Global Epidemiology of Pediatric Central Nervous System Infection: A Systematic Review and Meta-Analysis

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Abstract:

Objective: Central nervous system (CNS) infections lead to death and disability in children globally, yet the true burden of the disease is currently unknown. We performed a systematic review and a meta-analysis to provide a global annual incidence of pediatric CNS infection (pCNSi) and estimated pCNSi case burden.
Method: A comprehensive search of PubMed, Embase, and Scopus was conducted to identify relevant articles. The pCNSi annual incidence was calculated using an estimated bacterial meningitis incidence from a meta-analysis and the estimated BM:pCNSi ratio. The burden of annual cases of pCNSi was then estimated based on World Bank pediatric population data.
Result: Fifty-eight articles were reviewed. The annual pCNSi incidence was estimated at 47.55/100,000 children ≤ 18 years and the projected number of pCNSi worldwide is 1,254,647 yearly. Across WHO regions, the majority of projected cases are found in SEAR (295,737 cases). AFR had the highest pCNSi case consult to neurosurgeon ratio (222.2 per neurosurgeon). About 50% of the total number of projected cases worldwide are located in lower MICs (624,047 cases). LICs had the highest pCNSi case consult to neurosurgeon ratio (211.1 per neurosurgeon). Frequently reported pathogens include Haemophilus influenzae (21.6%), viruses (15.8%), and Streptococcus pneumoniae (14.3%). 41% require neurosurgical intervention.
Conclusion: More than an estimated 1.2 million children suffer from CNS infections each year, with the vast majority residing in low- and lower middle-income countries with a high case to neurosurgeon ratio. Continued preventive measures, and timely diagnostic and therapeutic support are necessary to curb a still common childhood condition worldwide.

KEYWORDS: *Global, pediatric, incidence, central nervous*

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Introduction

The Global Burden of Diseases, Injuries, and Risk Factors Study by the Lancet in 2019 found six infectious diseases, including central nervous system (CNS) infections among the leading causes of disability-adjusted life-years (DALYs) in children younger than 10 years.[1] Despite large reductions in the burden of infectious diseases affecting children over the last 30 years due to vaccine initiatives and other preventative measures, infectious diseases remain a health challenge among the pediatric population.[2]

Pediatric CNS infections (pCNSi) are significant drivers of morbidity and mortality and are a major source of disease burden especially in low- and middle- income countries (LMIC).[3] The fatality rate can be as high as 30% and neurological disabilities may occur in about one–third of survivors.[4] Beyond preventative measures, rapid diagnosis, prompt initiation of antimicrobial medications, urgent control of neurological sequalae such as raised intracranial pressure and/or status epilepticus alongside appropriate adjunctive therapies can significantly improve outcome of CNS infections.[3] Providing a reliable global estimate of the volume and burden of pCNSi is difficult due to the lack of population-wide data, poor healthcare and research infrastructure to track data, lack of disease registries, and the heterogeneity in CNS infection type. As a result, the true burden – particularly in resource-limited settings – is unknown.

The purpose of this study is to conduct a systematic review and meta-analysis of literature to provide a global incidence of pCNSi and estimated case burden across different World Health Organization (WHO) and World Bank Income regions. We also report on common pathogens associated with pCNSi globally and in each WHO and World Bank income region. Finally, an estimate of the neurosurgical burden of pCNSi is explored.

Methods

Literature Search Strategy

A systematic database search was completed utilizing key terms for pediatric neurosurgery and CNS infections according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[5] CNS infections include meningitis, encephalitis, cerebral and spinal abscesses, osteomyelitis, and discitis; multiple etiological agents were considered including bacteria, viruses, fungi, and parasites. The full search strategies are presented in the Online Appendix. The PubMed (National Library of Medicine), Embase (Elsevier), and Scopus (Elsevier) databases were searched from inception to the date of search with no restrictions on language or article type. No protocol was prepared or registered for this study.

Screening

Search results were aggregated and deduplicated in Endnote X9 (Clarivate Analytics, London, UK). Articles were screened for relevance by title and abstract. Remaining articles were screened via full text to determine final inclusion using a priori inclusion and exclusion criteria. Inclusion criteria were: 1) full text available, 2) study population of pediatric patients, defined per the definitions of the included studies, with CNS infections, and 3) reporting

the incidence of CNS infections in the population; the breakdown of pathogens causing CNS infections; or the proportion of infections leading to neurological or neurosurgical sequelae or necessitating surgical management. Articles not written in English were translated into English for review. Exclusion criteria were study designs of letters to the editor, commentaries, case reports, literature reviews, meta-analyses, and clinical practice guidelines. Studies with no epidemiological data, nor data on etiology, sequelae, or surgical management were excluded. Finally, studies reporting data on only a subset of pediatric patients with pCNSi were also excluded (e.g., children seen in a neurology clinic, children with an underlying condition, or only children with Haemophilus influenzae meningitis), or clinical practice guidelines. During both stages, screening was conducted by two reviewers independently (JWC, JHC), with a third reviewer (MCD) serving to resolve any conflicts. Each article was screened twice. A flowchart of the review process is outlined in **Figure 1**.

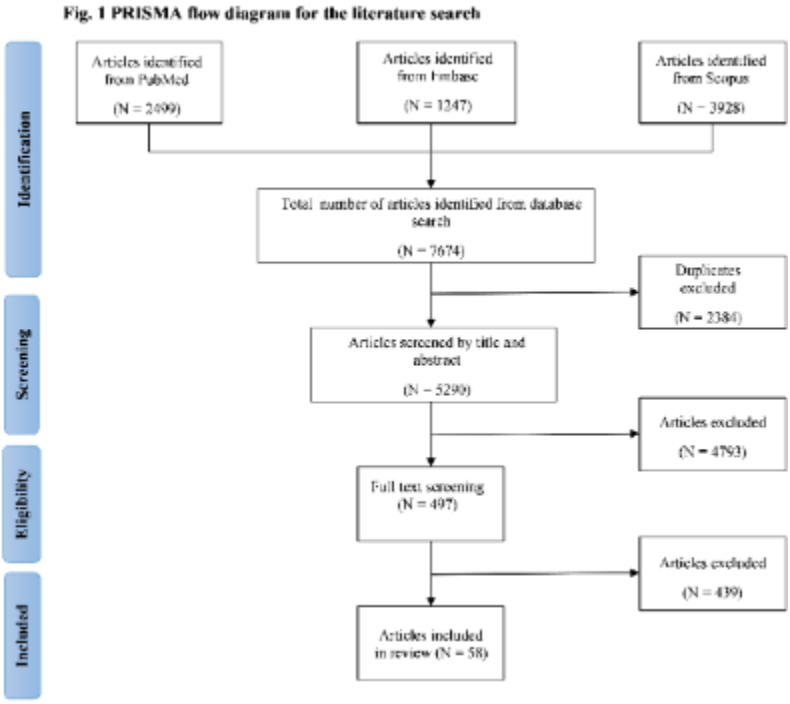

Figure 1: PRISMA flow diagram for the literature search

Data Extraction for Systematic Review

All included articles were reviewed for relevant data. Bibliometric data abstracted included title, year of publication, authors, study design, hospital or population-based structure, study period, and country of publication. The WHO region for each study was determined based on the country of origin of the study; the Americas region (AMR), European region (EUR), African region (AFR), Western Pacific region (WPR), South-East Asia region (SEAR), and Eastern Mediterranean region (EMR).[6] An income level was assigned to each study based on the World Bank income classification for the country of origin of the study, and is delineated as low income country (LIC) with per capita of $1,135 or less; lower middle income country (lower MIC) per capita between $1,136 and $4,465; upper middle income country (upper MIC) with per capita between $4,466 and $13,845; and high income country (HIC) per capita of $13,846 or greater.[7] Clinical data abstracted included the type of CNS infection (meningitis, abscess, other), number of pediatric patients with each type of CNS infection, incidence of CNS infection, total population size, pathogen responsible for CNS infections, number of patients with sequelae/complications, and the patients requiring neurosurgical intervention. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework was used to ascertain the quality of each included study.[8] The Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool was used to determine the risk of bias for each included study.[9] The overall risk of bias for this systematic review and meta-analysis was determined by aggregating the risk of bias of all included studies. of associated vascular lesions with a risk of ischemia [7].

pCNSi burden estimation

There was insufficient epidemiological data on pCNSi in general from studies reviewed to conduct a meta-analysis to directly estimate the global incidence of total pCNSi. Instead, the global incidence of pCNSi was modeled from epidemiologic data derived from pediatric bacterial meningitis (BM) studies. We first identified studies which reported on pCNSi cases including pediatric BM, viral infections and parasitic infections. Next, we calculated the ratio of pediatric BM to pCNSi cases as the weighted average proportion of pediatric BM cases among all pCNSi from each study with such data available as outlined below: using estimated weighted proportions.

