

A systematic literature review on the prevalence and etiology of meningitis among critically ill and hospitalized patients in India

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Abstract

Background: In India, owing to multiple factors, such as insufficient laboratory capacity, poor reporting systems due to limited access to healthcare facilities and limited disease surveillance programmes, the actual disease burden of meningitis is unknown and may be largely under-reported.

Objective: A systematic literature review was performed to describe: (a) the prevalence of meningitis; and (b) its etiological pathogen across different regions, age groups and patients with comorbidities.

Method: A systematic literature search was conducted between 1990 and 2020 using PubMed and Google Scholar databases to identify Indian studies reporting the prevalence rates and etiology of meningitis. A total of 51 studies were included in the final analysis.

Results: A total of 38 studies reported prevalence of meningitis and 21 studies reported data on the etiology of meningitis in India. These studies included mixed patient populations: (a) pyogenic meningitis; (b) meningitis in sick or hospitalized patients with tuberculosis, acute febrile encephalopathy syndrome, septicaemia, invasive pneumococcal disease or respiratory compromise; and (c) meningitis patients with comorbidities. The prevalence of confirmed bacterial meningitis in the pediatric population (0–14 years) ranged between 0.5% and 61.8%. A total of seven studies reported the prevalence of meningitis in patients of all age groups (0–75 years), with prevalence ranging between 8.68% and 78.85%. Cryptococcal meningitis was predominant in patients with positive HIV/AIDS, with a prevalence ranging between 2.09% and 53.1%. *Streptococcus pneumoniae* was found to be the predominant pathogen causing meningitis across different regions of India, with a frequency ranging from 4% to 61.8% in patients of all age groups.

Conclusion: This systematic literature review displayed the possible range of frequency of bacterial meningitis pathogens across a wide variety of age groups in different regions of India. Further studies are warranted to monitor meningitis cases, which may facilitate the development of prevention and treatment strategies in India.

Keywords: disease burden, etiology, India, meningitis, systematic review

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Introduction

Meningitis, an inflammatory condition involving the meninges and the spinal cord, is a devastating disease with a high mortality rate.^{1,2} Even in the survivors, meningitis is associated with significant long-term sequelae, and thus is regarded as a

major global public health challenge. Outbreaks of meningitis have been considered as a global threat that warrant immediate attention.² Meningitis can be caused by several different pathogens including bacteria, viruses, fungi and other parasites; the highest global burden reported

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for meningitis has been caused by bacteria.^{3,4} Cryptococcal meningitis caused by fungi is a common meningitis with increasing significance among adult patients with positive HIV.⁴ Besides infectious causes, non-infectious factors, such as certain medications, malignancy and autoimmune diseases, may also cause meningitis.²

As per the 2016 Global Burden of Disease (GBD) Study, the incident cases of meningitis have increased globally from 2.50 million (2.19–2.91) in 1990 to 2.82 million (2.46–3.31) in 2016.^{1,2} Over 1.2 million people are affected by bacterial meningitis each year across the globe.⁵ In the United States of America, an estimated 4100 cases of bacterial meningitis were reported annually between 2003 and 2007.⁶ In Europe, the yearly incidence of bacterial meningitis is 2.6–6.0 cases per 100,000.⁷ With a much higher disease burden,^{8,9} resource-poor countries may exhibit even a 10-fold higher incidence of meningitis *versus* resource-rich countries.^{7,8} According to the World Health Organization, approximately 290,000 patients lost their lives due to meningitis in 2015.² The meningitis-associated mortality rate varies based on region, country, age, pathogen, etc., and may climb up to 70% without treatment.⁵ Despite attenuation in the overall meningitis-related mortality rate by 21% from 1990 to 2016, the overall burden of meningitis remains high. Besides a high mortality rate, potentially life-threatening infections, such as bacterial meningitis, may cause significantly high disability in the survivors.^{10–12} One in five survivors of bacterial meningitis may be left with permanent sequelae and prolonged neurological sequelae, such as cranial nerve palsies, hydrocephalus, seizures, hemiparesis and visual and hearing impairment. This may have a detrimental impact on the quality of life of the survivors.^{5,10} Out of the 5.6 million disability-adjusted life years globally caused by meningitis, 98% of the cases occur in low-income and middle-income countries.¹²

Before the development of immunization programmes, bacterial meningitis was predominantly caused by *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Hemophilus influenzae* type b (Hib).^{13,14} Meningitis ranks among the top 10 causes of death in children younger than 14 years in high-income countries.¹² The mortality rate associated with meningitis caused by *S. pneumoniae* and *N. meningitidis* was 30% and 7%, respectively, in

high-resourced countries.¹⁵ Post-introduction of Hib and *S. pneumoniae* vaccines, high-income nations have witnessed a significant reduction in bacterial meningitis caused by these bacteria. However, the scenario is different in low and middle-income countries (LMICs), where bacterial meningitis continues to be a major concern. Inadequate vaccine coverage or lack of availability of these vaccines in the national immunization programmes are some of the factors responsible for this menace.¹³ The detrimental impact of meningitis in terms of mortality and morbidity is more profound among children under 5 years of age, especially in settings that lack proper implementation of vaccination as per national immunization programmes for *H. influenzae* type b, *S. pneumoniae* and *N. meningitidis*.¹³ Efforts to reduce mortality associated with meningitis lags substantially compared to that for other vaccine-preventable diseases (VPDs) such as measles, tetanus and diarrheal diseases.²

Cryptococcal meningitis is predominantly observed in adults with HIV. Unlike high-income countries, despite the widespread availability of antiretroviral therapy (ART), the prevalence of cryptococcal infection remains unaltered in LMICs. The estimation of regional as well as the national burden of cryptococcal meningitis is essential to devise optimal preventive and management strategies.⁴

In India, as a result of multiple factors, such as inadequate laboratory capacity, poor reporting due to the lack of access to the healthcare system and limited disease surveillance programmes, the actual disease burden of meningitis is unknown and may be largely underestimated.¹⁶ Considering the wide variability in the prevalence and causative pathogens of bacterial meningitis across regions, a comprehensive differentiation between them is essential for optimum management.¹⁴ The accurate estimation of meningitis disease burden and its causative pathogens in Indian settings may assist policy-makers to consider the inclusion of necessary vaccines under the national immunization programme.¹³ This will also help in the uniform expansion and distribution of these vaccines in the remote areas of the country. With that outlook, a comprehensive literature search was performed to describe: (a) the disease burden of meningitis; and (b) its etiological pathogens across different regions, age groups and patients with comorbidities.

Methods

This systematic literature review was conducted per the preferred recording items for systematic reviews and meta-analysis (PRISMA).¹⁷ Publications on meningitis disease burden and the etiology of meningitis in India were considered eligible for inclusion based on the eligibility criteria.

Eligibility criteria for studies

All human studies published from 1 January 1990 to 30 September 2020 in the English language that evaluated Indian patients of all age groups, and reported the prevalence of meningitis and the etiology for meningitis were eligible for inclusion.

Exclusion criteria for studies

Non-consecutive case series, series with incomplete reporting of results, case reports, newsletters, editorials, non-Indian data, and publications before 1990 were excluded from the list. Review articles and other publications citing data from more than one study were excluded from the final review. However, those articles were used to identify individual studies that had not already been identified in the literature search.

Measurements

The primary outcome of this study was to report the prevalence of different types of meningitis; i.e. bacterial, viral, or fungal in India. The secondary outcome was to determine the etiological pathogens across different regions, age groups and patients with comorbidities in India. Comorbidity was defined as the presence of one or more additional underlying medical conditions co-occurring with the primary condition (meningitis).

