Meningococcal Disease Burden in India: A Systematic Review and Meta-Analysis

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ABSTRACT

OBJECTIVE: To perform systematic review and meta-analysis of meningococcal disease burden in India.

METHODS: We searched publications on meningococcal disease in India between 1996 and 2020 using PubMed and Google Scholar. Prevalence (proportion) of *Meningococcal meningitis* and Case-fatality ratio (CFR) were pooled using random effects model. Other outcomes were pooled qualitatively.

RESULTS: The prevalence of *Meningococcal meningitis* in epidemic and endemic conditions was 12.1% (95% CI: 5.2-21.4) and 0.76% (95% CI: 0.3-1.4), respectively, with a CFR of 12.8% (95% CI: 6.8-20.4) in epidemic settings; *N. meningitis* caused 3.2% (95% CI: 1.6-5.3) of Acute Bacterial Meningitis (ABM) cases in endemic settings. The disease appeared in infants, adolescents, and adults with Serogroup A prevalence. Treatment and prophylaxis were limited to antibiotics despite increased resistance.

CONCLUSION: The study reveals epidemic and endemic presence of the disease in India with high fatality and serogroup A prevalence. Further monitoring and immunization are required to prevent outbreaks.

KEYWORDS: Meningococcal, meningitis, India, burden of disease

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Introduction

Meningitis is an infection of the meninges or membrane that covers the brain and spinal cord. Meningococcal meningitis is a highly fatal disease caused by the bacterium, *Neisseria meningitides*. It is a human-specific bacterium that spreads through the exchange of respiratory and throat secretions, and travels via the bloodstream to the brain. This bacterium infects the cerebrospinal fluid (CSF) to cause an inflammation of the meninges. It may also sometimes multiply in the bloodstream and release endotoxins causing Meningococcemia or Septicemia.[1]

In India, *N. meningitidis* is the third most common cause of acute bacterial meningitis (ABM) in children <5 years, and accounts for an estimated 1.9% of all ABM cases regardless of age.[2] The disease remains endemic in India, with major outbreaks reported in Delhi (2005-08), Meghalaya (2008-09), and Tripura (2009) over the last 25 years. Twelve serotypes of *N. meningitidis* have been identified, of which, 6 (A, B, C, W, X, and Y) have been associated with disease outbreak.[3] The National Health Profiles published from the year 2005 to 2012 by the Central Bureau of Health Intelligence (CBHI) in India show that the number of cases reported for meningococcal meningitis have increased by 39% that is from 3397 in 2005 to 5609 in 2012, and number of deaths by 25% that is from 311 in 2006 to 413 in 2012.[4-10] The disease is potentially fatal and therefore considered as a medical emergency. The National Centre for Disease Control (NCDC) in India recommends a combination of antimicrobial therapy and supportive treatment for patients suffering from disease and chemoprophylaxis for those in close contact.

According to the Global Meningococcal initiative (GMI) meeting held in India,[11] the actual incidence of this disease is not reliably known due to suboptimal surveillance and insufficient diagnostic support. Many cases in rural areas go unreported; even true magnitude large outbreaks remains underestimated.[11,12] Moreover, conventional culture techniques are used for diagnoses which are often incapable of isolating *N. meningitidis* because of rampant antibiotic use in the country. Non-culture-based methods, such as polymerase chain reaction (PCR) have limited availability while other techniques like antigen tests lack standardization and quality control. This results in under-representation of the true burden of the disease.

Vaccination is the best prevention strategy for a country to curb any infectious disease. However, in India, meningococcal vaccines are recommended either for the high risk groups or during an outbreak/epidemic situation (defined as more than 10 cases per 100 000 populations)[13]; routine immunization is not recommended. This is because of the potentially low numbers reported in the country. Information on the epidemiology of a disease is an important input to understand health priorities and implement decisions on suitable interventions.

In India, *Meningococcal meningitis* has shown its presence in several situations, from sporadic cases to huge epidemics effecting

*Both the authors have contributed equally to this work.