1. The weight for each study (SW) = study sample size (ss) /sum of sample sizes of included (S)
2. The proportion of BM cases (or other specific disease complication/sequelae and cases requiring surgical management) reported by each study (P) =var/ss, where var = number of cases with BM, etiology, sequalae, or surgical cases reported by each study
3. The weighted average proportion of variable = sum(P x SW) across all studies included.

The annual incidence of pediatric BM was estimated from a meta-analysis using a random effects model to account for clinical diversity and differences in study populations. Incidence was reported as cases per 100,000 person-years with 95% confidence intervals (CIs). Heterogeneity

between studies was expressed with the I2 statistic. This meta-analysis of BM incidence was conducted in R (R Foundation, Vienna, Austria).

With the estimated pediatric BM/pCNSi ratio (weighted average proportion) and the estimated incidence of pediatric BM above, we computed the global incidence of pCNSi as below:

pCNSi Incidence = pediatric BM Incidence Global x Ratio (pediatric BM/pCNSi)

The annual number of new cases of pCNSi in children aged 0-18 overall and by WHO region and World Bank income status was then estimated based on World Bank pediatric population data.[10]

pCNSi Burden = pCNSi Incidence x PopulationPediatric

From the calculated weighted proportion of cases who required neurosurgical intervention based on the available data, we estimated the proportion of cases who would require a neurosurgical intervention in each WHO region and World Bank income group. Using the estimated case burden and the global neurosurgery workforce data published by Gupta et al,[11] we estimated the ratio of pCNSi case consults and surgical cases per neurosurgeon in each World Bank income group and WHO regions.

Results

Search Strategy Findings and Study Characteristics

Of 7,674 studies initially identified from the literature search, 59 were included after title/abstract screening and full text review. Studies included 41 retrospective cohort studies (71%), 12 prospective cohort studies (21%), and 5 cross-sectional studies (8%). By World Bank income group, 7 studies (12%) were from LICs, 14 studies (24%) from lower MICs, 17 studies (29%) from upper MICs, and 20 studies (34%) from HICs. By WHO Region, 6 studies (10%) from SEAR, 6 studies (10%) from EMR, 11 studies (19%) from WPR, 11 studies (19%) from AMR, 12 studies (21%) from AFR, and 12 studies (21%) from EUR. Fifty-one studies (86.4%) were graded as moderate quality, and 8 studies (13.6%) graded as low quality. Based on the ROBINS-I criteria, 8 studies (13.6%) had a low risk of bias, 47 studies (79.7%) had a moderate risk of bias, and 4 studies (6.8%) had a high risk of bias. A summary of these studies is included in **Table 1**.

Authors & Year	Study Type	Study Period	Country of Study	WHO Region	Income Group	Number of Patients	Study Quality (GRADE)	Risk of Bias (ROBINS-I)
[12]Chintu and Bathirunathan, 1975	Prospective Cohort	*	Zambia	AFR	Low	85	Moderate	Moderate
[13]Hailemeskel and Tafari, 1978	Retrospective Cohort	*	Ethiopia	AFR	Low	120	Moderate	Low
[14]Rantakallio et al, 1986	Retrospective Cohort	1966-1983	Finland	EUR	High	127	Low	Serious
[15]Bahemuka et al, 1988	Retrospective Cohort	1983-1986	Saudi Arabia	EMR	High	46	Low	Moderate
[16]Koorevaar et al, 1992	Retrospective Cohort	1981-1989	Netherlands	EUR	High	48	Moderate	Moderate
[17] Bent et al, 1994	Retrospective Cohort	1986-1991	USA	AMR	High	470	Moderate	Moderate
[18]Gomes et al, 1996	Cross-sectional	1993	El Salvador	AMR	Lower Middle	281	Moderate	Moderate
[19]Gebremariam 1998	Retrospective Cohort	1987-1996	Ethiopia	AFR	Low	55	Low	Low
[20]Almuneef et al, 1998	Retrospective Cohort	1984-1995	Saudi Arabia	EMR	High	70	Moderate	Moderate
[21]Lee et al, 2000	Retrospective Cohort	1974-1999	Philippine	SEAR	Lower Middle	2021	Moderate	Moderate
[22]Sakata and Maruyama, 2000	Retrospective Cohort	1994-1998	Japan	WPR	High	82	Moderate	Moderate
[23]Sahai et al, 2001	Prospective Cohort	1994-1996	India	SEAR	Lower Middle	100	Moderate	Moderate
[24]Chinchankar et al, 2002	Prospective Cohort	1997-1999	India	SEAR	Lower Middle	54	Moderate	Moderate

[25]Basualdo and Arbo et al, 2004	Retrospective Cohort	1991-1995	Paraguay	AMR	Upper Middle	83	Moderate	Moderate
[26]Sakata et al, 2005	Cross-sectional	1999-2003	Japan	WPR	High	83	Moderate	Moderate
[27]Khorasani et al, 2006	Retrospective Cohort	1999-2001	Yemen	EMR	Low	160	Moderate	Moderate
[28]Husain et al, 2007	Retrospective Cohort	2001-2003	Kuwait	EMR	High	172	Moderate	Moderate
[29]Franco-Paredes et al, 2008	Retrospective Cohort	1993-2003	Mexico	AMR	Upper Middle	218	Moderate	Moderate
[30]Pelkonen et al, 2008	Retrospective Cohort	2004	Angola	AFR	Lower Middle	555	Moderate	Moderate
[31]Seltz et al, 2009	Retrospective Cohort	2002-2006	Canada	AMR	High	7	Moderate	Moderate
[30]Pelkonen et al, 2009	Retrospective Cohort	2004	Angola	AFR	Lower Middle	594	Moderate	Low
[32]Libreralesso et al, 2009	Retrospective Cohort	2007-2008	Brazil	AMR	Upper Middle	722	Moderate	Moderate
[33]Bentlin et al, 2010	Retrospective Cohort	1997-2006	Brazil	AMR	Upper Middle	22	Low	Serious
[34]Gaschignard et al, 2011	Prospective Cohort	2001-2007	France	EUR	High	439	Moderate	Moderate
[35]Baş et al, 2011	Retrospective Cohort	1999-2008	Turkey	EUR	Upper Middle	19	Moderate	Moderate
[36]Bargui et al, 2012	Retrospective Cohort	1995-2004	France	EUR	High	89	Moderate	Low
[37]Mihailidou et al, 2012	Retrospective Cohort	1997-2002	Kosovo	EUR	Upper Middle	277	Moderate	Moderate
[38]Namani et al, 2012	Retrospective Cohort	1984-2008	Greece	EUR	High	48	Moderate	Moderate

[39]Laman et al, 2012	Retrospective Cohort	2007-2010	Papua New Guinea	WPR	Lower Middle	47	Moderate	Low
[40]Namani et al, 2012	Prospective Cohort	1997-2002	Kosovo	EUR	Upper Middle	277	Moderate	Moderate
[41]Adhikari et al, 2013	Retrospective Cohort	2007-2011	Nepal	SEAR	Lower Middle	148	Moderate	Moderate
[42]Biaukula et al, 2013	Prospective Cohort	2004-2007	Fiji	WPR	Upper Middle	46	Moderate	Moderate
[43]Fitzwater et al, 2013	Retrospective Cohort	2008-2011	India	SEAR	Lower Middle	51	Moderate	Moderate
[44]Kuchar et al, 2014	Retrospective Cohort	2002-2010	Poland	EUR	High	43	Moderate	Moderate
[45]Basri et al, 2015	Retrospective Cohort	2004-2011	Malaysia	WPR	Upper Middle	125	Low	Serious
[46]Kuti et al, 2015	Retrospective Cohort	2011-2013	Nigeria	AFR	Lower Middle	92	Very Low	Low
[47]Meng-Chin et al, 2015	Retrospective Cohort	1984-2012	Taiwan/China	WPR	Upper Middle	98	Moderate	Moderate
[48]Olson et al, 2015	Prospective Cohort	2000-2007	Guatemala	AMR	Upper Middle	809	Moderate	Low
[49]Ceyhan et al, 2016	Prospective Cohort	2013-2014	Turkey	EUR	Upper Middle	94	Moderate	Moderate
[50]Bari et al, 2016	Retrospective Cohort	2012	Pakistan	EMR	Lower Middle	199	Moderate	Moderate
[51]Briand et al, 2016	Retrospective Cohort	2001-2013	France	EUR	High	34	Low	Moderate
[52]Jawaid et al, 2016	Retrospective Cohort	2000-2014	Pakistan	EMR	Lower Middle	64	Moderate	Moderate
[53]Wee et al, 2016	Cross-sectional	1998-2013	Singapore	WPR	High	112	Moderate	Moderate