Search strategy

A systematic literature search was conducted using PubMed and Google Scholar database using search terms, such as ‘meningitis AND epidemiology AND India,’ ‘meningitis AND prevalence AND India,’ ‘meningitis AND disease burden AND India,’ for identifying epidemiological studies. The literature search was further extended using search engines, such as ‘pneumococcal meningitis AND India,’ ‘*Hemophilus influenzae* AND meningitis AND India,’ ‘viral meningitis

AND India,’ ‘meningitis AND *Streptococcus pneumoniae* AND India,’ ‘meningitis AND group B *Streptococcus agalactiae* AND India,’ ‘meningitis AND *Staphylococcus aureus* AND India,’ ‘meningitis AND *Escherichia coli* AND India,’ ‘meningitis AND *Listeria monocytogenes* AND India,’ ‘meningitis AND *Neisseria meningitidis* AND India,’ to identify relevant articles. The search was performed after applying constant filters based on these additional search criteria: article types – clinical study, clinical trial, phase III, phase IV, comparative study, controlled clinical trial, evaluation study, meta-analysis, multicenter study, observational study, randomized controlled trial; language – English; publication date – 1 January 1990 to 30 September 2020; species – humans. A bibliographic search was also performed while assessing the full-text articles.

Data extraction

Literature searches were performed and retrieved publications were evaluated for eligibility by two independent reviewers in a two-phase screening process according to the predefined eligibility criteria. Data were extracted from the final list of publications that were considered relevant for this systematic literature review. The study characteristics extracted included authors’ details, year of publication, the title of the study, the place of study and type of study. Any disagreements among reviewers were resolved by discussion.

Our study did not require an ethical board approval because it did not contain human or animal trials.

Results

Literature selection

The primary literature searches in PubMed and Google Scholar yielded 706 relevant articles. Ten more articles were added after a bibliographic search. After the removal of 344 duplicate titles and abstracts, 372 articles (200 articles for epidemiology and 172 articles for meningitis etiology) were screened. Following a precise screening and review of the articles, a total of 321 studies were excluded and the remaining 51 studies were included in the systematic review. Figure 1 represents the flowchart of articles included in the analysis.

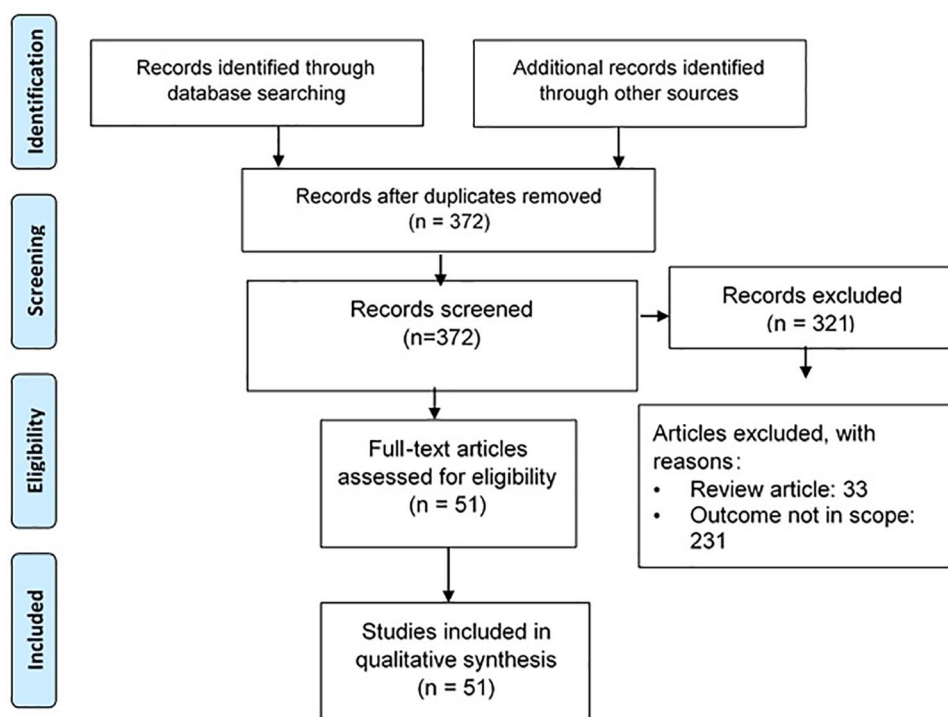


Figure 1. Flowchart for study inclusion.

Findings of the analysis

Out of the total 716 unique records screened, a total of 51 studies reported data on either disease burden or etiology or both across different regions and different age-group populations.

Epidemiology/burden of meningitis in India across different regions, age groups and in patients with comorbidities. Out of the total 51 studies included, a total of 38 studies reported the prevalence of meningitis in India. These studies included mixed patient population: (a) pyogenic meningitis; (b) meningitis in sick or hospitalized patients with tuberculosis, acute febrile encephalopathy syndrome, septicaemia or invasive pneumococcal disease (IPD); and (c) meningitis patients with comorbidities. Table 1 shows the prevalence of meningitis in individual studies. A total of 18 studies conducted across various regions of India reported data exclusively on the pediatric population.^{13,18–34} Among these, a total of seven studies were conducted in northern India,^{18–24} whereas a total of four, two and four studies were conducted in the southern region,^{13,25–27} western region^{28,29} and multiple cities/states^{30–33} of India, respectively. One study was

conducted in north-east India.³⁴ The age of the study participants ranged from one day to 14 years. Two studies reported hospital-acquired meningitis in neonates/newborns, with a prevalence of 5.41% and 10%, respectively.^{18,22} Studies conducted in multiple states demonstrated the prevalence of confirmed bacterial meningitis in the range of 0.5% (15 cases out of 2904 study participants) to 35% (78 cases out of 226 study participants).^{30–33} The prevalence of bacterial meningitis ranges from 3% (four cases out of 147 study participants) to 21.81% (484 cases out of 2219 study participants) in north India.^{18–24} This included two studies that exclusively reported tubercular meningitis in pediatric patients, with a prevalence of 7.9% (12 cases out of 151 patients with acute febrile encephalopathy syndrome) and 20.97% (13 cases out of 62 patients with tuberculosis), respectively.^{19,21} In the western and southern regions, the prevalence of meningitis ranged from 12% to 20.25%^{28,29} and 8.28% to 38%,^{13,25–27} respectively. Three studies included patients with IPD from the southern region, multiple states and north-east India, with a reported prevalence of pneumococcal meningitis of 21.81%,²⁷ 35%³³ and 61.8%,³⁴ respectively. The data for patients

Table 1. Epidemiological studies on meningitis.

Author name	Study period/ duration	Study place	Study region	Study participants	Age group	Overall prevalence	Bacterial/ fungal/ viral
Pediatric population							
1 Goel <i>et al.</i> ¹⁸	2010–2011	Delhi	North	591 neonates	0–28 days	Hospital-associated meningitis: 5.41%	Bacterial
2 Gupta <i>et al.</i> ¹⁹	NS	New Delhi	North	62 children with TB	Median age: 7.73 years (0–12 years)	Tubercular meningitis: 20.97% (13 of the 62 cases)	Bacterial
3 Kapil and Bagga ²⁰	1986–1992	Delhi	North	3025 children admitted in ICU	Median age: 32.4 months (1 day–14 years)	8.6% (261 children)	Bacterial
4 Karmakar <i>et al.</i> ²¹	2004–2005	Delhi	North	151 patients with acute febrile encephalopathy syndrome	3.21 ± 2.9 years	<ul style="list-style-type: none"> Pyogenic meningitis: 33.8% (51 patients) Tubercular meningitis: 7.9% (12 patients) 	Bacterial
5 Kumar <i>et al.</i> ²²	NS/1 year	Delhi	North	300 new-borns with sign and symptoms of sepsis	Newborns (age NR)	Prevalence of healthcare-associated meningitis: 10% (30 patients)	Bacterial
6 Saluja ²³	NS/18 months	Delhi	North	200 cases of febrile seizure	6–18 months	3%	Bacterial
7 Jhamb <i>et al.</i> ²⁴	2005–2006	Delhi	North	100 hospitalized children with group A meningococcal infection	Not mentioned	67%	Bacterial
8 Minz <i>et al.</i> ²⁵	1997–1999	Vellore	South	97 suspected meningitis cases	<5 years	18.56%	Bacterial
9 Das <i>et al.</i> ²⁶	1994–1995	Pondicherry	South	65 neonates with septicaemia	Neonates (age NR)	38% (17 neonates)	Bacterial
10 Jayaraman <i>et al.</i> ¹³	2012–2013	Chennai	South	3104 suspected meningitis	1–59 months	8.28% (257 cases)	Bacterial
11 Shah <i>et al.</i> ²⁷	January–December 2006	Bangalore	South	2219 children with pneumococcal disease	0–5 years	21.81% (484 cases)	Bacterial