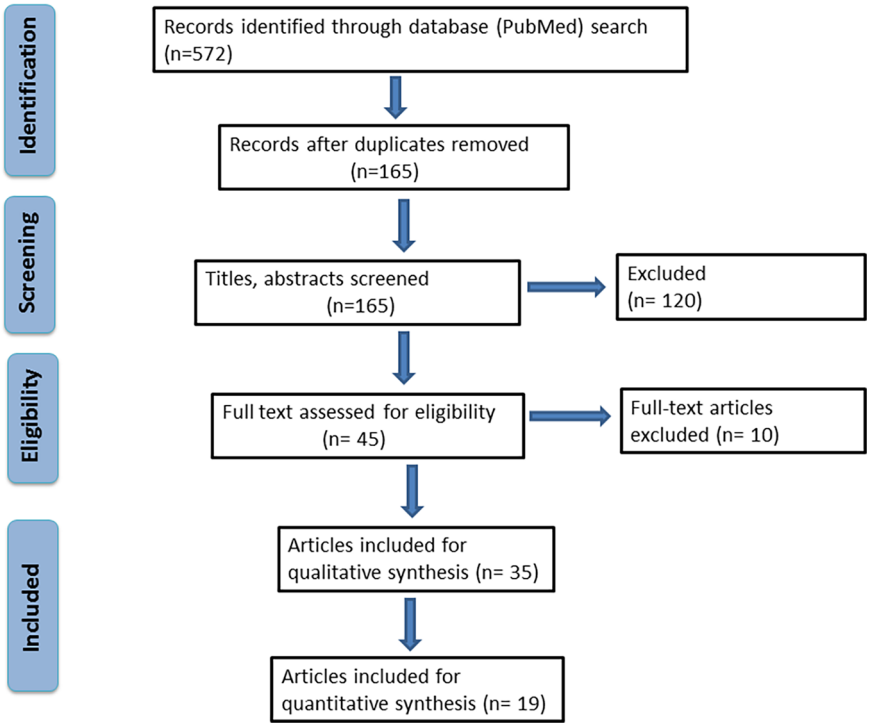


Figure 1. PRISMA flowchart describing study selection process.

all age groups. Many individual studies have prospectively or retrospectively reported the cases of meningococcal infection during epidemic and endemic conditions. However, no study has been conducted to pool the available data quantitatively to determine the overall prevalence of the disease in India and its fatality. There are a few studies done in the past to review the same[12,14] in a narrative (qualitative) manner. This is the first systematic review and meta-analysis conducted to gain further insights into the presence of the disease in epidemic and endemic conditions by qualitatively pooling the available data and statistically analyzing the results wherever applicable. The current review also aims to discuss meningococcal vaccine recommendations in India, highlighting the unmet need in the country.

Materials and Method

Literature search and screening

Types of studies. We conducted this systematic review using Preferred Reporting items for systematic review and meta-analysis (PRISMA) statements.[15] Because prevalence and case fatality are the primary outcome of the study, we included all observational studies that reported burden of the meningococcal disease with respect to outcomes such as incidence, prevalence, mortality, morbidity, and case fatality. Other outcomes like age-specific estimates, serotype distribution, clinical presentation, complications, drug resistance, and treatment were also interpreted in the included studies.

Search methods and identification of studies. The PRISMA flowchart summarizing the entire literature search and selection process is explained in Figure 1. The following databases were searched for observational studies on meningococcal disease burden published from 1996 to 2020 in English: PubMed/Medline and Google scholar. Bibliographies of relevant studies were also screened. A set of keywords representing the concept of "Meningococcal infection, *Neisseria meningitidis*, and epidemiology in India" were used to identify relevant publications. The search strategy for PubMed is shown in the Supplemental File S1. As per the standard PRISMA process,[15] title and abstracts of each study were screened independently by 2 reviewers followed by examination of the full text. Any disagreement was resolved by consensus.

Data extraction

For data extraction, we collected all relevant information from the included articles pertaining to primary and secondary outcomes of the study. The primary outcomes were (1) prevalence-(proportion) of *meningococcal meningitis* among the suspected cases of ABM in both epidemic and endemic conditions; (2) proportion of cases with N. meningitis among culture-positive cases of ABM and; (3) case fatality ratio (proportion of persons with a particular condition (cases) who die from that condition) in epidemic conditions. The secondary outcomes were age distribution, serogroup distribution, clinical symptoms, complications, drug resistance, and antibiotic sensitivity.

Assessment of risk of bias

We assessed the risk of bias by using Joanna Briggs Institute (JBI) Prevalence critical appraisal checklist[16] for all observational studies and the JBI critical appraisal checklist for case reports.[17] Critical assessment of all studies was done and reviewer response to each question of the checklist was noted as "Yes," "No," "unclear," or "not applicable." Each question to

Table 1. Geographical distribution of studies reporting *Meningococcal meningitis* in India.

REGIONS	NO. OF STUDIES	REFERENCES
Delhi	n=9	Arya et al,[32] Jhamb et al,[34] Kumar et al,[35] Aggarwal et al,[38] Agarwal and Sharma,[39] Sood et al,[49] Duggal et al,[51] Nair et al,[53] Saha et al[54]
Uttar Pradesh	n=5	Khan et al,[27] Singh et al,[30] Jhamb et al,[34] Abbas and Mujeeb,[37] Dinkar et al[43]
Chandigarh	n=2	Singhi et al[31] and Gawalkar et al[44]
Jammu and Kashmir	n=2	Bali[23] and Kushwaha et al[52]
Assam	n=2	Devi et al,[24] Devi and Mahanta[42]
Karnataka	n=4	Gangane and Kumar,[26] Mani et al,[28] Shameem et al,[29] Mutreja et al[46]
Himachal Pradesh	n=1	Chauhan et al[21]
Meghalaya	n=2	Dass Hazarika et al[33] and Dass et al[40]
Maharashtra	n=1	Chinchankar et al[22] and Sonavane et al[48]
Odisha	n=1	Sahu et al[47]
Tripura	n=1	Majumdar et al[36]
Bihar	n=1	Modi and Anand[55]
Tamil Nadu	n=3	Fitzwater et al[25] and David et al[41]

which the reviewer marked "Yes" was given 1 point. Studies scoring more than 60% as per the reviewer's judgment were included for further analysis (Supplemental Files S2 and S3). The risk of bias was assessed by 2 reviewers and any discrepancies were resolved by mutual discussion.