[54]Jiang et al, 2017	Retrospective Cohort	2012-2015	China	WPR	Upper Middle	179	Moderate	Moderate
[55]Li et al, 2018	Retrospective Cohort	2014-2016	China	WPR	Upper Middle	837	Moderate	Moderate
[56]Tshimangani et al, 2018	Prospective Cohort	2015-2016	Democratic Republic of the Congo	AFR	Low	299	Moderate	Moderate
[19]Gebremariam, 2018	Retrospective Cohort	2011-2013	Ethiopia	AMR	Low	80	Moderate	Moderate
[57]Ackermann et al, 2019	Retrospective Cohort	2000-2010	South Africa	AFR	Upper Middle	246	Moderate	Moderate
[58]El-Naggar et al, 2019	Case-Control	2010-2016	Canada	AMR	High	246	Moderate	Low
[59]Huo et al, 2019	Retrospective Cohort	2010-2016	China	WPR	Upper Middle	267	Moderate	Moderate
[60]Abdelrahim et al, 2019	Cross-sectional	2010	Sudan	AFR	Low	503	Low	Moderate
[61]Link-Gelles et al, 2020	Retrospective Cohort	1997-2014	USA	AMR	High	35	Moderate	Moderate
[62]Guillén-Pinto et al, 2020	Retrospective Cohort	2017-2018	Peru	AMR	Upper Middle	53	Moderate	Low
[63]Shinjoh et al, 2020	Cross-sectional	2016-2018	Japan	WPR	High	197	Moderate	Moderate
[64]Svendsen et al, 2020	Retrospective Cohort	1998-2016	Denmark	EUR	High	88	Moderate	Moderate
[65]Adil et al, 2021	Retrospective Cohort	2008-2015	USA	AMR	High	1928	Moderate	Moderate
[66]Obiero et al, 2021	Retrospective Cohort	2002	Kenya	AFR	Lower Middle	323	Moderate	Moderate
[67]Pelkonen et al, 2021	Prospective Cohort	2016-2017	Angola	AFR	Lower Middle	574	Moderate	Moderate

Table 1: Overview of Articles.
WHO – World Health Organization.
GRADE - Grading of Recommendations, Assessment, Development and Evaluations).
ROBINS-I - risk of bias in nonrandomized studies of interventions.

A total of 14,859 pCNSi cases aged between 0 to 19 years were reported out of which majority were meningitis cases including bacterial, viral, TB, and fungal meningitis (90.2%). Other pCNSi cases reported included cerebral abscess (2.5%), neurocysticercosis (0.8%), and ventriculitis (0.7%) (shown in **Fig. 2**). Nine articles reported underlying conditions in 352 patients including malnutrition (36%), hydrocephalus (28%), traumatic brain injury (12%), HIV (9%), and others (15%).

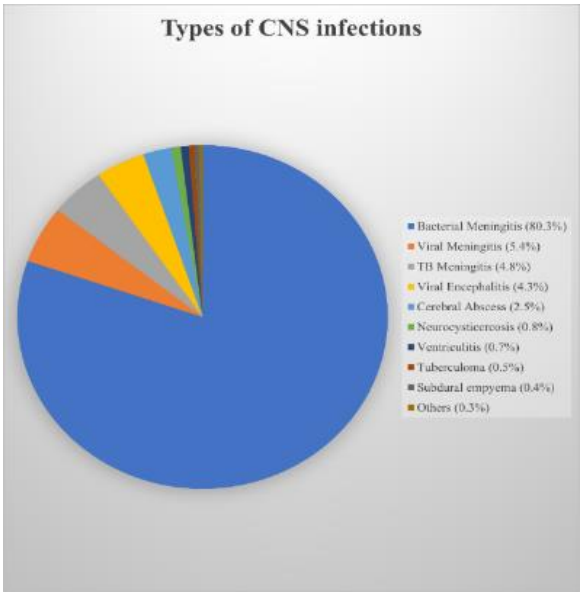

Figure 2: Types of CNS infections in the pediatric population.

Fifty-eight articles reported on the pathogens identified in 9,126 pCNSi cases. Weighted percentages across all 58 studies found Haemophilus influenzae (21.6%), viruses (15.8%), and Streptococcus pneumoniae (14.3%) as the most frequently reported pathogens. Other reported pathogens included Mycobacterium tuberculosis (9.1%), Neisseria meningitidis (8.6%), and Group B streptococcus (22%). Citrobacter spp, Moraxella catarrhalis, and Burkholderia cepacea were the least reported (<0.1% each) (shown in **Fig. 3**).

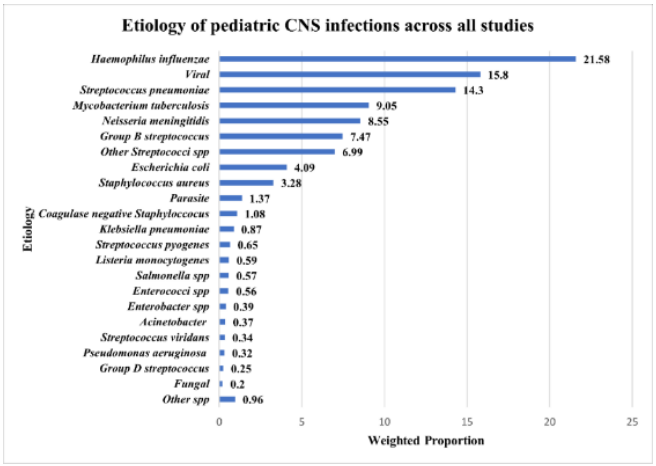

Figure 3: Etiology of pediatric CNS infections across all studies.
Other spp includes Burkholderia cepacian; Moraxella catarrhalis; Citrobacter spp; Serratia spp; Proteus spp; Elizabethkingia spp.

Taenia solium (96.8%) was the most frequently reported parasite with Toxoplasma gondii forming the remaining 3.2%. Candida spp formed 66.7% of fungal infections and 33.3% were Cryptococcus spp infections. Most studies reviewed did not report specific viral etiologies. The commonly reported pathogens differed slightly per region or income group when the pediatric cohort was stratified by WHO region or World Bank income group. In LICs,

the most commonly reported pathogens were Neisseria meningitidis (27.2%), Streptococcus pneumoniae (27%), Haemophilus influenzae (18.4%), and Mycobacterium tuberculosis (15.7%) (shown in **Fig. 4A**).

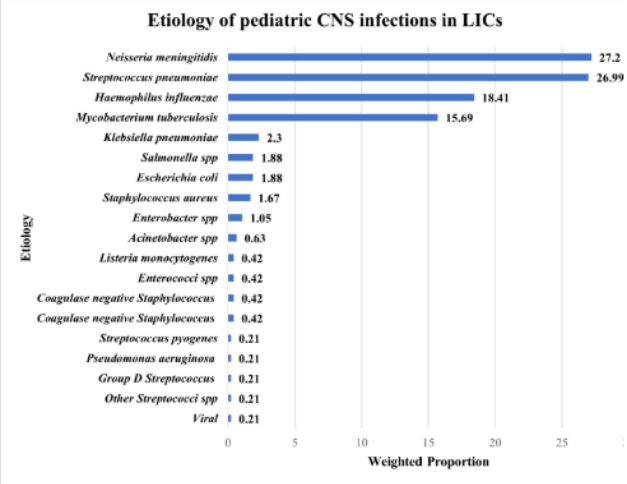

Figure 4a: Etiology of pediatric CNS infections in low-income countries.

The most common pathogens identified in lower MICs, Haemophilus influenzae (29.3%), Mycobacterium tuberculosis (22.1%), viral (20.1%), and Streptococcus pneumoniae (14.5%) (shown in **Fig. 4B**).