(continued)

Table 1. (continued)

Author name	Study period/ duration	Study place	Study region	Study participants	Age group	Overall prevalence	Bacterial/ fungal/ viral
12 Debnath <i>et al.</i> ²⁸	NS/1-year	Pune	West	79 suspected cases of meningitis	Median age: 2.7 years (0–12 years)	20.25% (16 cases)	Bacterial
13 Jain <i>et al.</i> ²⁹	2010–2012	Pune	West	223 children with suspected TB	31 months	TB meningitis: 4.04% (9 cases)	Bacterial
14 Hazarika <i>et al.</i> ³⁰	2008–2009	Shillong	North-East	children with IPD	8.48 ± 5.09 year	Meningococcal meningitis: 61.8%	Bacterial
15 Kabra <i>et al.</i> ³¹	1990/1 year	New Delhi Calcutta Rajasthan	Multiple states	56,338 admissions (Calcutta: 3400; Jaipur: 11134; Delhi KSch: 20307; Delhi AIIMS: 3348; Calcutta: 2904; Jodhpur 5245)	1–12 years	1.5% (852 cases; range: 0.5% to 2.6%) For prevalence of 0.8% in Calcutta (28 cases out of 3400 admissions) For prevalence of 2.6% in Jaipur (287 cases out of 11134 admissions) For prevalence of 1.9% in Delhi KSch (394 cases out of 20301) For prevalence of 1.4% in Delhi AIIMS (48 cases out of 3348 admissions) For prevalence of 0.5% in Calcutta (15 cases out of 2904 admissions) For prevalence of 1.1% in Jodhpur (80 cases out of 5245 admissions)	Bacterial
16 Chauhan <i>et al.</i> ³²	NS/1 year	Shimla, Himachal Pradesh	Multiple states	250 CSF samples	1–59 months	32.4% (81 cases)	Bacterial
17 Ramchandran <i>et al.</i> ³³	2008–2010	Chennai New Delhi Vellore Lucknow	Multiple states	708 cases with abnormal CSF finding	1–23 months	12.57% (89 cases)	Bacterial

(continued)

Table 1. (continued)

Author name	Study period/ duration	Study place	Study region	Study participants	Age group	Overall prevalence	Bacterial/ fungal/ viral
18 Manoharan <i>et al.</i> ³⁴	2011–2015	New Delhi Chennai Pune Kerala Bengaluru, Karnataka Mumbai, Maharashtra Hyderabad, Telangana	Multiple states	4377 enrolled patients, 361 children with pneumococcal disease Among 361 patients with culture proven pneumococcal disease, all clinical data were known for 226 patients	<5 years	Pneumococcal meningitis: 35% (78 cases)	Bacterial
All-age patient group							
19 Mishra <i>et al.</i> ³⁵	2011–2012	Lucknow	North	235 critically ill neurological patients 76 patients with CNS infection	Median age: 37.5 (4–75 years)	<ul style="list-style-type: none"> TB meningitis: 4.7% Pyogenic meningitis: 11% Fungal meningitis: 5% 	Bacterial and fungal
20 Bhagawati <i>et al.</i> ³⁶	2009–2010	Assam	North-East	316 CSF samples	0–70 years	16.14%	Bacterial and fungal
21 Yerramilli <i>et al.</i> ³⁷	2012–2014	Hyderabad	South	147 cases of meningitis		<ul style="list-style-type: none"> Viral/aseptic meningitis: 39% Tuberculous meningitis: 28% Pyogenic meningitis: 28% Fungal meningitis: 3% (4 cases) 	Bacterial, viral, and fungal
22 Nair <i>et al.</i> ³⁸	2005–2006	New Delhi	North	380 suspected cases of meningococcal disease	<5–>45 years	8.68% (33 cases)	Bacterial
23 Verghese <i>et al.</i> ³⁹	2008–2016	Vellore, Tamil Nadu	South	830 invasive pneumococcal isolates	All age groups	20.1% (167 cases)	Bacterial
24 Srinivas <i>et al.</i> ⁴⁰	2001–2007	Bangalore	South	18,092 patients who underwent neurosurgery 415 patients with infection following a neurosurgery	NR	Post-operative meningitis: 2.2%	

(continued)

Table 1. (continued)

Author name	Study period/ duration	Study place	Study region	Study participants	Age group	Overall prevalence	Bacterial/ fungal/ viral
25	2010–2012	Karnataka	South	304 CSF samples with suspected meningitis 104 cases of confirmed meningitis	0–>60 years	Bacterial meningitis: 78.85% Fungal meningitis: 9.62% Acid-fast bacilli meningitis: 10.58%	Bacterial and fungal
Adult population							
26	1993–2008	Vellore	South	1037 patients with suspected invasive bacterial infection	>18 years	Meningitis: 34.3%	Bacterial
27	2007–2017	Vellore	South	408 adults with IPD	>18 years	Meningitis: 24.3%	Bacterial
Patients with comorbidities							
28	2011–2012	Pune, Maharashtra	West	208 HIV patients	40 years	Cryptococcal meningitis: 19%	Fungal
29	1996–2005	Pune	West	1922 samples clinically diagnosed with cryptococcosis and 475 of them were HIV positive	NR	Cryptococcal meningitis in HIV patients: 53.1% (252/475)	Fungal
30	1992–2001	Indore	West	483 AIDs cases	NR	Fungal meningitis: 3.1% (15 cases) • Cryptococcal meningitis: 2.48% (12 cases) • <i>Candida</i> meningitis: 0.62% (3 cases)	Fungal
31	NS	Pune	West	1527 HIV-positive subjects 457 HIV-positive subjects with neurological complications		Prevalence of meningitis: 17.88% • Cryptococcal meningitis: 67.44% • Tubercular meningitis: 18.60%	Fungal and bacterial

(continued)

Table 1. (continued)

Author name	Study period/ duration	Study place	Study region	Study participants	Age group	Overall prevalence	Bacterial/ fungal/ viral
32 Wadhwa <i>et al.</i> ⁴⁸	2005–2006	New Delhi	North	17 HIV-positive patients with CNS involvement	NR	<ul style="list-style-type: none"> • Cryptococcal meningitis: 29.4% • Tubercular meningitis: 52.9% 	Fungal and bacterial
33 Mathur and Devesh ⁴⁹	2006–2011	Jaipur, Rajasthan	North	Total study patients: 40 20 HIV patients with neurological complications	25–45 years	<ul style="list-style-type: none"> • Cryptococcal meningitis: 20% • Tubercular meningitis: 20% • Pyogenic meningitis: 5% • <i>Candida</i> meningitis: 5% 	Fungal and Bacterial
34 Lakshmi <i>et al.</i> ⁵⁰	1997–2005	Hyderabad	South	359 CSF samples of HIV-reactive cases suspected for cryptococcal meningitis	NR	Cryptococcal meningitis: 2.09%	Fungal
35 Kumaraswamy <i>et al.</i> ⁵¹	1996–2001	Chennai	South	594 patients with HIV	Median age: 32 years (18–72 years)	Cryptococcal meningitis: 4.7%	Fungal
36 Teja <i>et al.</i> ⁵²	NS/11 years	Hyderabad	South	1606 hospitalized patients with HIV and neurological manifestation	36 years	Meningitis: 39.4% <ul style="list-style-type: none"> • Tubercular: 25.06% • Cryptococcal: 10.95% • Pyogenic: 1.95% 	Bacterial and fungal
37 Indira <i>et al.</i> ⁵³	2011–2012	Chennai, Tamil Nadu Mangalore, Karnataka	South	37 PLHIV-DM 37 PLHIV	47 years	Cryptococcal meningitis: <ul style="list-style-type: none"> • PLHIV-DM: 19% • PLHIV: 16% 	Fungal
38 Sakhuja <i>et al.</i> ⁵⁴	1980–1999	Chandigarh	North	79 patients with CNS infection following renal transplantation	33.16 ± 3.4 years	<ul style="list-style-type: none"> • Cryptococcal meningitis: 15.19% • Bacterial meningitis: 8.86% 	Fungal and bacterial