Data analysis

Methodological heterogeneity was assessed by the authors by examining the study design. Statistical heterogeneity was assessed using I^2 and Cochrane Q statistics, P-value $<.1$ with results ranging from 0% to 100%, and values of 25%, 50%, and 75% representing low, moderate, and high levels of heterogeneity, respectively.[18] Meta-analysis of the primary outcomes was done using windows based "MedCalc Statistical Software" version 19.6.1 (2020). Data computations and imputations were done in Stata-IC 13.1 (Stata corp., USA). For each study, primary outcomes were summarized as proportions and associated 95% confidence intervals were computed. Freeman and Tukey[19] transformation (arcsine square root transformation) for variance stabilization of proportions and random-effects models (DerSimonian and Laird)[20] for meta-analyses of computed data was employed. The forest plot diagram was used summarize the meta-analysis and to display the effect size and confidence interval. Secondary outcomes as well as individual case reports were pooled qualitatively in a narrative manner.

Results

Literature search and screening

A total of 572 articles were obtained following electronic and manual search of which 165 articles were screened for title and abstract following removal of duplicates. One-hundred and twenty articles were excluded after screening the title and abstract and 10 articles were excluded on full-text review. Thus, 35 articles were included for qualitative analysis of which 19 were pooled for quantitative analysis. Case reports were included only for qualitative analysis.

Characteristics of included studies

Of the total 35 studies, 16 were observational studies,[21-36] 13 were case reports.[37-49] No study design was reported for the remaining studies.[50-55] The geographical distribution of studies reporting *N. meningitidis* is presented in Table 1. All studies reported cases from a single location except 2 studies; of which 1 study was a multi-centric sentinel survey conducted at 10 locations in India[50] and the other involved travel history to Delhi and Chennai.[45] Of the 16 observational studies, 13 were in non-outbreak (endemic) settings[21-31,50,55] while 9 reported cases during outbreak (epidemic) settings.[32-36,51-54] Male predominance was observed in all the studies.

The baseline characteristics of the included studies are given in Supplemental File S4.

Primary outcomes

Prevalence (proportion) of laboratory/hospital confirmed Meningococcal meningitis *cases*

Epidemic. Of the 9 studies in the epidemic settings, 4 studies (in hospital/laboratory settings) conducted over a period of January 2005 to August 2009 reported the number of confirmed *Meningococcal meningitis* cases among clinically suspected patients.[36,51,53,54] The overall estimate of the preva-

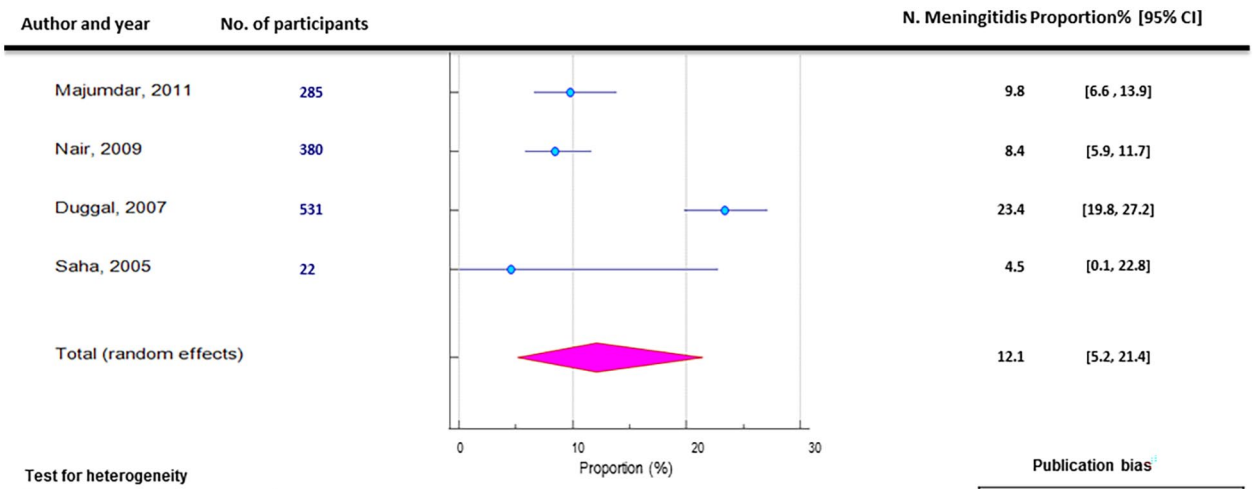


Figure 2. Forest plot of the prevalence (proportion) of the confirmed N. meningitidis cases among clinically suspected cases of ABM in epidemic settings.
Abbreviations: DF, degree of freedom; Q, Cochran's heterogeneity statistic.

