

MEETING REPORT



Proceedings of the Expert Consensus Group meeting on meningococcal serogroup B disease burden and prevention in India

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ABSTRACT

Meningococcal disease is highly transmissible, life-threatening and leaves significant sequelae in survivors. Every year, India, which has a plethora of risk factors for meningococcal disease, reports around 3000 endemic cases. However, the overall disease burden and serogroup distribution are unknown, creating a setting of general disease negligence and unawareness. Vaccination with quadrivalent meningococcal conjugate vaccine A, C, W, and Y is only recommended for high-risk children, and there is no overall guidance for meningococcal serogroup B (MenB) vaccination. MenB vaccines, which recently have been licensed in many countries but not in India, have significantly aided the fight against meningococcal disease. However, these MenB vaccines are not available in India. An Expert Consensus Group meeting was held with leading meningococcal disease experts to better understand the current disease epidemiology, particularly serogroup B, the prevalence gaps, and feasible ways to bridge them. The proceedings are presented in this paper.

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Introduction

Meningococcal disease is highly transmissible, rapidly progressing life-threatening disease with potentially serious medical sequelae.¹ It is caused by the obligate human bacterium *Neisseria meningitidis* (*N. meningitidis*).^{2,3} The two most common clinical presentations of the disease are meningococcal meningitis and meningococcal septicemia.¹ Both forms could be developed simultaneously.⁴

In India, several large meningococcal outbreaks have been reported, and the disease is considered notifiable.⁵ Based on hospital records, *N. meningitidis* bacteria were isolated from 40% to 50% of suspected cases during epidemics;⁶ they were also detected in 1.9% (range 0.0–20.0%) of endemic meningitis cases published from 1953 to 2008.⁶ However, meningococcal disease cases are not routinely reported, and there is limited availability of diagnostic facilities.⁵ In the absence of surveillance data, meningococcal disease is considered as a low background incidence in India, based only on the limited published reports.⁶ Nevertheless, the available empirical evidence suggests that India is susceptible to epidemic meningococcal disease.⁶ Meningococcal serogroup B (MenB) is not prevalent in India, according to published reports. However, due to the combination of underreporting and underdiagnosis, the true epidemiology and disease burden are likely to be underestimated.⁵

Meeting objectives

There is a gap between officially recorded and empirical epidemiology of MenB disease in India, as well as other serogroups (A, C, W, and Y). An Expert Consensus Group



meeting was held with the goal of gathering perspectives and data on this gap, as well as reviewing the current epidemiology and serotyping of MenB disease in India.

Meeting participants were eminent meningococcal disease experts from different geographical regions of the country: 12 pediatricians and 4 representatives of GlaxoSmithKline (GSK) India Vaccines Team. The Expert Consensus Group meeting was held on 24 November 2020, via an online platform due to the prevalent coronavirus disease 2019 pandemic. After a brief presentation by the representatives from GSK, the meeting experts deliberated on the different aspects of meningococcal disease in India, particularly MenB, existing surveillance, outbreaks, and their management as well as immunization practices. The proceedings are presented in this paper.

Meeting output

A severe disease with high case fatality rate

There was unanimous agreement among the meeting experts that meningococcal disease, whether in the form of meningitis or septicemia, is an extremely serious condition having unexpected onset, high case fatality rates (CFRs), and poor outcomes.^{7,8} In 20 out of 100 individuals who survive meningococcal disease, serious complications such as hearing or limb loss, as well as brain impairment, occur.⁹ In a meta-analysis of 40 studies published worldwide between 2000 and 2018, an 8.3% pooled CFR was reported (95% confidence interval [CI], 7.5–9.1; range 4.1%–20.0%).⁸ The estimated CFR by age groups was 9.0% in infants, 7.0% in children 7–10 years old, 10.4%–15.0% in 16–28 years old, remained stable until 45 years old after which it started to increase

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rapidly reaching 32.8% in patients aged 80 years.⁸ From 1994 to 2019, nine publications on meningococcal disease epidemics in India reported CFRs ranging from 0% to 21.8%; no data on endemic (non-outbreaks settings) disease mortality were reported.⁵ To the meeting experts' clinical practice experience, CFR could reach 70% in septicemic cases and 20% in meningitis cases. This is particularly important for a country such as India with significant numbers of meningococcal septicemia cases reported in outbreaks.⁶ According to the meeting experts, the CFR rises during an outbreak because the increasing patient intake in hospitals causes saturation of the limited resources available. During the 2005–2006 outbreak, the incidence of meningococemia reached 40% of cases in a tertiary hospital in New Delhi.¹⁰ Furthermore, the meeting experts emphasized that the mortality rate varies according to clinical presentation characteristics.