CNS, central nervous system; CSF, cerebrospinal fluid; DM, diabetes mellitus; IPD, invasive pneumococcal disease; NR, not reported; NS, not specified; PLHIV-DM, people living with HIV and DM; TB, tuberculosis.

belonging to all age groups were reviewed from seven studies.^{35–41} Unlike the majority of the studies that reported the predominance of bacterial meningitis, Yerramilli *et al.*,³⁷ in an observational study, reported a high prevalence of aseptic/viral meningitis (39%). The majority of the studies reported bacterial meningitis. In a prospective surveillance study, conducted in 1037 adult subjects with a suspected invasive bacterial infection, 34.3% of the patients were diagnosed with meningitis.⁴² In a prospective, laboratory-based study, comprising 408 adults with IPD, the prevalence of meningitis was reported to be 24.3%.⁴³

The systematic review included a total of 10 studies that demonstrated the prevalence of meningitis in AIDS/HIV-positive patients.^{44–53} The prevalence of meningitis, especially cryptococcal meningitis is high in this patient population, ranging from 2.09% to 53.1%. One of these studies included HIV patients with diabetes mellitus (DM) and the prevalence of cryptococcal meningitis in this patient population was 19%, which was higher than patients with HIV but no DM (16%).⁵³ A total of five studies reported mixed-pathogen meningitis in patients with comorbidities.^{47–49,52,54} One retrospective study included 792 renal allograft recipients with neurological complications; 10% (79 patients) of them had central nervous system (CNS) complications, and among them 15.19% of the patients (12 patients) were diagnosed with cryptococcal meningitis.⁵⁴

Etiology

Out of the total 51 studies included, 21 studies reported data on the etiology of meningitis. These studies included mixed patient populations: (a) pyogenic meningitis; and (b) meningitis in sick patients with fever, tuberculosis hydrocephalus or respiratory compromise. Of the total 21 studies,^{13,28,32,33,36,40,41,46,55–67} 12 studies reported data on the pediatric population,^{13,28,32,33,55–62} whereas eight publications reported data on patients belonging to all age groups including neonates, older children, adolescents and adults.^{36,40,41,63–67} Table 2 highlights all the studies that reported the etiology of meningitis. The commonest cause of meningitis in these studies was *S. pneumoniae*, across different regions of India, with a frequency (in percentage) ranging from 12% to 82.9% in children and 4% to 61.8% in patients of all age groups. Out of the 12 studies in the pediatric population, a total of eight studies reported *S. pneumoniae* as the causative

pathogen.^{13,32,33,55–57,59,61} The second commonest causative pathogen in the pediatric population was *H. influenzae*, predominantly type b, reported in nine studies,^{13,32,33,55–59,61} with a frequency ranging from 4.5% to 70%. In one study, conducted in 25 children with aseptic meningitis, enterovirus was found to be the causative pathogen in 56% of the cases.⁶⁰ One of the studies found group B *Streptococcus* as a causative pathogen in more than 49% of the children aged between one and 59 months.³² In a retrospective study in 100 children with group A meningococcal infection, 67% of children had meningococcal meningitis.²⁴

In studies reporting data on patients belonging to all age groups, apart from *S. pneumoniae*, *Staphylococcus aureus* (seven studies; frequency range 1.8–41.38%),^{36,41,63–67} *N. meningitidis* (five studies; frequency range 1–27.59%),^{36,41,63,65,67} *Klebsiella pneumoniae* (five studies; frequency range 5.5–20.7%),^{36,40,41,63,64,66} *Escherichia coli* (five studies; frequency range 4.76–27.08%),^{36,40,41,64,66} *H. influenzae* (four studies; frequency range 1.8–19.4%),^{41,63,66,67} etc. were the other causative pathogens. Table 3 lists all the major etiological bacteria responsible for causing meningitis.

Discussion

This systematic literature review provides an overview of the meningitis disease burden (1990–2020) and the etiology of meningitis across different age groups and regions in India. To our knowledge, this is the first systematic review of meningitis in India that focused on all forms of meningitis instead of limiting only to bacterial, viral or fungal meningitis. For this review, we considered published results from studies that were randomized controlled, cross-sectional, prospective cohort or observational. Non-consecutive case series, series with incomplete reporting of results, case reports, newsletters, editorials and non-Indian data were excluded in the systematic literature review.

Owing to the immense heterogeneity of the articles and study design, analyzing the true prevalence of meningitis was highly challenging. A total of 38 studies reported the prevalence of meningitis and 21 studies reported data on the etiology of meningitis in India. These studies included mixed patient populations: (a) pyogenic meningitis; (b) meningitis in sick or hospitalized patients with tuberculosis, acute febrile encephalopathy syndrome,

Table 2. Etiological factors/pathogens responsible for meningitis.

Author	Study period/ duration	Region	Patient age	No. of patients with meningitis	<i>S. pneumoniae</i>	<i>H. influenzae</i>	<i>N. meningitidis</i>	<i>S. aureus</i>	<i>GBS</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>Pseudomonas</i>	Others
Pediatric population													
1	Chinchankar <i>et al.</i> ⁵⁵	West	1 month– 5 years	54 patients with ABM	39%	26%	1.85%					33.15%	
2	Debnath <i>et al.</i> ²⁸	West	Median age: 2.7 years	16 suspected cases of meningitis				6.25%	31.20%				<ul style="list-style-type: none"> • CoNS: 12.5% • Nonfermenters: 25% • <i>Streptococcus</i> <i>pyogenes</i>: 18.8% • <i>Citrobacter freundii</i>: 6.25%
3	Vashishth <i>et al.</i> ⁵⁶	North	41.5 (±26.9) months	67 patients with ABM	25.37%	4.50%	3%	3.30%	3.30%	7.50%	3.30%	3.30%	
4	Chauhan <i>et al.</i> ³²	North	1–59 months	81 ABM cases	23.40%	6.10%	1.20%	7.40%	49.30%	6.10%	6.10%		
5	Sankar <i>et al.</i> ⁵⁷	North	2 months– 12 years	24 children with ABM	41.67%	29.17%		20.83%				8.33%	
6	Pulickal <i>et al.</i> ⁵⁸	South	NR	80 children with ABM		5%		10%			7.50%		CoNS: 9%
7	Sahai <i>et al.</i> ⁵⁹	South	1 month– 12 years	100 children with ABM	12%	17%							<i>Salmonella</i> : 6%
8	Satish <i>et al.</i> ⁶⁰	South	0–12 years	25 children with aseptic meningitis									Enterovirus: 56%
9	Shameem <i>et al.</i> ⁶¹	South	1 month– 3 years	199 cases of meningitis	44.70%	25.60%	6.00%	5.50%	9.50%	3%	4%	1.50%	
10	Jayaraman <i>et al.</i> ¹³	South	1–59 months	257 cases of meningitis	82.90%	14.40%	2.70%						
11	Devi <i>et al.</i> ⁶²	East		67 cases of neonatal meningitis			3%	1.50%	12%	9%			<ul style="list-style-type: none"> • <i>baumannii</i>: 18% • <i>Enterococcus</i> spp: 15% • CoNS: 12% • <i>Cronobacter</i> <i>sakazakii</i>: 1.5% • <i>Roseomonas</i> <i>cervicalis</i>: 1.5%

(continued)

Table 2. (continued)