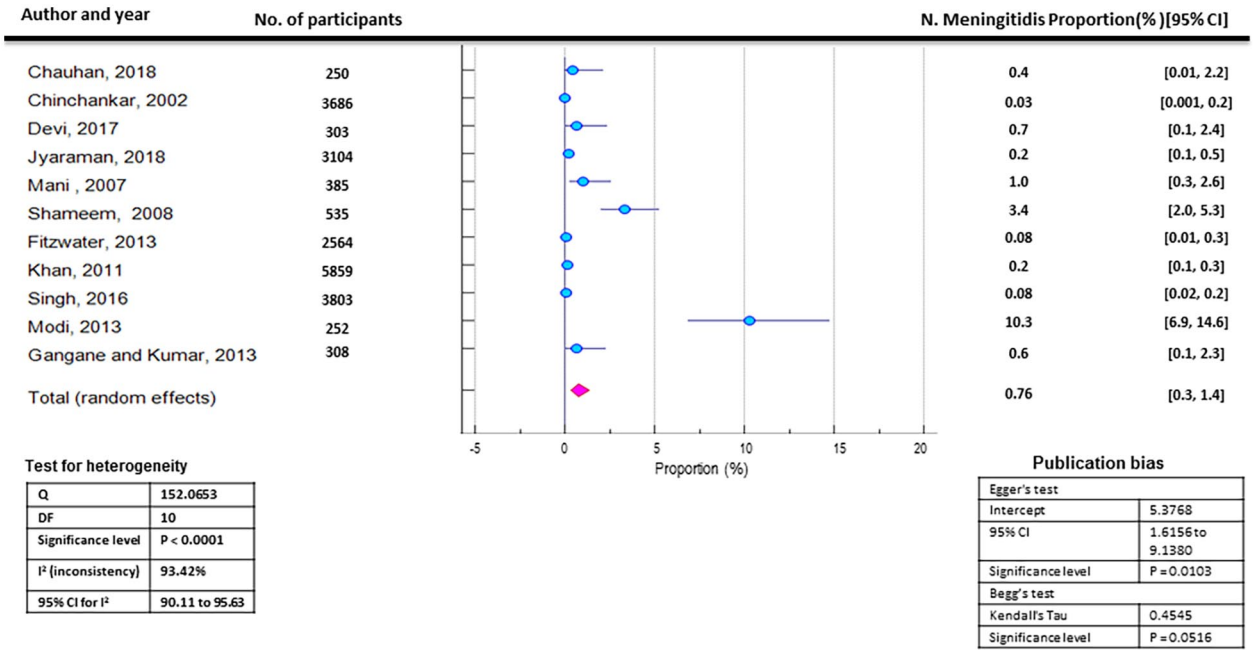
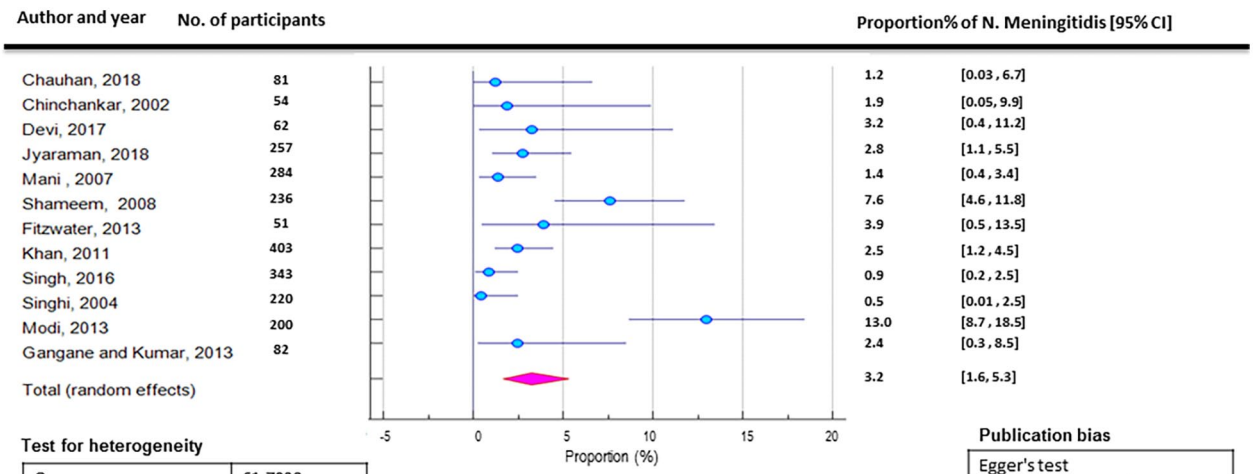


Figure 3. Forest plot of the proportion of the confirmed N. meningitidis cases among clinically suspected cases of ABM in endemic settings.
Abbreviations: DF, degree of freedom; Q, Cochran's heterogeneity statistic.

lence (proportion) of the confirmed *Meningococcal meningitis* cases among 1218 clinically suspected cases of ABM was 12.1% (95% CI: 5.2-21.4) (Figure 2). The forest plot showed significant heterogeneity among studies ($I^2 = 93.82\%$; $P < .0001$; 95% CI: 87.35-96.98) (Figure 2).