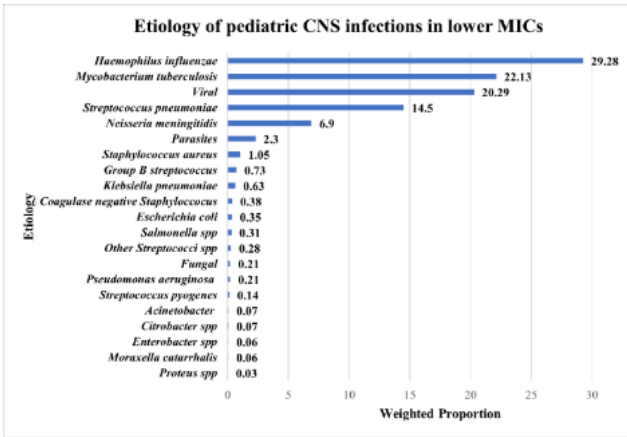

Figure 4b: Etiology of pediatric CNS infections in lower middle-income countries.

In upper MICs, viruses (39.4%) were the leading cause of pCNSi followed by *Haemophilus influenzae* (27.1%), *Streptococcus pneumoniae* (24.9%), and *Listeria monocytogenes* (14.9%) were commonly reported (shown in **Fig. 4C**).

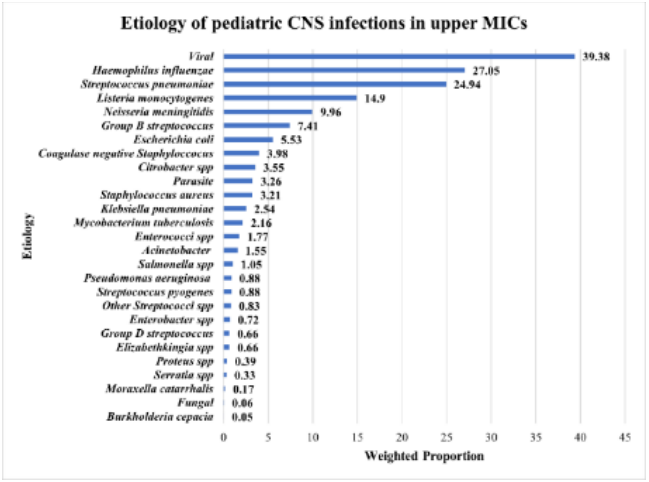

Figure 4c: Etiology of pediatric CNS infections in upper middle-income countries.

In HICs, about half of pCNSi were caused by Streptococcus spp with Group B streptococcus (17.9%) and Streptococcus pneumoniae (10.5%) being the most frequently reported. Other etiologies of pCNSi in HICs reported include Haemophilus influenzae (18.7%), Neisseria meningitidis (9%), and Escherichia coli (8.2%) (shown in **Fig. 4D**).

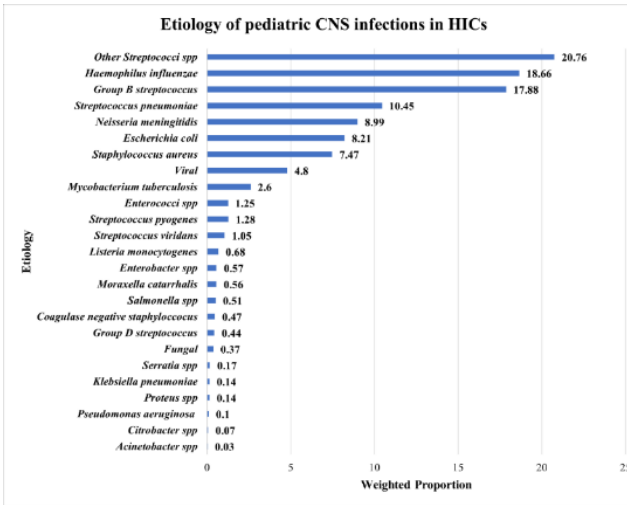

Figure 4d: Etiology of pediatric CNS infections in high income countries.

Parasitic infections were reported in lower and upper MICs. Across WHO Regions, Haemophilus influenzae (48.5%), Streptococcus pneumoniae (27.2%), Neisseria meningitidis (11.4%) and Mycobacterium tuberculosis (7.3%) were commonly reported in the AFR (shown in Fig. **5a**).

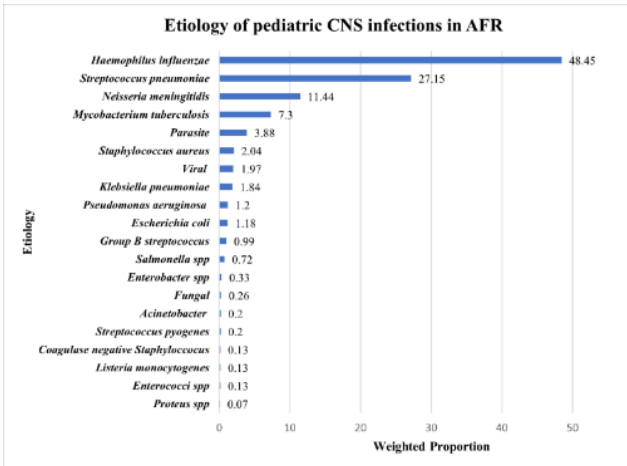

Figure 5a: Etiology of pediatric CNS infections in Africa Region.

In the EUR, commonly reported pathogens include viruses (40.7%), Neisseria meningitidis (17.6%), Group B streptococcus (15.7%), and Streptococcus pneumoniae (8.5%) (shown in **Fig. 5b**).

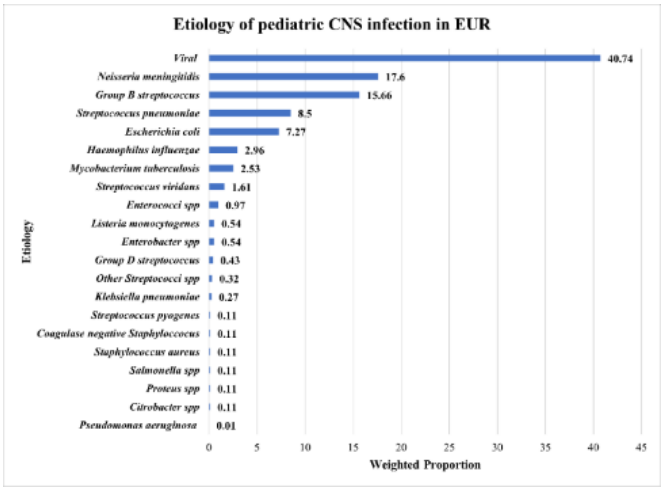

Figure 5b: Etiology of pediatric CNS infections in European Region.

Streptococcus pneumoniae (25.8%), Group B streptococcus (17.4%), and Haemophilus influenzae (14.2%), and Escherichia coli (9.8%) were frequently reported among cases from WPR (shown in **Fig. 5c**).

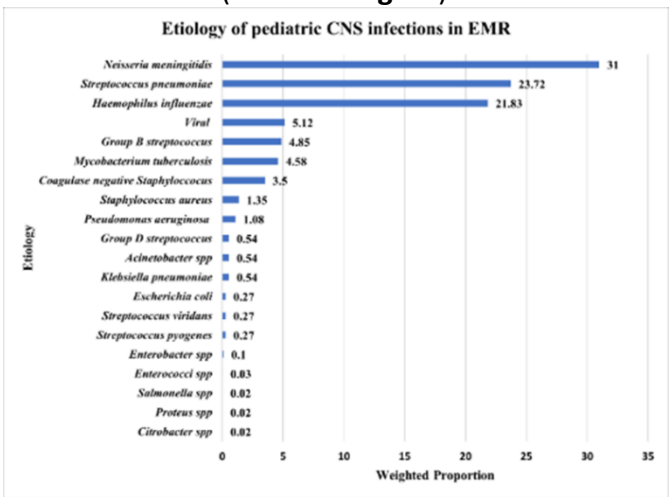

Figure 5c: Etiology of pediatric CNS infections in Western Pacific Region.

In the EMR, Neisseria meningitidis (31%), Streptococcus pneumoniae (23.7%), Haemophilus influenzae (21.8%), and viruses (5.1%) were most frequently reported (shown in **Fig. 5d**).

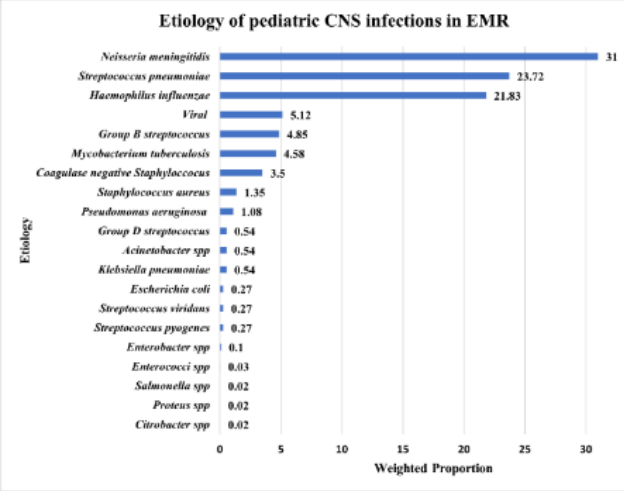

Figure 5d: Etiology of pediatric CNS infections in the Eastern Mediterranean Region.