Author	Study period/ duration	Region	Patient age	No. of patients with meningitis	S. pneumoniae	H. influenzae	N. meningitidis	S. aureus	GBS	E. coli	K. pneumoniae	Pseudomonas	Others
12 Ramchandran et al. ³³	2008–2010	Multiple states	1–23 months	89 cases of bacterial meningitis	13%	70%	3.37%*	8%	8%		1.12%	1.12%	<ul style="list-style-type: none"> Enterobacter spp.: 2.25% Citrobacter freundii: 1.12% Group D Salmonella: 1.12%
All age groups													
13 Mirdha et al. ⁴³	1988–1989	North	1 month–60 years	18 cases of bacterial meningitis	16.67%	11.11%	22.22%	11.11%			5.50%		<ul style="list-style-type: none"> Staph. Albus: 11.11% Moraxella spp: 5.5% Propionibacterium acnes: 5.5%
14 Raza et al. ⁴⁴	2015–2017	North	NR	400 CSF samples of suspected HAM	6.25%*			8.33%		27.08%	10.42%	8.33%	<ul style="list-style-type: none"> baumannii: 25% Enterococcus faecium: 6.25% CoNS: 4.16%
15 Mital et al. ⁴⁵	NS	North	15–70 years	50 cases of pyogenic meningitis	31.03%		27.59%	41.38%					
16 Pandit et al. ⁴⁶	2002/10 months	South	2–65 years	21 positive CSF samples for bacterial meningitis	9.52%	19.04%		4.76%		4.76%	4.76%	4.76%	<ul style="list-style-type: none"> Mycobacterium tuberculosis: 33.33% Listeria monocytogenes: 4.76%
17 Srinivas et al. ⁴⁰	2001–2007	South	NR	415 cases of post-operative meningitis				8.67%		12.53%	15.42%		<ul style="list-style-type: none"> NFGNB: 26.98% CoNS + S. epidermidis: 8.19% MSSA: 6.75% MRSA: 6.50% MR-CoNS: 3.86% Enterococcus spp.: 2.17% Others: 2.65%

(continued)

Table 2. (continued)

Author	Study period/ duration	Region	Patient age	No. of patients with meningitis	<i>S. pneumoniae</i>	<i>H. influenzae</i>	<i>N. meningitidis</i>	<i>S. aureus</i>	<i>GBS</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>Pseudomonas</i>	Others
18 Mani <i>et al.</i> ⁶⁷	1996–2005	South	NR	284 cases of meningitis	61.80%	1.80%	1%	1.80%					<ul style="list-style-type: none"> Gram-negative bacilli: 4.9% <i>Streptococcus</i> spp.: 2.3%
19 Gangane and Doddamani ⁴¹	2010–2012	South	NR	308 CSF samples were collected from clinically diagnosed cases of bacterial meningitis.	31.70%	3.60%	2.40%	7.30%		12.10%	20.7%	9.70%	Bacterial sample (n = 82) <i>Proteus</i> : 6.09% <i>Acinetobacter</i> : 2.4% <i>Enterococci</i> : 2.4% <i>Citrobacter freundii</i> : 1.2% Fungal sample (n = 10) <i>Cryptococcus</i> : 70% <i>Candida albicans</i> : 30%
20 Bhagawati <i>et al.</i> ³⁶	2009–2010	East	Newborn to >45 years	51 cases of meningitis	4%		4%	29.41%		11.76%	15.70%	5.88%	<ul style="list-style-type: none"> <i>Acinetobacter</i> spp.: 7.84% <i>Cryptococcus neoformans</i>: 7.84% <i>Candida albicans</i>: 5.88% <i>Listeria</i> spp.: 4% <i>Citrobacter</i> spp.: 4%
Patients with comorbidities													
21 Jaiswal <i>et al.</i> ⁴⁶	1992–2001	South	NR	15 AIDS patients with meningitis									<ul style="list-style-type: none"> <i>Cryptococcus</i> spp.: 80% (12) <i>Candida</i>: 20% (3)

*Two from groups A, C, Y or W135, one isolate that was either *Neisseria meningitidis* group B or *Escherichia coli* K1;

[†]Community-acquired cases. Others are hospital-acquired meningitis cases; NS: Not specified.

A. baumannii, *Acinetobacter baumannii*; ABM, acute bacterial meningitis; CoNS, coagulase negative *Staphylococci*; *E. coli*, *Escherichia coli*; GBS, Group B *Streptococcus*; *H. influenzae*, *Hemophilus influenzae*; HAM, hospital-acquired meningitis; *K. pneumoniae*, *Klebsiella pneumoniae*; MR-CoNS, Methicillin-resistant coagulase negative *Staphylococci*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; NFGNB, non-lactose fermenting Gram-negative bacillus; NR, not reported; *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*.

Table 3. Major bacteria responsible for causing meningitis in the included studies.

<i>S. pneumoniae</i>					
Author	Study period/ duration	Region	Study details	Age group	Frequency
Chinchankar <i>et al.</i> ⁵⁵	NS/2 years	West	54 patients with ABM. Chief presentation was high fever, refusal of feeds, altered sensorium and seizures. <ul style="list-style-type: none"> • 26% of patients had meningeal signs. • 39% patients developed acute neurological complications during the hospital course. 	1 month–5 years	39%
Vashishtha <i>et al.</i> ⁵⁶	2009–2010	North	67 patients with ABM Fever (91%), altered sensorium (62.7%), vomiting (50.8%), seizures (47.8%) and refusal of feeds (23.9%) were the most presenting features.	41.5 (±26.9) months	25.37%
Chauhan <i>et al.</i> ³²	NS/1 year	North	81 ABM cases. Observed complications included seizures (23.4%), increased intracranial pressure (20.9%), infarct on imaging (4.9%), coma (4.9%), and respiratory compromise leading to ventilator support (3.7%)	1–59 months	23.40%
Sankar <i>et al.</i> ⁵⁷	2002–2003	North	24 children with ABM	2 months–12 years	41.67%
Sahai <i>et al.</i> ⁵⁹	1994–1996	South	100 children with ABM	1 month–12 years	12%
Shameem <i>et al.</i> ⁶¹	NS/48 months	South	199 cases of meningitis	1 month–3 years	44.70%
Jayaraman <i>et al.</i> ¹³	2012–2013	South	257 cases of meningitis Male: female ratio in confirmed meningitis patients was 1.3:1	1–59 months	82.90%
Ramchandran <i>et al.</i> ³³	2008–2010	Multiple states	89 cases of bacterial meningitis	1–23 months	13%
Mirdha <i>et al.</i> ⁶³	1988–1989	North	18 cases of bacterial meningitis	1 month–60 years	16.67%
Raza <i>et al.</i> ⁶⁴	2015–2017	North	400 CSF samples of suspected HAM	NR	6.25% [^]
Mital <i>et al.</i> ⁶⁵	NS	North	50 cases of pyogenic meningitis, 29 culture positive cases of bacterial meningitis Male: female ratio of 5:1	15–70 years	31.03%
Pandit <i>et al.</i> ⁶⁶	2002/10 months	South	21 positive CSF samples for bacterial meningitis	2–65 years	9.52%
Mani <i>et al.</i> ⁶⁷	1996–2005	South	CSF samples from 385 clinically suspected cases of pyogenic meningitis were analysed. Proof of infective agent was studied in 284 cases of meningitis	NR	61.80%

(continued)

Table 3. (continued)

<i>S. pneumoniae</i>					
Author	Study period/ duration	Region	Study details	Age group	Frequency
Gangane and Doddamani ⁴¹	2010–2012	South	308 CSF samples were collected from clinically diagnosed cases of bacterial meningitis. Out of 308 samples 92 samples were culture positive (30.6%). Out of which 82 were bacterial culture, 10 fungal cultures and 11 smears were AFB positive.	NR	31.70%
Bhagawati <i>et al.</i> ³⁶	2009–2010	East	51 cases of meningitis	Newborn to >45 years	4%
<i>H. influenzae</i>					
Chinchankar <i>et al.</i> ⁵⁵	NS/2 years	West	54 patients with ABM. Chief presentation was high fever, refusal of feeds, altered sensorium and seizures. <ul style="list-style-type: none"> • 26% of patients had meningeal signs. • 39% patients developed acute neurological complications during the hospital course. 	1 month–5 years	26% (Hib)
Vashishtha ⁵⁶	2009–2010	North	67 patients with ABM Fever (91%), altered sensorium (62.7%), vomiting (50.8%), seizures (47.8%) and refusal of feeds (23.9%) were the most presenting features.	41.5 (±26.9) months	4.50% (Hib)
Chauhan <i>et al.</i> ³²	NS/1 year	North	81 ABM cases. Observed complications included seizures (23.4%), increased intracranial pressure (20.9%), infarct on imaging (4.9%), coma (4.9%), and respiratory compromise leading to ventilator support (3.7%)	1–59 months	6.10% (Hib)
Sankar <i>et al.</i> ⁵⁷	2002–2003	North	24 children with ABM	2 months–12 years	29.17% (Hib)
Putlickal <i>et al.</i> ⁵⁸	NS/18 months	South	80 children with ABM	NR	5% (Hib)
Sahai <i>et al.</i> ⁵⁹	1994–1996	South	100 children with ABM	1 month–12 years	17% (Hib)
Shameem <i>et al.</i> ⁶¹	NS/48 months	South	199 cases of meningitis	1 month–3 years	25.60% (Hib)
Jayaraman <i>et al.</i> ¹³	2012–2013	South	257 cases of meningitis Male: female ratio in confirmed meningitis patients was 1.3:1	1–59 months	14.40% (Hib)
Ramchandran <i>et al.</i> ³³	2008–2010	Multiple states	89 cases of bacterial meningitis	1–23 months	70% (Hib)
Mirdha <i>et al.</i> ⁶³	1988–1989	North	18 cases of bacterial meningitis	1 month–60 years	11.11%
Pandit <i>et al.</i> ⁶⁶	2002/10 months	South	21 positive CSF samples for bacterial meningitis	2–65 years	19.04%