The remaining 5 studies retrospectively analyzed a total of 246 confirmed cases of *Meningococcal meningitis* in hospital-based tertiary care centers/military settings.[32-35,52]

Endemic. Of the 13 studies in the endemic conditions, 11 studies (in hospital/laboratory settings) reported the number of confirmed cases of *Meningococcal meningitis* among clinically suspected patients in different regions of India.[21-30,50,55] The overall estimate of the prevalence (proportion) of the confirmed *Meningococcal meningitis* cases among 21 049 clinically suspected patients was 0.76% (95% CI: 0.3-1.4) (Figure 3). The forest plot showed significant heterogeneity



Test for heterogeneity

Q	61.7038
DF	11
Significance level	P < 0.0001
I^2 (inconsistency)	82.17%
95% CI for I^2	70.08 to 89.38

Publication bias

Egger's test	
Intercept	1.1040
95% CI	-3.7937 to 6.0016
Significance level	P = 0.6264
Begg's test	
Kendall's Tau	0.3333
Significance level	P = 0.1314

Figure 4. Forest plot of the prevalence (proportion) of the confirmed N. meningitidis cases among culture positive cases of ABM in endemic settings. Abbreviations: DF, degree of freedom; Q, Cochran's heterogeneity statistic.

amongstudies (I^2 = 93.42%; P < .0001; 95% CI: 90.11-95.63) (Figure 3).

Twelve studies in the endemic settings also reported the number of confirmed *Meningococcal meningitis* cases among culture positive cases of ABM.[21,22,24-31,50,55] The overall estimate of the proportion of *Meningococcal meningitis* among 2273 culture positive cases of ABM was 3.2% (95% CI: 1.6-5.3) (Figure 4). The forest plot showed significant heterogeneity among studies (I^2 = 82.17%; P < .0001; 95% CI: 70.08-89.38) (Figure 4).

Case fatality

Epidemic. Of the 9 studies reporting meningococcal infection in epidemic settings[32-36,51-54] 6 reported case fatality ratio (number of deaths among the total confirmed cases of *Meningococcal meningitis*) and these studies were pooled for meta-analysis.[33,34,36,51-53] Three studies were excluded; 2 studies were considered as weak evidence due to small denominator which affected the overall meta-estimate[32,54] 1 study did not report the number of deaths.[35] The overall estimate of the case fatality ratio among 824 cases of *Meningococcal meningitis* was 12.8% (95% CI: 6.8-20.4). The forest plot showed significant heterogeneity among studies (I^2 = 86.73%; P < .0001; 95% CI: 73.36-93.39) (Figure 5).

$$\text{Case fatality ratio} = \frac{\textit{Number of deaths due to N. meningitidis}}{\textit{Total number of cases of N. meningitidis}} \times 100$$

Endemic. Only 1 study reported case fatality ratio of 3.6%[55]

Secondary outcomes

Age distribution

Epidemic. Of the 9 studies in the epidemic settings, age distribution of the confirmed *Meningococcal meningitis* cases was reported in 6 studies[32-35,52,54] which ranged from <1 to 60 years. In the remaining 3 studies, age group distribution was reported for suspected cases of *Meningococcal meningitis*.[36,51,53] These studies showed an increased trend of the disease among adolescent and adults.

Endemic. Of the 13 studies, 10 reported age distribution for sporadic cases of *Meningococcal meningitis*. Seven studies involved pediatric patients[21,22,25,27,29,31,50] one involved adults,[23] and 1 study reported the presence of *N. meningitidis* in neonates (n = 1)[24] and mixed population (involving adolescents and adults).[28] In the remaining 3 studies, age distribution was unclear for confirmed cases of *Meningococcal meningitis but defined for* total cases (which included suspected cases of the disease) and indicated a trend among adolescents and adults.[26,30,55]

Serogroup distribution

Epidemic. Eight studies clearly reported the prevalence of serogroup A specific disease.[32-36,52-54] One study reported the prevalence of both serogroup A and ACWY in 34% and 51% of cases respectively; and due to the unavailability of the meningococcal antigen kit in this study the outbreak was however presumed to be due to serogroup A.[51]

Endemic. Only 4 studies reported information of serogroup, of which 2 studies reported non-specific serogroup ACWY.[21,25]