In the AMR, the most frequently reported pathogens were Haemophilus influenzae (34.5%), viruses (30.8%), Streptococcus pneumoniae (11.2%), and Staphylococcus aureus (8.3%) (shown in **Fig. 5e**).

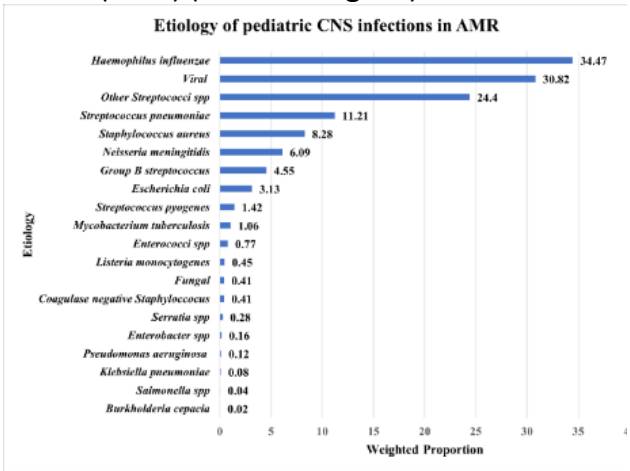

Figure 5e: Etiology of pediatric CNS infections in the Region of the Americas.

In the SEAR pCNSi were largely caused by Mycobacterium tuberculosis (44.8%) and viruses (39.9%). Parasites (4.7%), Haemophilus influenzae (4.4%), and Streptococcus pneumoniae (3.1%) were other frequently reported etiologies (shown in Fig. 5f).

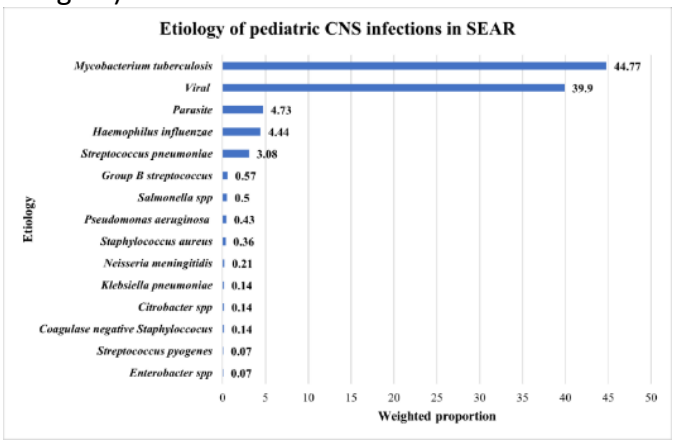

Figure 5f: Etiology of pediatric CNS infections in South-East Asia Region.

Twenty-five articles reported on neurologic complications observed in 5540 pediatric patients. Seizure disorder (16.7%) was the most common complication followed by subdural effusion (15.6%), and hydrocephalus (13.9%) (shown in **Fig. 6**). Other sequalae reported included hearing loss, developmental delay, intellectual disability, stroke, and cerebral palsy. Fifty-two articles reported mortality data on 11,816 patients out of which 1,303 (11%) died.

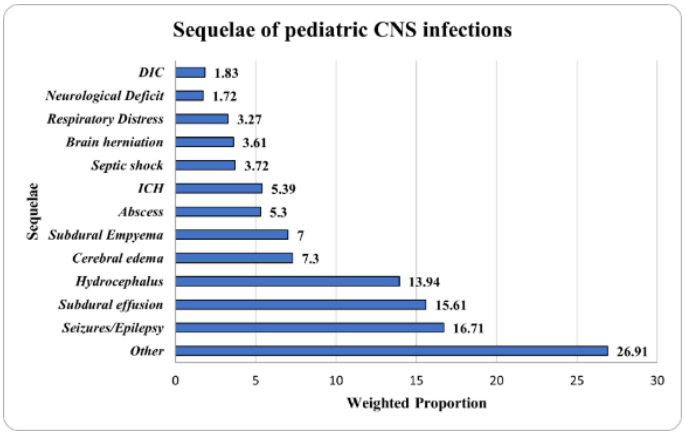

Figure 6: Sequelae of pediatric CNS infections.

Seven articles reported on neurosurgical intervention with 41% of pediatric patients reported to have received neurosurgical intervention. The type of neurosurgical procedure was reported in 35% of patients who received neurosurgical intervention; 18% had a shunt or external ventricular drainage insertion only, 6% had an incision and drainage for intracranial or extra-cranial collections only, 4% had therapeutic lumbar puncture only, 3% had a craniotomy/craniectomy only, and 69% underwent more than one neurosurgical procedure.

pCNSi Burden

Of the 59 studies reviewed, 6 studies on bacterial meningitis provided sufficient epidemiological data for a meta-analysis to estimate annual incidence; 3 studies from HICs, 2 studies from lower MICs and 1 study from LIC. The estimated annual global incidence of BM using random effects model was 12.58/100,000 children ≤ 18 years (shown in **Fig. 7**).

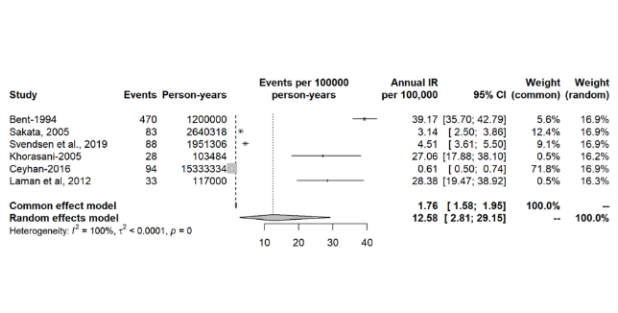

Figure 7: Forest plot of pediatric CNS infections incidence.

The pediatric BM/pCNSi ratio based on the number of pediatric BM and pCNSi cases between ages 0 to 18 reported in 6 studies involving 3307 patients was 1:3.78. Using this ratio, the global incidence of pCNSi was estimated to be 47.55/100,000 children ≤ 18 years annually. Based on this estimate, the projected number of pCNSi worldwide is 1,254,647 yearly. By WHO region, the majority of projected cases are found in SEAR (295,737 cases) while EUR had the least number of projected cases (93,061 cases). AFR had the highest pCNSi case consult and surgical case to neurosurgeon ratio; 222.2 per neurosurgeon and 91.1 per neurosurgeon, respectively. Meanwhile EUR had the lowest pCNSi case consult and surgical case to neurosurgeon ratio; 6.4 and 2.6 per neurosurgeon, respectively (**Table 2**).

WHO region	Pediatric Population (0-14 years)	Number of Projected pCNSi Cases	Cases requiring Neurosurgical intervention	Number of neurosurgeons	pCNSi Case consults per neurosurgeon	pCNSi surgical cases per neurosurgeon
AFR	500,342,806	291,295	119,431	1,311	222.2	91.1
AMR	155,719,056	125,435	51,428	14,799	8.5	3.5
EMR	241,626,225	147,525	60,485	4,674	31.6	12.9
EUR	101,774,018	93,061	38,155	14,547	6.4	2.6
SEAR	519,598,896	295,737	121,252	7,020	42.1	17.3
WPR	375,451,371	205,062	84,075	30,616	6.7	2.7

Table 2: Estimated Case Burden of pCNSi by WHO Region per year.

By World Bank income group, about 50% of the total number of projected cases worldwide are located in lower MICs (624,047 cases) relative to roughly 10% occurring in HICs (129,187 cases). LICs had the highest pCNSi case consult and surgical case to neurosurgeon ratio; 211.1 and 86.5 per neurosurgeon, respectively. HICs had the lowest pCNSi case consult and surgical case to neurosurgeon ratio: 4.1 and 1.7 per neurosurgeon, respectively (**Table 3**).