(continued)

Table 3. (continued)

<i>S. pneumoniae</i>									
Author	Study period/ duration	Region	Study details	Age group	Frequency				
Mani <i>et al.</i> ⁶⁷	1996–2005	South	CSF samples from 385 clinically suspected cases of pyogenic meningitis were analysed. Proof of infective agent was studied in 284 cases of meningitis	NR	1.80%				
Gangane and Doddamani ⁴¹	2010–2012	South	308 CSF samples were collected from clinically diagnosed cases of bacterial meningitis. Out of 308 samples 92 samples were culture positive (30.6%). Out of which 82 were bacterial culture, 10 fungal cultures and 11 smears were AFB positive.	NR	3.60%				
<i>K. pneumoniae</i>									
Debnath <i>et al.</i> ²⁸	NS/21 years	West	79 suspected cases of meningitis with majority of cases (74.7%) under-five. 16 suspected cases of meningitis. Male to female ratio was 1.82:1	Median age: 2.7 years	31.2%				
Vashishtha <i>et al.</i> ⁵⁶	2009–2010	North	67 patients with ABM Fever (91%), altered sensorium (62.7%), vomiting (50.8%), seizures (47.8%) and refusal of feeds (23.9%) were the most presenting features.	41.5 (±26.9) months	3.30%				
Chauhan <i>et al.</i> ³²	NS/1 year	North	81 ABM cases. Observed complications included seizures (23.4%), increased intracranial pressure (20.9%), infarct on imaging (4.9%), coma (4.9%), and respiratory compromise leading to ventilator support (3.7%)	1–59 months	6.10%				
Shameem <i>et al.</i> ⁶¹	NS/48 months	South	199 cases of meningitis	1 month–3 years	4%				
Devi <i>et al.</i> ⁶²	2013–2015	East	67 cases of neonatal meningitis		12%				
Mirdha <i>et al.</i> ⁶³	1988–1989	North	18 cases of bacterial meningitis	1 month–60 years	5.50%				
Raza <i>et al.</i> ⁶⁴	2015–2017	North	400 CSF samples of suspected HAM	NR	10.42%				
Srinivas <i>et al.</i> ⁴⁰	2001–2007	South	415 cases of post-operative meningitis (underwent neurosurgical procedures). The overall incidence of meningitis was 2.2%. The incidence of meningitis was high (7.7%) in patients who had a pre-existing infection like post-pyogenic meningitis or tuberculosis hydrocephalus.	NR	12.53%				
Gangane and Doddamani ⁴¹	2010–2012	South	308 CSF samples were collected from clinically diagnosed cases of bacterial meningitis. Out of 308 samples 92 samples were culture positive (30.6%). Out of which 82 were bacterial culture, 10 fungal cultures and 11 smears were AFB positive.	NR	20.7%				

(continued)

Table 3. (continued)

<i>S. pneumoniae</i>					
Author	Study period/ duration	Region	Study details	Age group	Frequency
Bhagawati <i>et al.</i> ³⁶	2009–2010	East	51 cases of meningitis	Newborn to >45 years	15.70%
<i>P. aeruginosa</i>					
Vashishtha <i>et al.</i> ⁵⁶	2009–2010	North	67 patients with ABM Fever (91%), altered sensorium (62.7%), vomiting (50.8%), seizures (47.8%) and refusal of feeds (23.9%) were the most presenting features.	41.5 (±26.9) months	3.30%
Pulickal <i>et al.</i> ⁵⁸	NS/18 months	South	80 children with ABM	NR	7.50%
Shameem <i>et al.</i> ⁶¹	NS/48 months	South	199 cases of meningitis	1 month–3 years	1.50%
Devi <i>et al.</i> ⁶²	2013–2015	East	67 cases of neonatal meningitis		9%
Ramchandran <i>et al.</i> ³³	2008–2010	Multiple states	89 cases of bacterial meningitis	1–23 months	1.12%
Raza <i>et al.</i> ⁶⁴	2015–2017	North	400 CSF samples of suspected HAM	NR	8.33%
Pandit <i>et al.</i> ⁶⁶	2002/10 months	South	21 positive CSF samples for bacterial meningitis	2–65 years	4.76%
Srinivas ⁴⁰	2001–2007	South	415 cases of post-operative meningitis (underwent neurosurgical procedures). The overall incidence of meningitis was 2.2%. The incidence of meningitis was high (7.7%) in patients who had a pre-existing infection like post-pyogenic meningitis or tuberculosis hydrocephalus.	NR	15.42%
Gangane and Doddamani ⁴¹	2010–2012	South	308 CSF samples were collected from clinically diagnosed cases of bacterial meningitis. Out of 308 samples 92 samples were culture positive (30.6%). Out of which 82 were bacterial culture, 10 fungal cultures and 11 smears were AFB positive.	NR	9.70%
Bhagawati <i>et al.</i> ³⁶	2009–2010	East	51 cases of meningitis	Newborn to >45 years	5.88%
<i>S. aureus</i>					
Vashishtha <i>et al.</i> ⁵⁶	2009–2010	North	67 patients with ABM Fever (91%), altered sensorium (62.7%), vomiting (50.8%), seizures (47.8%) and refusal of feeds (23.9%) were the most presenting features.	41.5 (±26.9) months	3.30%

(continued)

Table 3. (continued)

<i>S. pneumoniae</i>					
Author	Study period/ duration	Region	Study details	Age group	Frequency
Chauhan <i>et al.</i> ³²	NS/1 year	North	81 ABM cases. Observed complications included seizures (23.4%), increased intracranial pressure (20.9%), infarct on imaging (4.9%), coma (4.9%), and respiratory compromise leading to ventilator support (3.7%)	1–59 months	7.40%
Sankar <i>et al.</i> ⁵⁷	2002–2003	North	24 children with ABM	2 months–12 years	20.83%
Pulickal <i>et al.</i> ⁵⁸	NS/18 months	South	80 children with ABM	NR	10%
Shameem <i>et al.</i> ⁶¹	NS/48 months	South	199 cases of meningitis	1 month–3 years	5.50%
Mirdha <i>et al.</i> ⁶³	1988–1989	North	18 cases of bacterial meningitis	1 month–60 years	11.11%
Raza <i>et al.</i> ⁶⁴	2015–2017	North	400 CSF samples of suspected HAM	NR	8.33%
Mital <i>et al.</i> ⁶⁵	NS	North	50 cases of pyogenic meningitis, 29 culture positive cases of bacterial meningitis Male: female ratio of 5:1	15–70 years	41.38%
Pandit <i>et al.</i> ⁶⁶	2002/10 months	South	21 positive CSF samples for bacterial meningitis	2–65 years	4.76%
Mani <i>et al.</i> ⁶⁷	1996–2005	South	CSF samples from 385 clinically suspected cases of pyogenic meningitis were analysed. Proof of infective agent was studied in 284 cases of meningitis	NR	1.80%
Gangane and Doddamani ⁴¹	2010–2012	South	308 CSF samples were collected from clinically diagnosed cases of bacterial meningitis. Out of 308 samples 92 samples were culture positive (30.6%). Out of which 82 were bacterial culture, 10 fungal cultures and 11 smears were AFB positive.	NR	7.30%
Bhagawati <i>et al.</i> ³⁶	2009–2010	East	51 cases of meningitis	Newborn to >45 years	29.41%
<i>E. coli</i>					
Debnath <i>et al.</i> ²⁸	NS/21 years	West	79 suspected cases of meningitis with majority of cases (74.7%) under-five. 16 suspected cases of meningitis. Male to female ratio was 1.82:1	Median age: 2.7 years	6.25%