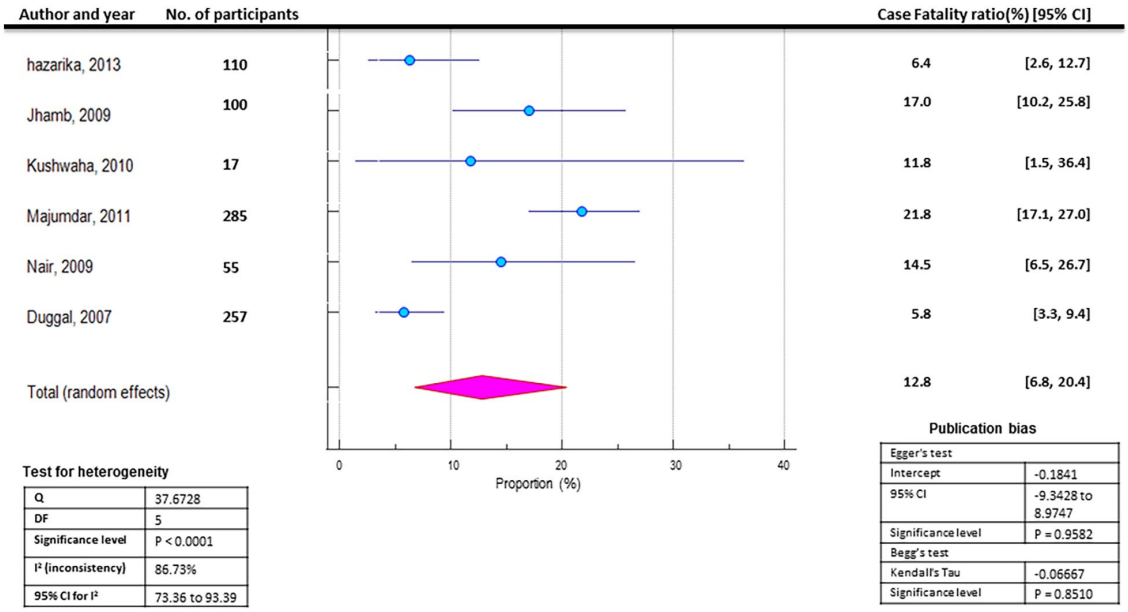


Figure 5. Forest plot showing case fatality ratio of N. meningitidis in epidemic settings.
Abbreviations: DF, degree of freedom; Q, Cochran's heterogeneity statistic.

One study identified serogroup Y for 1 of the 2 neonates[24] and 1 study reported the presence of serogroup B in 4 nasopharyngeal samples of college hostellers.[23]

Antibiotic sensitivity and resistance. Seven studies in the epidemic settings[32-36,51,53] 3 in the endemic settings[26,28,29] reported information on resistance and sensitivity to drugs. Studies reported variability in sensitivity to different antibiotics—penicillin, ampicillin, ciprofloxacin, ceftriaxone, cefotaxime, erythromycin, azithromycin, and chloramphenicol.

Epidemic. Of the studies reported in outbreak settings, 1 study showed high resistance of the isolates to quinolones[53] (MIC $_{50}$: 0.125 mg/ml)—levofloxacin (100%; MIC_{90}: 0.19 mg/ml), ofloxacin (84.6%; 0.5 mg/ml), and ciprofloxacin (65.4%; MIC_{90}: 0.19 mg/ml). This study also reported increased resistance to ceftriaxone (0.125 mg/ml) (MIC_{90}: and penicillin (MIC_{50}: 0.032 mg/ml) and attributed mortality to drug resistance. Resistance and/or decreased sensitivity to ciprofloxacin,[32,36] penicillin,[35] and ceftriaxone[33] were also reported in other studies. Two studies reported resistance and decreasing sensitivity to cotrimoxazole.[32,51] Kumar et al[35] reported erythromycin resistance in 5.9% isolates while Jhamb et al[34] reported ampicillin and erythromycin resistance in only one isolate.

Endemic. Two studies in the endemic settings reported information on antibiotic resistance and sensitivity; Shameem et al[29] reported tetracycline and amoxicillin resistance while Gangane and Kumar[26] reported decreased sensitivity to ampicillin, gentamycin, and amikacin.

Clinical characteristics and complications

Epidemic. The most common clinical symptoms reported in infants with meningococcal meningitis were fever, bulging fontanelle, vomiting, altered sensorium, neck stiffness, irritability (in infants).[33,34,51] In adults, common clinical presentations were fever, headache, rash, seizures, impaired mental status, stiffness of the neck, nausea, vomiting, lethargy, and confusion.[32,36,51] Complications such as arthritis, gangrene,[34] and Waterhouse-Friderichsen Syndrome were also reported.[52]

Endemic. In infants, clinical features commonly observed in the sporadic cases of Meningococcal meningitis were fever, headache, lethargy, neck stiffness, altered sensorium, refusal to feed, bulging anterior fontanelle, seizure, and impaired unconsciousness.[21,22,25,27,50] In adolescents and adults, the common symptoms were fever, headache, vomiting, impaired mental status, and stiffness of the neck.[30,55] Complications such as increased intracranial pressure, coma, respiratory compromise, seizures, and subdural effusion were reported in some cases.[21,22]

Treatment

Epidemic. Four studies in epidemic settings reported information on antibiotic sensitivity and resistance. Treatment in the majority of the studies was limited to intravenous ceftriaxone,[32,36,51] chloramphenicol,[33,36] penicillin[36] alone, or in combination along with supportive measures such as intravenous fluids, steroids, and antacids.

Endemic. None of the studies in the endemic settings reported information on treatment or antibiotic resistance for *Meningococcal meningitis* infection.