World Bank Income Group	Pediatric Population (0-14 years)	Number of Projected pCNSi Cases	Cases requiring Neurosurgical intervention	Number. of neurosurgeons	pCNSi Case Consults per neurosurgeon	pCNSi surgical cases per neurosurgeon
LIC	291,252,855	180,878	74,160	857	211.1	86.5
LMIC	984,713,752	624,047	255,859	11,930	52.3	21.4
UMIC	499,366,612	315,427	129,325	28,952	10.9	4.5
HIC	201,676,925	129,187	52,967	31,228	4.1	1.7
Worldwide	1,977,010,144	1,254,647	514,405	72,967	17.2	7.0

Table 3: Estimated Case Burden of pCNSi by World Bank Income Group per year

Discussion

The study sought to estimate the global incidence of pCNSi, determine burden of cases globally, and to assess the common pathogens causing these infections and their associated neurological complications. The estimated annual global incidence of pCNSi was 47.55/100,000 children ≤18 years amounting to 1,254,647 projected cases worldwide each year. Globally, Haemophilus influenzae, viruses, Streptococcus pneumoniae, and Mycobacterium tuberculosis were the most frequently reported pathogens in pCNSi. A majority of parasitic pCNSi were caused by Taenia solium. The most frequently reported complications included seizures, subdural effusion, and hydrocephalus.

pCNSi Case Burden

Projecting the burden of pCNSi from the estimated global incidence, more than 50% of projected cases worldwide are found in low resource settings where the majority of the pediatric population resides. By World Bank income group, most projected cases are in lower MIC and upper MIC with a high case to neurosurgeon ratio while HICs had the least burden of cases with a lower case to neurosurgeon ratio. By WHO region the highest burden of pCNSi cases were found in SEAR and AFR with the highest case to neurosurgeon ratio. EUR had the least burden of pCNSi cases with the lowest case to neurosurgeon ratio. Delayed diagnosis or improper medical management risks disease progression which can often lead to the development of surgical pathologies including subdural empyema, intracerebral abscess, and post-infectious hydrocephalus. Nearly 200 neurosurgeons from more than 50 countries surveyed in 2018 estimated that 44% of CNS infections require neurosurgical evaluation, with even higher estimate derived from low-income countries.[68] Similarly, from the few articles which reported on neurosurgical management, 41% of pCNSi cases received surgery including burr hole drainage, craniotomy, evacuation of abscess, and shunt as part of their management.[14],[21],[37],[38],[50],[65] Accordingly, up to an estimated 514,000 children will require neurosurgical evaluation each year as a result of pCNSi. Instituting the needed timely neurosurgical interventions in LMICs especially AFR and SEAR is extremely challenging for several reasons. These regions bear a disproportionately large burden of pCNSi and other pediatric neurosurgical diseases yet have the lowest neurosurgery workforce densities.[11] The burden of disease and coupled with the existing fragile surgical health systems including limited pediatric neurosurgical workforce negatively impacts access to neurosurgical care.[3],[68] The scarcity of neurosurgeons leads to delayed treatment, suboptimal care, and poor outcomes for patients requiring neurosurgical intervention.[68] Investment in training and increasing the number of neurosurgeons in these regions may improve the quality and timeliness of neurosurgical care with a resultant reduction of the morbidity and mortality associated with pCNSi and other pediatric neurosurgical diseases.[68]

Etiological Profile

Based on our review, we found that there were slight variations in common infectious etiologies by WHO Region and World Bank income groups. While HICs grappled with a relatively higher rate of viral, streptococcal,

and Haemophilus influenzae infections, LICs and lower MICs reported a higher prevalence of Neisseria meningitidis, Haemophilus influenzae, Mycobacterium tuberculosis and parasitic infections. Upper MICs reported a high burden pCNSi of both viral and bacterial origin most commonly Streptococcus pneumoniae and Haemophilus influenzae. Stratified by WHO region, there was a higher prevalence of viral pCNSi in AMR and EUR with predominantly bacterial and parasitic infection reported in the other WHO regions. A point worth noting is the relatively higher prevalence of vaccine preventable infections across all regions, especially LMICs.

Vaccine preventable infections remain a challenge despite the implementation of the WHO Expanded Immunization Program (EPI) in 1974 across all countries and the additional vaccine development since the 2000s.[69] This highlights the fact that while there has been a decline in vaccine preventable diseases globally, there still exists a significant burden of vaccine preventable diseases as well as disparities in disease burden across countries. Previous studies conducted in different countries/regions have reported a substantial decrease (50% - 99%) in meningococcal meningitis cases in both pediatric and adult populations with over 85% uptake of the polysaccharide conjugate vaccine.[70],[71] A high vaccine uptake/coverage within a population was also observed to be associated with herd protection with up to 50% reduction in incidence among unvaccinated cohorts.[70],[71]

Not all countries or regions have reached the target immunization coverage of 90% in the pediatric population with some LMICs reporting less than 50% immunization coverage.[72] In 2021, WHO reported a drop in global immunization coverage from 86% to 81%.[73] Existing barriers to achieving good immunization coverage include lack of reliable data and infrastructure, COVID-19–related issues, increased misconceptions surrounding immunization, and shortages of trained healthcare workers.[73] Thorough planning, communication, public health education, and social mobilization are essential to successfully implementing immunization programs.[73] Infections could also be contributed to by non-vaccine pathogen serotypes which have been noted to be on rise after the introduction of vaccines.[74] This calls for continuous advancements in vaccine development.

Quite striking is the large burden of Mycobacterium tuberculosis and parasitic pCNSi in SEAR. Parasitic CNS infections, especially neurocysticercosis, is also a major public health challenge in LMICs largely due to poor sanitary standards and veterinary services, and inadequate regulation of animal farming and food processing.[75] Systemic barriers to care together with cultural beliefs regarding neurological manifestations hinders diagnosis, treatment, and surveillance in communities.[75] Mitigating parasitic CNS infections will require interventions targeted at improving sanitation and hygiene, creating public awareness, veterinary control, meat inspection and active surveillance monitoring of food vendors.[75]

Aside implementing preventive measures, there is also a need for prompt diagnosis and treatment of pCNSi to improve outcomes and decrease risk of both short term and long term complications as outlined by WHO.[76] Untreated pCNSi are associated with high morbidity and mortality rates.[77]

The many types of infectious pathogens implicated in pCNSi makes empiric antimicrobial therapy suboptimal.[78] Adding to the therapeutic challenge is the growing trend of antimicrobial resistance.[79, 80] This is particularly concerning for multidrug-resistant (MDR) Mycobacterium tuberculosis and gram negative and positive pathogens including Acinetobacter baumannii, Klebsiella pneumoniae, and Streptococcus pneumoniae classified by WHO as critical priority on the 2024 WHO Bacterial Priority Pathogens List.[81] Improving outcomes would require advancements in pathogen-specific detection techniques and pharmacotherapeutics as well as antimicrobial stewardship to promote the optimal use and sustainability of antimicrobials currently available.

Limitations

It is important to acknowledge study limitations in interpreting the results. The regional representation in the meta-analysis was not uniform, with half of studies (n=3) included in the meta-analysis coming from HICs leading to a potential source of bias in the estimation of incidence. There was insufficient data available to estimate specific regional incidence. Thus, the use of global incidence to extrapolate case burden across regions may lead to an overestimation or underestimation of cases in some regions. Also, limited studies reported on the neurosurgical management of patients which may cause an error in the estimate on patients who received neurosurgical intervention. This risk is mitigated by referencing a prior study corroborating the estimated proportion of infectious neurosurgical disease. There is a need for additional epidemiological studies to estimate the true burden of pCNSi especially in LMICs which bear a disproportionate burden of the disease as well as studies reporting on treatment paradigms and outcomes.

Conclusion

More than an estimated 1.2 million children suffer from CNS infections each year, with the vast majority residing in LMICs with a high case to neurosurgeon ratio. These findings underscore the need for improved public health infrastructure, stronger immunization coverage, and enhanced access to medical and surgical care for pCNSi, particularly in vulnerable regions with the greatest disease burden.