(continued)

Table 3. (continued)

<i>S. pneumoniae</i>						
Author	Study period/ duration	Region	Study details	Age group	Frequency	
Vashishtha <i>et al.</i> ⁵⁶	2009–2010	North	67 patients with ABM Fever (91%), altered sensorium (62.7%), vomiting (50.8%), seizures (47.8%) and refusal of feeds (23.9%) were the most presenting features.	41.5 (±26.9) months	7.50%	
Chauhan <i>et al.</i> ³²	NS/1 year	North	81 ABM cases. Observed complications included seizures (23.4%), increased intracranial pressure (20.9%), infarct on imaging (4.9%), coma (4.9%), and respiratory compromise leading to ventilator support (3.7%)	1–59 months	6.10%	
Shameem <i>et al.</i> ⁶¹	NS/48 months	South	199 cases of meningitis	1 month–3 years	3%	
Devi <i>et al.</i> ⁶²	2013–2015	East	67 cases of neonatal meningitis		1.50%	
Raza <i>et al.</i> ⁶⁴	2015–2017	North	400 CSF samples of suspected HAM	NR	27.08%	
Pandit <i>et al.</i> ⁶⁶	2002/10 months	South	21 positive CSF samples for bacterial meningitis	2–65 years	4.76%	
Srinivas <i>et al.</i> ⁴⁰	2001–2007	South	415 cases of post-operative meningitis (underwent neurosurgical procedures). The overall incidence of meningitis was 2.2%. The incidence of meningitis was high (7.7%) in patients who had a pre-existing infection like post-pyogenic meningitis or tuberculosis hydrocephalus.	NR	8.67%	
Gangane and Doddamani ⁴¹	2010–2012	South	308 CSF samples were collected from clinically diagnosed cases of bacterial meningitis. Out of 308 samples 92 samples were culture positive (30.6%). Out of which 82 were bacterial culture, 10 fungal cultures and 11 smears were AFB positive.	NR	12.10%	
Bhagawati <i>et al.</i> ³⁶	2009–2010	East	51 cases of meningitis	Newborn to >45 years	11.76%	
<i>N. meningitidis</i>						
Chinchankar <i>et al.</i> ⁵⁵	NS/2 years	West	54 patients with ABM. Chief presentation was high fever, refusal of feeds, altered sensorium and seizures. <ul style="list-style-type: none"> • 26% of patients had meningeal signs. • 39% patients developed acute neurological complications during the hospital course. 	1 month–5 years	1.85%	

(continued)

Table 3. (continued)

<i>S. pneumoniae</i>					
Author	Study period/ duration	Region	Study details	Age group	Frequency
Vashishtha <i>et al.</i> ⁵⁶	2009–2010	North	67 patients with ABM Fever (91%), altered sensorium (62.7%), vomiting (50.8%), seizures (47.8%) and refusal of feeds (23.9%) were the most presenting features.	41.5 (\pm 26.9) months	3%
Chauhan <i>et al.</i> ³²	NS/1 year	North	81 ABM cases. Observed complications included seizures (23.4%), increased intracranial pressure (20.9%), infarct on imaging (4.9%), coma (4.9%), and respiratory compromise leading to ventilator support (3.7%)	1–59 months	1.20%
Shameem <i>et al.</i> ⁶¹	NS/48 months	South	199 cases of meningitis	1 month–3 years	6.00%
Jayaraman <i>et al.</i> ¹³	2012–2013	South	257 cases of meningitis Male: female ratio in confirmed meningitis patients was 1.3:1	1–59 months	2.70%
Devi <i>et al.</i> ⁶²	2013–2015	East	67 cases of neonatal meningitis		2.70%
Ramchandran <i>et al.</i> ³³	2008–2010	Multiple states	89 cases of bacterial meningitis	1–23 months	3%*
Mirdha <i>et al.</i> ⁶³	1988–1989	North	18 cases of bacterial meningitis	1 month–60 years	22.22%
Mital <i>et al.</i> ⁶⁵	NS	North	50 cases of pyogenic meningitis, 29 culture positive cases of bacterial meningitis Male: female ratio of 5:1	15–70 years	27.59%
Mani <i>et al.</i> ⁶⁷	1996–2005	South	CSF samples from 385 clinically suspected cases of pyrogenic meningitis were analysed. Proof of infective agent was studied in 284 cases of meningitis	NR	1%
Gangane and Doddamani ⁴¹	2010–2012	South	308 CSF samples were collected from clinically diagnosed cases of bacterial meningitis. Out of 308 samples 92 samples were culture positive (30.6%). Out of which 82 were bacterial culture, 10 fungal cultures and 11 smears were AFB positive.	NR	2.40%
Bhagawati <i>et al.</i> ³⁶	2009–2010	East	51 cases of meningitis	Newborn to >45 years	4%

*Community-acquired cases.

⁴¹Two from groups A, C, Y or W135, one isolate that was either *Neisseria meningitidis* group B or *Escherichia coli* K1.
 ABM, acute bacterial meningitis; *E. coli*, *Escherichia coli*; NR, not reported; HAM, hospital-acquired meningitis; CSF, cerebrospinal fluid; *H. influenzae*, *Hemophilus influenzae*; Hib, *Hemophilus influenzae* type b; NS, not specified; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*; *K. pneumoniae*, *Klebsiella pneumoniae*.

septicaemia, invasive pneumococcal disease or respiratory compromise; and (c) meningitis patients with comorbidities. In the current review, the prevalence of confirmed bacterial meningitis in the pediatric population suspected of meningitis ranged between 3% and 61.8%, whereas in studies reporting patients of all age groups, the prevalence ranged between 8.68% and 78.85%. This sheds light on a crucial aspect that meningitis is not a disease confined to children and can equally affect the adult population.

This systematic literature review demonstrated that *S. pneumoniae* is the predominant pathogen that causes bacterial meningitis in the pediatric population as well as in patients belonging to all age groups across different regions of India. *H. influenzae* is the second major pathogen that causes meningitis in the pediatric population. Our report on the predominance of *S. pneumoniae* in the pediatric population is in concordance with global systematic review and meta-analysis data that demonstrated *S. pneumoniae* as the most predominant pathogen responsible for 25.1–41.2% of all bacterial meningitis cases.¹⁴ A systematic review comprising 23 studies involving 36,714 South-East Asian children demonstrated *S. pneumoniae* as the predominant pathogen for causing invasive bacterial disease including meningitis, with a frequency of 12.8% and 28% in population-based and retrospective hospital-based studies, respectively.⁶⁸ Another systematic review and meta-analysis, comprising 21 studies, reported *S. pneumoniae* as the predominant causative pathogen for meningitis in adults and children, responsible for causing 25% of the total bacterial meningitis cases.⁶⁹

Unlike global meta-analyses where *N. meningitidis* was found to be the second most prevalent pathogen responsible for bacterial meningitis,¹⁴ in the current systematic review analysis, it was observed that *N. meningitidis* is the seventh predominant pathogen that causes bacterial meningitis in India. In developed countries, meningococcal meningitis is one of the leading causes of bacterial meningitis.⁷⁰ Out of 13 serogroups of meningococci, five serogroups (A, B, C, W135 and Y) are mostly responsible for invasive diseases.^{70,71} While in Europe, including England, and the US the predominance of serogroup B and serogroup Y, respectively, was observed, in parts of Asia, including India, the predominance of meningococcal A serogroup was observed.⁷¹ However, immunization targeting multiple serogroups may

be the optimum strategy to confer protection against this disease.⁷⁰

In this current literature review, viral meningitis was reported in only two studies, with a prevalence of 39% in one study³⁷ and 56% in a study on children suspected of aseptic meningitis.⁶⁰ In the pediatric study, most of the affected children were boys. A similar trend was observed in a meta-analysis reporting nation-wide data from five countries.⁷² A wide range of viruses are responsible for the occurrence of meningitis, yet there are limited treatment options, which limits its effective management. Intravenous acyclovir is widely used for the treatment of viral meningitis due to its associated benefits, such as the low risk of complications and mortality rate.⁷³ No vaccination is available for viral meningitis (except treatment for meningitis caused by the herpes virus).⁷⁴ Extensive research is warranted in this field to reduce the burden of viral meningitis.