Overview of the case reports

Age and serogroup distribution. Thirteen case reports from different regions of India involved patients from different age group—pediatric populations (n = 5),[37,38,41,47,49] adults (n = 4)[43,45,46,48] adolescents (n = 3)[39,40,44] and neonates (n = 1).[42]

Of the 13 case reports, serogroup was reported in only 6 studies which included serogroup A,[39] non-specific serogroups (A-D),[47] B,[38] and Y.[42] A case report involving 2 pediatric patients reported the presence of serogroup C which was uncommon and not observed in any studies reported during endemic and epidemic conditions.[41]

Clinical characteristics, complications. In adults, the most common clinical presentations reported were fever, chills, purpuric rash, vomiting, weakness, and headache. In infants, symptoms were limited to lethargy, bulging and pulsating anterior fontanelle.[38,42]

Eight case reports described complications such as purpura fulminans (n = 5),[37,39,40,44,46] myocarditis (n = 1),[44] arthritis (n = 1),[47] Waterhouse-Friderichsen syndrome (n = 1),[48] immune complex reaction (n = 1). Purpura fulminans was associated with complications like gangrene and amputation of toes and limbs[37,39] and Waterhouse-Friderichsen syndrome resulted in meningococcal sepsis and multi-organ failure.[48] A rare case of genital meningococcus was reported in 1 study with symptoms similar to gonorrhea that is vaginal discharge, redness, itching, and mild inflammation over the labia majora and labia minora.[49] Of the 13 case reports, 10 patients recovered fully or were stable and discharged, while 2 died due to meningococcal sepsis with multi-organ failure[46] and adrenal hemorrhage following Waterhouse-Friderichsen syndrome[48] respectively, and 1 was lost to follow-up.[49]

Treatment. Most of the patients responded best to ceftriaxone. Steroids and intravenous fluids were given for supportive care. A rare symptom of immune complex reaction was reported in a patient who recovered following treatment with intravenous immunoglobulin (IVIG). Another case report identified neonatal meningitis due to serogroup Y that recovered following treatment with amikacin followed by piperacillin-tazobactam.[42]

Discussion

In India, the true estimate of meningococcal disease remains unknown due to poor surveillance systems and limited diagnostic measures. Data is collected randomly during inter-epidemic periods from the Central Bureau of Health Intelligence, Integrated Disease Surveillance Project (IDSP), and individually published reports. However, this data is not always a part of the public domain and often unreliable due to extensive use of antibiotics in India. Despite frequent outbreaks reported in the country, surveillance measures are still in its infancy which results in markedly low reported incidence of the disease in the country.[14] This has impacted decisions of the policy makers regarding routine immunization program in India. Moreover, no efforts have been taken to analyze the data and understand its presence in the country.

In this systematic review of 35 studies, we found that meningococcal disease occurs as an endemic as well as epidemic illness in India with occasional outbreaks documented in different regions of the country. The disease targets not only pediatric population but shows an equal presence in adolescents and adults.

Most studies included in the review were hospital-based studies. Meta-analysis of these studies showed that the prevalence (proportion) of meningococcal disease (in hospital/laboratory/settings) in epidemic and endemic conditions was 12.1% (95% CI: 5.2-21.4) and 0.76% (95% CI: 0.3-1.4) respectively. N. Meningitis accounted for 3.2% (95% CI: 1.6-5.3) of the total cases of acute bacterial meningitis (ABM) in the endemic settings. Case fatality of 12.8% (95% CI: 6.8-20.4) and 3.2% was reported in the epidemic and endemic settings respectively. The wide range in the confidence interval can be attributed to the differences in study design, age of the participants, and diagnostic measures.

Qualitative analysis of the information from the studies showed that serogroup A was primarily responsible for all the outbreaks reported in India during 1996 to 2020. Occasional cases of serogroup B and Y were also identified but in endemic conditions. This finding is in line with other previously reported studies[12,14] and indicates emergence of other serotypes besides serogroup A. The review also showed a shift in the affected age group. Apart from the vulnerable groups of children less than 5 years of age, an increase in trend was seen in the proportion of cases in adolescents and adults. This observation may suggest the emergence of a potentially new epidemic clone, against which the population is immunologically naïve. Treatment and prophylaxis in all the studies was limited to antibiotics to prevent complications and disease transmission. Some patients and culture isolates showed increased resistance to some of the common antibiotics which can be attributed to the extensive antibiotic use in India. This is also one of the factors responsible for poor diagnosis and culture isolation of *N. meningitidis* and hence underestimation of the true burden of the disease.[56]

Despite increased resistance, antibiotics remains the gold standard for treatment as well as chemoprophylaxis of this disease. During epidemics, chemoprophylaxis and/or reactive vaccination is used for controlling the disease. However, mass chemoprophylaxis during outbreaks is not considered epidemiologically appropriate and cost-effective due to large deployment of resources.[57] Also, routine immunization is not considered in India due to low reported incidence of the disease which has further impacted the efforts to control and manage the disease. Hence, there is a need for a strong surveillance system in India for accurate epidemiologic quantification of the burden of meningococcal disease. However, until such system is established, routine vaccination of high-risk population as well as infants, adolescents, and adults are the only way to prevent further outbreaks.

Globally, meningococcal vaccines are available against antigens related to serogroup A, C, Y, and W135 and B. These are available as (1) Meningococcal Capsular Polysaccharide Vaccines (MPVs), and (2) Meningococcal Conjugate Vaccines (MCVs).

