: 2519–2523. https://doi.org/10.18203/2320-6012.ijrmeds20172440

22. McCormick DW, Wilson ML, Mankhambo L, Phiri A, Chimalizeni Y, Kawaza K, et al. Risk factors for death and severe sequelae in malawian children with bacterial meningitis, 1997–2010. Pediatr Infect Dis J. 2013; 32: e54–e61. https://doi.org/10.1097/INF.0b013e31826fa5fa PMID: 22914560

23. Shrestha RG, Tandukar S, Ansari S, Subedi A, Shrestha A, Poudel R, et al. Bacterial meningitis in children under 15 years of age in Nepal. BMC Pediatr. 2015; 15: 1–7. https://doi.org/10.1186/s12887-015-0318-7 PMID: 25626628

24. Pelkonen T, Roine I, Monteiro L, Correia M, Ptkæranta A, Bernardino L, et al. Risk factors for death and severe neurological sequelae in childhood bacterial meningitis in Sub-Saharan Africa. Clin Infect Dis. 2009; 48: 1107–1110. https://doi.org/10.1086/597463 PMID: 19275501

25. Khowaja AR, Mohiuddin S, Cohen AL, Khalid A, Mehmoood U, Naqvi F, et al. Mortality and neurodevelopmental outcomes of acute bacterial meningitis in children aged <5 years in Pakistan. J Pediatr. 2013; 163: S86–S91. https://doi.org/10.1016/j.jpeds.2013.03.035 PMID: 23773600

26. Bierenbach AL, Minamisawa R, Alencar AP, Alencar GP, Andrade AL. Combined effect of PCV10 and meningococcal C conjugate vaccination on meningitis mortality among children under five years of age in Brazil. Hum Vaccines Immunother. 2018; 14: 1138–1145. https://doi.org/10.1080/21645515.2017.1391431 PMID: 29086749

27. Hirose TE, Maluf EMCP, Rodrigues CO. Pneumococcal meningitis: Epidemiological profile pre- and post-introduction of the pneumococcal 10-valent conjugate vaccine. J Pediatr (Rio J). 2015; 91: 130–135. https://doi.org/10.1016/j.jped.2014.07.002 PMID: 25451210

28. Koelman DLH, van Kassel MN, Bijlsma MW, Brouwer MC, van der Ende A. Changing Epidemiology of Bacterial Meningitis Since Introduction of Conjugate Vaccines: 3 Decades of National Meningitis Surveillance in The Netherlands. Clin Infect Dis. 2020 [cited 17 Jun 2021]. https://doi.org/10.1093/cid/ciaa1774 PMID: 33247582

29. Gaschignard J, Levy C, Romain O, Cohen R, Bingen E, Aujard Y, et al. Neonatal Bacterial Meningitis: 444 Cases in 7 Years. Pediatr Infect Dis J, 2011; 30: 212–217. Available: https://journals.lww.com/pidj/FullText/2011/03000/Neonatal_Bacterial_Meningitis_444_Cases_in_7.7.aspx PMID: 21416693

30. Borchorst S, Moller K. The role of dexamethasone in the treatment of bacterial meningitis—A systematic review. Acta Anaesthesiologica Scandinavica. Acta Anaesthesiol Scand; 2012. pp. 1210–1221. https://doi.org/10.1111/j.1399-6576.2012.02698.x PMID: 22545566

31. Lebel M, Freij B, Syrigianopoulos G, Chrane D, Hoyt M, Stewart S, et al. Dexamethasone therapy for bacterial meningitis. Results of two double-blind, placebo-controlled trials. N Engl J Med. 1988; 319: 286–287. https://doi.org/10.1056/NEJM198810133191502 PMID: 3047581

32. Lebel MH, Hoyt MJ, Waagner DC, Rollins NK, Finitzo T, Mccracken GH. Magnetic Resonance Imaging and Dexamethasone Therapy for Bacterial Meningitis. Am J Dis Child. 1989; 143: 301–306. https://doi.org/10.1001/archpedi.1989.02150150055017 PMID: 2644815
33. Marguet C, Mallet E. [Value of dexamethasone in purulent meningitis in children. Apropos of a comparative study of 85 children]. Arch Fr Pediatr. 1993; 50: 111–117. Available: https://pubmed.ncbi.nlm.nih.gov/8343015/

34. de Gans J, van de Beek D. Dexamethasone in Adults with Bacterial Meningitis. N Engl J Med. 2002; 347: 1549–1556. https://doi.org/10.1056/NEJMoa021334 PMID: 12432041

35. Molyneux EM, Walsh AL, Forsyth H, Tembo M, Mwenechanya J, Kayira K, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: A randomised controlled trial. Lancet. 2002; 360: 211–218. https://doi.org/10.1016/s0140-6736(02)09458-8 PMID: 12133656

36. Sankar J, Singh P, Bansal A, Ray P, Singh S. Role of dexamethasone and oral glycerol in reducing hearing and neurological sequelae in children with bacterial meningitis. Indian Pediatr. 2007; 44: 649–656. PMID: 17921553

37. Girgis NI, Farid Z, Mikhail IA, Farrag I, Sultan Y, Kilpatrick ME. Dexamethasone treatment for bacterial meningitis in children and adults. Pediatr Infect Dis J. 1989; 8: 848–851. https://doi.org/10.1097/00006454-198912000-00004 PMID: 2626285

38. Ciana G, Parmar N, Antonio C, Pivetta S, Tamburlini G, Cuttini M. Effectiveness of Adjunctive Treatment with Steroids in Reducing Short-term Mortality in a High-risk Population of Children with Bacterial Meningitis. J Trop Pediatr. 1995; 41: 164–168. https://doi.org/10.1093/tropej/41.3.164 PMID: 7636936

39. Mathur NB, Garg A, Mishra TK. Role of Dexamethasone in Neonatal Meningitis: A Randomized Controlled Trial. Indian J Pediatr. 2012; 80: 102–107. https://doi.org/10.1007/s12098-012-0875-9 PMID: 23054852

40. Gudina EK, Tesfaye M, Wieser A, Pfister HW, Klein M. Outcome of patients with acute bacterial meningitis in a teaching hospital in Ethiopia: A prospective study. PLoS One. 2018; 13: e0200067. https://doi.org/10.1371/journal.pone.0200067 PMID: 30020952