References

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet (London, England). 2020;396(10258):1204-22.
2. Davis S, Feikin D, Johnson HL. The effect of Haemophilus influenzae type B and pneumococcal conjugate vaccines on childhood meningitis mortality: a systematic review. BMC public health. 2013;13 Suppl 3(Suppl 3):S21.
3. Robertson FC, Lepard JR, Mekary RA, Davis MC, Yunusa I, Gormley WB, et al. Epidemiology of central nervous system infectious diseases: a meta-analysis and systematic review with implications for neurosurgeons worldwide. Journal of neurosurgery. 2018.
4. Sahu RN, Kumar R, Mahapatra AK. Central nervous system infection in the pediatric population. Journal of pediatric neurosciences. 2009;4(1):20-4.
5. D Moher, A Liberati, J Tetzlaff, DG Altman. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
6. WHO. WHO Regions 2021 [Available from: https://www.who.int/countries.
7. World Bank Country and Lending Groups. 2021 [Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.
8. Siemieniuk R and Guyatt G. What is GRADE? | BMJ Best Practice 2021 [Available from: https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/.
9. Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
10. Total Population by Country 2021. 2021 [Available from: https://worldpopulationreview.com/countries.
11. Gupta S, Gal ZT, Athni TS, Calderon C, Callison WE, Dada OE, et al. Mapping the global neurosurgery workforce. Part 1: Consultant neurosurgeon density in: Journal of Neurosurgery - Ahead of print Journals. Journal of Neurosurgery. 2024:1-9.
12. Chintu C, Bathirunathan N. Bacterial meningitis in infancy and childhood in Lusaka (One year prospective sturdy). Medical journal of Zambia. 1975;9(6):150-7.
13. Hailemeskel H, Tafari N. Bacterial meningitis in childhood in an African city. Factors influencing aetiology and outcome. Acta paediatrica Scandinavica. 1978;67(6):725-30.
14. Rantakallio P, Leskinen M, von Wendt L. Incidence and prognosis of central nervous system infections in a birth cohort of 12,000 children. Scandinavian journal of infectious diseases. 1986;18(4):287-94.
15. Bahemuka M, Babiker MA, Wright SG, Al Orainey I, Obeid T. The pattern of infection of the nervous system in Riyadh: a review of 121 cases. The Quarterly journal of medicine. 1988;68(255):517-24.
16. Koorevaar CT, Scherpenzeel PG, Neijens HJ, Derksen-Lubsen G, Dzoljic-Danilovic G, de Groot R. Childhood meningitis caused by enterococci and viridans streptococci. Infection. 1992;20(3):118-21.

17. Bent JP, Beck RA. Bacterial meningitis in the pediatric population: paradigm shifts and ramifications for otolaryngology-head and neck surgery. International journal of pediatric otorhinolaryngology. 1994;30(1):41-9.
18. Gomes I, Melo A, Lucena R, Cunha-Nascimento MH, Ferreira A, Góes J, et al. Prognosis of bacterial meningitis in children. Arquivos de neuro-psiquiatria. 1996;54(3):407-11.
19. Gebremariam A. Neonatal meningitis in Addis Ababa: a 10-year review. Annals of tropical paediatrics. 1998;18(4):279-83.
20. Almuneef M, Memish Z, Khan Y, Kagallwala A, Alshaalan M. Childhood bacterial meningitis in Saudi Arabia. The Journal of infection. 1998;36(2):157-60.
21. Lee LV. Neurotuberculosis among Filipino children: an 11 years experience at the Philippine Children's Medical Center. Brain & development. 2000;22(8):469-74.
22. Sakata H, Maruyama S. [A study of bacterial meningitis in Hokkaido between 1994 and 1998]. Kansenshogaku zasshi The Journal of the Japanese Association for Infectious Diseases. 2000;74(4):339-44.
23. Sahai S, Mahadevan S, Srinivasan S, Kanungo R. Childhood bacterial meningitis in Pondicherry, South India. Indian journal of pediatrics. 2001;68(9):839-41.
24. Chinchankar N, Mane M, Bhave S, Bapat S, Bavdekar A, Pandit A, et al. Diagnosis and outcome of acute bacterial meningitis in early childhood. Indian pediatrics. 2002;39(10):914-21.
25. Basualdo W, Arbo A. Invasive Haemophilus influenzae type b infections in children in Paraguay. Archives of medical research. 2004;35(2):126-33.
26. Sakata H. [A study of bacterial meningitis in Hokkaido between 1999 and 2003]. Kansenshogaku zasshi The Journal of the Japanese Association for Infectious Diseases. 2005;79(9):680-7.
27. Al Khorasani A, Banajeh S. Bacterial profile and clinical outcome of childhood meningitis in rural Yemen: a 2-year hospital-based study. The Journal of infection. 2006;53(4):228-34.
28. Husain EH, Al-Shawaf F, Bahbahani E, El-Nabi MH, Al-Fotooh KA, Shafiq MH, et al. Epidemiology of childhood meningitis in Kuwait. Medical science monitor : international medical journal of experimental and clinical research. 2007;13(5):CR220-3.
29. Franco-Paredes C, Lammoglia L, Hernández I, Santos-Preciado JI. Epidemiology and outcomes of bacterial meningitis in Mexican children: 10-year experience (1993-2003). International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2008;12(4):380-6.
30. Pelkonen T, Roine I, Monteiro L, Correia M, Pitkäranta A, Bernardino L, et al. Risk factors for death and severe neurological sequelae in childhood bacterial meningitis in sub-Saharan Africa. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2009;48(8):1107-10.
31. Seltz LB, Cohen E, Weinstein M. Risk of bacterial or herpes simplex virus meningitis/encephalitis in children with complex febrile seizures. Pediatric emergency care. 2009;25(8):494-7.
32. Paulo Breno Noronha Liberalesso, Izabella Celidônio Bertoldo da Silva, Karlin Fabianne Klagenberg, Ari Leon Jurkiewicz, Bianca Simone Zeigelboim, Victor Horácio Costa Júnior. Incidence and risk factors for seizures in central nervous system infections in childhood. Journal of Epilepsy and Clinical Neurophysiology. 2009;15(2):83-8.

33. Bentlin MR, Ferreira GL, Rugolo LM, Silva GH, Mondelli AL, Rugolo Júnior A. Neonatal meningitis according to the microbiological diagnosis: a decade of experience in a tertiary center. Arquivos de neuro-psiquiatria. 2010;68(6):882-7.
34. Gaschignard J, Levy C, Romain O, Cohen R, Bingen E, Aujard Y, et al. Neonatal Bacterial Meningitis: 444 Cases in 7 Years. The Pediatric infectious disease journal. 2011;30(3):212-7.
35. Baş AY, Demirel N, Aydin M, Zenciroglu A, Tonbul A, Tanir G. Pneumococcal meningitis in the newborn period in a prevaccination era: a 10-year experience at a tertiary intensive care unit. The Turkish journal of pediatrics. 2011;53(2):142-8.
36. Bargui F, D'Agostino I, Mariani-Kurkdjian P, Alberti C, Doit C, Bellier N, et al. Factors influencing neurological outcome of children with bacterial meningitis at the emergency department. European journal of pediatrics. 2012;171(9):1365-71.
37. Mihailidou E, Goutaki M, Nanou A, Tsiatsiou O, Kavaliotis J. Tuberculous meningitis in Greek children. Scandinavian journal of infectious diseases. 2012;44(5):337-43.
38. Namani SA, Koci RA, Kuchar E, Dedushi KH. Surgical treatment of neurologic complications of bacterial meningitis in children in Kosovo. Journal of tropical pediatrics. 2012;58(2):139-42.
39. Laman M, Manning L, Greenhill AR, Mare T, Michael A, Shem S, et al. Predictors of acute bacterial meningitis in children from a malaria-endemic area of Papua New Guinea. The American journal of tropical medicine and hygiene. 2012;86(2):240-5.
40. Namani S, Milenkovic Z, Kuchar E, Koci R, Mehmeti M. Mortality from bacterial meningitis in children in Kosovo. Journal of child neurology. 2012;27(1):46-50.
41. Adhikari S, Sathian B, Koirala DP, Rao KS. Profile of children admitted with seizures in a tertiary care hospital of Western Nepal. BMC pediatrics. 2013;13:43.
42. Biaukula VL, Tikoduadua L, Azzopardi K, Seduadua A, Temple B, Richmond P, et al. Meningitis in children in Fiji: etiology, epidemiology, and neurological sequelae. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2012;16(4):e289-95.
43. Fitzwater SP, Ramachandran P, Nedunchelian K, Kahn G, Santosham M, Chandran A. Bacterial meningitis in children. The Journal of pediatrics. 2013;163(1 Suppl):S32-7.
44. Kuchar E, Nitsch-Osuch A, Rorat M, Namani S, Pabianek D, Topczewska-Cabanek A, et al. Etiology and complications of central nervous system infections in children treated in a pediatric intensive care unit in Poland. Journal of child neurology. 2014;29(4):483-6.
45. Basri R, Zueter AR, Mohamed Z, Alam MK, Norsa'adah B, Hasan SA, et al. Burden of bacterial meningitis: a retrospective review on laboratory parameters and factors associated with death in meningitis, kelantan malaysia. Nagoya journal of medical science. 2015;77(1-2):59-68.
46. Kuti BP, Bello EO, Jegede TO, Olubosede O. Epidemiological, clinical and prognostic profile of childhood acute bacterial meningitis in a resource poor setting. Journal of neurosciences in rural practice. 2015;6(4):549-57.
47. Lin MC, Chiu NC, Chi H, Ho CS, Huang FY. Evolving trends of neonatal and childhood bacterial meningitis in northern Taiwan. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi. 2015;48(3):296-301.
48. K. E. Rusthoven, C. Olsen, W. Franklin, B. K. Kleinschmidt-DeMasters, B. D. Kavanagh, L. E. Gaspar, et al. Favorable prognosis in patients with high-grade glioma with radiation necrosis: the University of Colorado reoperation series. Int J Radiat Oncol Biol Phys. 2011;81(1):211-7.