During disease outbreaks in countries with limited economic resources, WHO recommends the use of polysaccharide vaccines to curb the disease.[58,59] Hence, in India, MPVs have been largely used due to their low cost. These are distributed in freeze-dried form and are available in bivalent (A + C) and quadrivalent forms (A + C + Y + W135).[11] MPVs have favorable safety and tolerability profile but are associated with limitations such as poor immunogenicity in children <2 years, inability to induce immunological memory resulting in transient and incomplete protection as well as[11] lowering of antibody titers necessitating revaccination. Moreover, hypo-responsiveness or lowering of antibody titers upon revaccination is observed with polysaccharide vaccine which further limits its benefits.[60] MCVs, on the hand, are immunogenic in infants, reduce acquisition of bacterial carriage among the immunized, interrupt bacterial transmission, and contribute to the generation of herd protection within a population. The Indian academy of Pediatrics (IAP) recommends conjugate meningococcal vaccines as they overcome each of the above shortcomings. In India, currently 2 conjugate vaccines have been licensed for use.[61] Both these vaccines are quadrivalent MCVs and target serogroup A, C, Y, and W-135. Another conjugate vaccine—a monovalent vaccine for serogroup A—is manufactured in India but is licensed for use only in sub-Saharan Africa.[11]

Many countries have included meningococcal vaccine as a part of their routine immunization program to eliminate the disease and have been successful in achieving the same.[62] World Health Organization (WHO)[3] recommends that countries with high (>10 cases per 100 000 population/year) or intermediate (2-10 cases per 100 000 population/year) endemic rates and/or frequent epidemics of invasive meningococcal disease conduct appropriate large scale meningococcal vaccination programs . However, in India, routine immunization for Meningococcal disease is not adopted due to underestimated disease burden in the country. The Indian Academy of Pediatrics (IAP) and the Association of Physicians of India (API) recommend the use of the meningococcal vaccine only in certain high-risk population/conditions such as: (I) during the disease outbreak in healthcare workers, laboratory workers and close contacts of cases and (II) high-risk situations: children suffering from terminal complement component deficiency and functional/anatomic asplenia; immune-compromised individuals, health care workers routinely exposed to *N. meningitides*, first year students living in dormitories, military recruits and, (III) Hajj pilgrims, persons, students traveling to countries where the disease is hyperendemic or epidemic.[59,63] IAP recommends 2 doses for those <16 years and single dose for those >16 years of age.

In India, meningococcal vaccine recommendation also varies with the condition of use. In outbreaks, a single dose of Bivalent vaccine (A + C) is recommended for health care workers, laboratory workers, and close contacts of cases. In the recent outbreaks[64] of Meghalaya and Tripura, mass vaccination of the entire population (2-50 year age group) was done in selective districts including, East Khasi hills and Jaintia hills of Meghalaya, and Chawmanu and Manu Block districts of Tripura using Bivalent (A + C) MPV. For international travelers like Haj pilgrims, Quadrivalent Meningococcal Meningitis Vaccine (QMMV) is recommended, which is as per policy of the National Institute of Communicable Disease (NICD) Delhi, to fulfill the requirements of the Government of Saudi Arabia. QMMV is preferred due to its ability to protect against emerging W-135 and Y sero-specific disease.[65] In India, a large number of people travel for religious pilgrimages like Haj and Umrah, and about 200 000 doses of QMMV are given to Hajj Pilgrims per annum.[66] For military recruits, another high-risk population, an immunization program with quadrivalent MPV for military cadets was developed in 2012 but is not yet mandatory.[67] Meningococcal vaccination is mandatory for international travelers/students, as most of the institutions in countries like United States of America (USA) have policies necessitating vaccination before enrolling. Usually, a single dose of quadrivalent or monovalent vaccine is generally recommended in these students. In India, serotype A is the most prevalent, but occasional cases of Serogroup B have also been documented for which no vaccine is yet available in the country. Vaccine for serogroup B may be beneficial for travelers visiting places with high endemicity of this serotype.

Several risk factors in India such as overcrowding in public transport or shared accommodations, inadequate hygiene facilities, and mass gatherings, such as social functions, sports competitions, or political, religious, or cultural gatherings; increase the risk of rapid transmission of the disease in the country.[68] This can be seen with frequent outbreaks reported in the country at regular intervals. Hence, routine immunization of high-risk groups as well as infants, adults, and adolescents can be an effective measure to prevent disease transmission in India.

Limitations

Our systematic review had certain limitations. First, our study included only peer—reviewed literature. Data from sources like the Central Bureau of Health Intelligence, Integrated Disease Surveillance Project (IDSP) were excluded which may have provided additional information on the burden of the disease. Second, the studies included were mostly hospital-based which provides limited information on the community level presence of the disease. Third, some studies did not accurately define or used different definitions for the confirmed, probable, and suspected case of *Meningococcal meningitis* which might have impacted the results. Finally, many studies in the endemic settings did not report fatality which made it difficult to estimate the fatality rate in endemic conditions.

Conclusion

This systematic review of studies from different geographical locations of India revealed that meningococcal disease occurs as both epidemic and endemic illness causing substantial illness, death, and serious complications. The study showed that

the disease is increasingly affecting adolescents and adults apart from the most vulnerable group that is children and infants. Predominance of Serogroup A was observed with occasional cases of other sero-groups such as B and Y. Our review also identified the research gaps and suggests proper monitoring of the disease. However, until robust monitoring is implemented, immunization against the disease is the only measure to control further outbreaks.

Author Contribution

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.

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Supplemental Material

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