The current literature review has demonstrated the high prevalence of fungal meningitis in the adult patient population ranging between 3% and 9.62%. Cryptococcal meningitis was predominant in patients with HIV/AIDS, with a prevalence ranging between 2.09% and 53.1%. According to the Joint United Nations Program on AIDS/HIV (UNAIDS) 2014 country-level estimates of the global incidence and cases of HIV infection data, the annual global burden of cryptococcal meningitis in HIV-positive patients was 223,100 [95% confidence interval (CI) 150,600–282,400] with 73% of cases reported from sub-Saharan Africa, followed by 19% of total global cases from Asia.⁴ Despite being responsible for 15% of AIDS-related global mortality, cryptococcal meningitis remains a neglected condition. Cryptococcal meningitis may cause the failure of HIV treatment strategies.⁴ However, the adoption of available preventive strategies may confer survival benefits and aid in attenuating the potentially fatal CNS infection in HIV patients.^{4,75} Rapid and accurate diagnoses is also essential to initiate an appropriate therapy.⁷⁵ Robust screening of cryptococcal antigenemia along with pre-emptive fluconazole therapy needs to be an integral part of the routine HIV care package.⁴

As *S. pneumoniae* is the predominant pathogen responsible for bacterial meningitis globally as well as in India; we would like to emphasize the

burden of pneumococcal meningitis and the required preventive action in India. Bacterial meningitis continues to be a significant cause of morbidity and mortality.^{9,76} *S. pneumoniae* and *N. meningitidis* are the two predominant pathogens responsible in these cases, with the former being accountable for two-thirds of cases in Europe and the US. Globally, bacterial meningitis continues to be a significant cause of morbidity and mortality.^{9,76} *S. pneumoniae* and *N. meningitidis* are the two predominant pathogens responsible in these cases, with the former being accountable for two-thirds of cases in Europe and the US.⁷⁷

In the past two decades, post-implementation of vaccination strategies, an enormous change in the epidemiology of bacterial meningitis has been observed in the US. Owing to the administration of routine *H. influenzae* vaccines, a massive eradication of Hib-caused meningitis was evident among infants and children.^{78,79} Post-implementation of pneumococcal serotype vaccine, a similar declining trend was witnessed in terms of the incidence of pneumococcal meningitis among the pediatric population in the US.⁸⁰ However, in the current scenario, bacterial meningitis predominantly affects adults more than children and infants,⁷⁸ and *S. pneumoniae* is the predominant causative pathogen for bacterial meningitis in the US.^{69,78,81} In high-income countries, despite immense advancement in medical science, pneumococcal meningitis continues to be a serious disease among adults, with a high fatality rate and neurological sequelae ranging from 16% to 37% and 30% to 52%, respectively.^{15,82–85}

Unlike developed countries, bacterial meningitis continues to be a matter of grave concern in LMICs. An inadequate level of vaccine coverage or unavailability of these vaccines in the respective national immunization programmes could be the attributing factors for this continual menace. Not only in the pediatric population, but pneumococcal diseases are also associated with a high mortality rate among older adults in India.^{42,43} Invasive pneumococcal disease demonstrated a 26% rise in mortality among adults aged over 66 years from 1993 to 2008 in India.⁴² Recently, a study published by Nandi *et al.*⁸⁶ evaluated the associations of Hib vaccination on cognitive functioning and schooling attainment outcomes in Indian children (age groups 11–12 and 14–15 years). The study found that Hib-vaccinated children scored higher on the English test

($p < 0.001$) and mathematics test ($p < 0.001$), and attained more schooling grades ($p < 0.05$) than Hib-unvaccinated children, indicating cognitive benefits.⁸⁶ India has witnessed a declining trend in Hib-caused meningitis in children.⁸⁶ The Hib vaccine has been privately available in India since 1997.⁸⁶ In 2011, the government of India introduced Hib immunization as part of the pentavalent vaccine in combination with vaccines for diphtheria, tetanus, pertussis and hepatitis B.⁸⁶ This has led to *S. pneumoniae* being the most common causative pathogen for bacterial meningitis.¹³ Choosing an appropriate antibiotic is key to the optimum management of bacterial meningitis.^{5,13} However, emerging multidrug resistance in *S. pneumoniae* has raised a global concern, including in India,^{13,43} and has had a significant impact on its management. This signifies the necessity for the implementation of vaccination programmes for the prevention of the disease.^{5,13}

Vaccines are the cornerstone of prevention and control of bacterial, especially pneumococcal, meningitis.⁵ For adults, two vaccines, i.e. pneumococcal conjugate vaccine 13 (PCV13) and pneumococcal polysaccharide vaccine 23 (PPSV23), may confer protection against pneumococcal disease including meningitis. PCV13 and PPSV23 protect against 13 serotypes and 23 serotypes of pneumococcal bacteria, respectively.⁸⁷ PPSV23 has been available in the Indian market since the early 1980s but is not too effective in infants.⁸⁸ In the mid-2010s, PCV13 was launched in India.⁸⁹ In India, pneumococcal conjugate vaccine for adults is recommended for all healthy and at-risk adults (>50 years old) by the Indian Association of Occupational Health,⁹⁰ the Indian Medical Association⁹¹ and the Association of Physicians in India.⁹² Sadly, despite being recommended by several regulatory bodies, the routine use of adult pneumococcal vaccines is limited due to the paucity of data on the pneumococcal disease burden and its serotype distribution.¹³ In India, currently two meningococcal conjugate vaccines (MCVs) are licensed: (a) quadrivalent meningococcal polysaccharide-protein conjugate vaccine (A, C, W135, Y) licensed in 2012 for use among persons aged 2–55 years; and (b) meningococcal group A conjugate vaccine licensed in 2009 for individuals 1–29 years of age.⁹³ Therefore, the estimation of bacterial meningitis disease burden along with its predominant etiological pathogen is indispensable in a setting such as India, where an adult vaccination programme

is yet to be established and implemented as a national immunization programme for broader public health benefit. Considering the high mortality rate and associated complications in the survivors of bacterial, viral, or fungal meningitis, there is a need for active disease surveillance systems that help in the accurate estimation of the disease burden. Furthermore, the development and implementation of locally available guidelines are warranted for the optimum management of meningitis in India.

Limitations of the study

The study limitations include the lack of quality assessment of included studies, the potential for publication bias related to high variability among the studies selected and study period (1990–2020; present data not included). India is a large heterogeneous country with limited surveillance for meningitis in spite of considerable disease burden. Owing to the lack of diagnostic and treatment facilities; there is a lack of reporting of the study population. The study populations in most of the included studies were poorly defined, which further complicated the review analysis. Considering the wide heterogeneity of the patient population as well as the inclusion criteria (most of the studies included patients with suspected meningitis) in the selected published articles, concluding the true meningitis burden in India was challenging. However, we tried to minimize the concerns through our precise adherence to the PRISMA model in selecting studies for inclusion. Also, due to the heterogeneity of the studies and mixed population groups, obtaining a pooled analysis was not feasible.

Further studies are required to monitor meningitis cases to facilitate preventive measures such as the implementation of vaccine programmes for tackling the meningitis disease burden in the Indian subcontinent.

Conclusion

This systematic literature review displayed the possible range of frequency of bacterial meningitis pathogens across a wide variety of age groups in different regions of India. A predominance in the frequency of bacterial meningitis caused by different etiological pathogens, especially *S. pneumoniae*, was evident in this analysis. Continual robust monitoring is essential to estimate the

disease burden along with the distribution and variety of pneumococcal serotypes to assess further the emerging antibiotic resistance pattern in India. Wider implementation of adult immunization programmes may hold substantial potential for reducing the pneumococcal meningitis burden in India. Further studies are warranted to monitor meningitis cases, which may facilitate the further development of prevention and treatment strategies in India.

Authorship

Both the authors have contributed equally to the conception, design, analysis and interpretation of data; drafted the article or revised it critically for important intellectual content; approved the version to be published; are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest statement

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Supplemental material

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