49. Ceyhan M, Ozsurekci Y, Gürler N, Karadag Oncel E, Camcioglu Y, Salman N, et al. Bacterial agents causing meningitis during 2013-2014 in Turkey: A multi-center hospital-based prospective surveillance study. Human vaccines & immunotherapeutics. 2016;12(11):2940-5.
50. Bari A, Zeeshan F, Zafar A, Ejaz H, Iftikhar A, Rathore AW. Childhood Acute Bacterial Meningitis: Clinical Spectrum, Bacteriological Profile and Outcome. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP. 2016;26(10).
51. Briand C, Levy C, Baumie F, Joao L, Béchet S, Carbonnelle E, et al. Outcomes of bacterial meningitis in children. Medecine et maladies infectieuses. 2016;46(4):177-87.
52. Jawaid A, Bano S, Haque AU, Arif K. Frequency and Outcome of Meningitis in Pediatric Intensive Care Unit of Pakistan. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP. 2016;26(8):716-7.
53. Wee LY, Tanugroho RR, Thoon KC, Chong CY, Choong CT, Krishnamoorthy S, et al. A 15-year retrospective analysis of prognostic factors in childhood bacterial meningitis. Acta paediatrica (Oslo, Norway : 1992). 2016;105(1):e22-9.
54. Jiang H, Su M, Kui L, Huang H, Qiu L, Li L, et al. Prevalence and antibiotic resistance profiles of cerebrospinal fluid pathogens in children with acute bacterial meningitis in Yunnan province, China, 2012-2015. PloS one. 2017;12(6):e0180161.
55. Li C, Feng WY, Lin AW, Zheng G, Wang YC, Han YJ, et al. Clinical characteristics and etiology of bacterial meningitis in Chinese children >28 days of age, January 2014-December 2016: A multicenter retrospective study. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2018;74:47-53.
56. Tshimangani T, Pongo J, Bodi Mabiala J, Yotebieng M, O'Brien NF. Pediatric Acute Severe Neurologic Illness and Injury in an Urban and a Rural Hospital in the Democratic Republic of the Congo. The American journal of tropical medicine and hygiene. 2018;98(5):1534-40.
57. Ackermann S, Le Roux S, Wilmshurst JM. Epidemiology of children with epilepsy at a tertiary referral centre in South Africa. Seizure. 2019;70:82-9.
58. El-Naggar W, Afifi J, McMillan D, Toye J, Ting J, Yoon EW, et al. Epidemiology of Meningitis in Canadian Neonatal Intensive Care Units. The Pediatric infectious disease journal. 2019;38(5):476-80.
59. Huo L, Fan Y, Jiang C, Gao J, Yin M, Wang H, et al. Clinical Features of and Risk Factors for Hydrocephalus in Childhood Bacterial Meningitis. Journal of child neurology. 2019;34(1):11-6.
60. Abdelrahim NA, Fadl-Elmula IM, Ali HM. Bacterial meningitis in Sudanese children; critical evaluation of the clinical decision using clinical prediction rules. BMC pediatrics. 2019;19(1):319.
61. Link-Gelles R, Toews KA, Schaffner W, Edwards KM, Wright C, Beall B, et al. Characteristics of Intracranial Group A Streptococcal Infections in US Children, 1997-2014. Journal of the Pediatric Infectious Diseases Society. 2020;9(1):30-5.
62. Guillén-Pinto D, Málaga-Espinoza B, Ye-Tay J, Rospigliosi-López ML, Montenegro-Rivera A, Rivas M, et al. Neonatal meningitis: a multicenter study in Lima, Peru. Revista peruana de medicina experimental y salud publica. 2020;37(2):210-9.
63. Shinjoh M, Yamaguchi Y, Furuichi M, Yaginuma M, Takahashi T, Iwata S. Recent trends in pediatric bacterial meningitis in Japan, 2016-2018 - S. agalactiae has been the most common pathogen. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy. 2020;26(10):1033-41.

64. Svendsen MB, Ring Kofoed I, Nielsen H, Schønheyder HC, Bodilsen J. Neurological sequelae remain frequent after bacterial meningitis in children. Acta paediatrica (Oslo, Norway : 1992). 2020;109(2):361-7.
65. Adil SM, Hodges SE, Charalambous LT, Kiyani M, Liu B, Lee HJ, et al. Paediatric bacterial meningitis in the USA: outcomes and healthcare resource utilization of nosocomial versus community-acquired infection. Journal of medical microbiology. 2021;70(1).
66. Obiero CW, Mturi N, Mwarumba S, Ngari M, Newton CR, van Hensbroek MB, et al. Clinical features of bacterial meningitis among hospitalised children in Kenya. BMC medicine. 2021;19(1):122.
67. Pelkonen T, Urtti S, Cardoso O, Kyaw MH, Roine I, Peltola H. Risk factors for death in suspected severe bacterial infection in infants aged. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2021;106:223-7.
68. Dewan MC, Rattani A, Baticulon RE, Faruque S, Johnson WD, Dempsey RJ, et al. Operative and consultative proportions of neurosurgical disease worldwide: estimation from the surgeon perspective. Journal of neurosurgery. 2018;1:1-9.
69. Keja K, Chan C, Hayden G, Henderson RH. Expanded programme on immunization. World health statistics quarterly Rapport trimestriel de statistiques sanitaires mondiales. 1988;41(2):59-63.
70. Clark SA, Borrow R. Herd Protection against Meningococcal Disease through Vaccination. Microorganisms. 2020;8(11):1675.
71. Ladhani SN, Campbell H, Andrews N, Parikh SR, White J, Edelstein M, et al. First Real-world Evidence of Meningococcal Group B Vaccine, 4CMenB, Protection Against Meningococcal Group W Disease: Prospective Enhanced National Surveillance, England. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021;73(7):e1661-e8.
72. Bender RG, Shen J, Aravkin A, Bita Fouda AA, Bwaka AM, Galles NC, et al. Meningococcal A conjugate vaccine coverage in the meningitis belt of Africa from 2010 to 2021: a modelling study. EClinicalMedicine. 2023;56:101797.
73. Larkin HD. Backslide in Global Childhood Vaccinations. JAMA. 2022;328(11):1029.
74. Du QQ, Shi W, Yu D, Yao KH. Epidemiology of non-vaccine serotypes of Streptococcus pneumoniae before and after universal administration of pneumococcal conjugate vaccines. Human vaccines & immunotherapeutics. 2021;17(12):5628-37.
75. Ta R, Blond BN. The prevalence of and contributors to neurocysticercosis in endemic regions. Journal of the neurological sciences. 2022;441:120393.
76. World Health Organization. https://www.who.int/initiatives/defeating-meningitis-by-2030 2024 [
77. Autore G, Bernardi L, Perrone S, Esposito S. Update on Viral Infections Involving the Central Nervous System in Pediatric Patients. Children (Basel, Switzerland). 2021;8(9):782.
78. Guo Y, Yang Y, Xu M, Shi G, Zhou J, Zhang J, et al. Trends and Developments in the Detection of Pathogens in Central Nervous System Infections: A Bibliometric Study. Frontiers in cellular and infection microbiology. 2022;12:856845.
79. Nau R, Sörgel F, Eiffert H. Central nervous system infections and antimicrobial resistance: an evolving challenge. Current opinion in neurology. 2021;34(3):456-67.
80. Velkov T, Dai C, Ciccotosto GD, Cappai R, Hoyer D, Li J. Polymyxins for CNS infections: Pharmacology and neurotoxicity. Pharmacology & therapeutics. 2018;181:85-90.

81. World Health Organization. WHO Bacterial Priority Pathogens List, 2024 2024 [Available from: https://iris.who.int/bitstream/handle/10665/376776/9789240093461-eng.pdf?sequence=1