It was recognized that meningococcal disease is particularly difficult to identify during the early stages.⁷ This difficulty is due to the disease's short incubation period, of an average 4 days (2–10 days),¹¹ and rapid progression from nonspecific flu-like symptoms to even death within 24–48 hours.^{7, 11} Mild initial symptoms of febrile illness may rapidly progress to fulminant disease with multi-organ failure and death in spite of appropriate treatment.¹² This evolution depends on several factors such as the host immune response, the inflammatory response, the bacterial load, and the levels of circulating endotoxin.¹² The initial symptoms in children, which occurs during the first 4–6 hours of disease onset, are not unique to meningococcal disease and include fever, poor feeding or decreased appetite, nausea, and vomiting.⁷ Initial symptoms also include irritability, lethargy, and inconsolable crying in children aged <2 years, and headache, drowsiness, and irritation in children aged >5 years.¹² After a median of 12–15 hours from symptoms onset, bulging fontanel might appear in infants, and neck stiffness and photophobia in children.¹² Rash is present in about one out of four children, and seizures may develop in less than one out of three children.¹² Lower limb pain, skin pallor, cold peripheries, and maculopapular blanching rash are early signs of developing sepsis that may occur as early as 12 hours from disease onset. Petechial or purpuric rash is typical in meningococcal septicemia occurring in 40%–80% of cases.^{7, 12} In an Indian study conducted by one of the meeting expert's scientific group,¹³ it was shown that rash was limited to only 24% of meningococcal disease cases. Therefore, from the discussions by the meeting experts, the perceived high association of the typical rash with meningococcal disease could be misleading for the physicians and could lead to missed cases and underdiagnoses.

The meeting experts also emphasized the need of starting therapy as soon as possible. The earlier the administration of antibiotic medication, the better the prognosis. Delays in treatment administration were associated with unfavorable outcomes and increased mortality.^{14, 15} If left untreated, one out of two patients could succumb to the disease (CRF 50%).¹¹ Therefore, the patient should be admitted to hospital and immediately receive appropriate antibiotic treatment from disease onset.^{11, 16} Laboratory investigations to confirm diagnosis and determine the exact type of pathogen should not delay treatment initiation.^{11, 14, 15}

Risk factors for meningococcal disease in India

All the meeting experts acknowledged that India has many risk factors commonly associated with a meningococcal outbreak thus, making the country vulnerable to the deadly disease. Extensive cross-border travel increases the risk, especially when it involves countries with endemic meningococcal disease and high MenB prevalence, like Europe, Australia, as well as North and South Americas.^{5, 17} Population density, as a risk factor, was also discussed. Meningococcal person-to-person transmission occurs through the inhalation of the respiratory droplets produced by the carrier.^{18, 19} Consequently, crowded conditions facilitate bacteria transmission and carriage acquisition, predisposing individuals to increased risk for meningococcal disease.^{20–22} Indeed, meningococcal disease outbreaks have been reported with large mass gatherings such as religious gatherings, sporting events, refugee camps, military barracks, university residential halls, and even some funerals, cruise ships, and dance parties.^{23–25} Such risk factors exist in abundance in India, especially in highly populated cities. Based on the 2011 Census data, the country's average population density was 325 persons/km² but in big cities reached a maximum of 29,468 persons/km² in the North East district of Delhi; the overall population density in Delhi was 9340 persons/km².²⁶ Household crowding also increases the risk of meningococcal disease by 252% (odds ratio [OR] 2.52; 95% CI, 1.75, 3.63).²⁷ The risk increases even further in mass gatherings like Kumbh Mela, festivals, and celebrations. Huge religious pilgrimages with millions of pilgrims such as Hajj and Umrah are well-known sources of regional and global spread of meningococcus.^{20, 21, 28, 29} Kumbh Mela, the largest mass gathering in the world reaching 150 million visitors in 2019,³⁰ has not been associated with any known meningococcal outbreak so far.³¹ However, this is reasonable to expect given that other mass gatherings, such as overcrowding, sets the conditions for transmission of meningococcus and other infectious diseases.^{24, 31, 32} Moreover, mass gatherings events are linked to unique social behaviors that increase the risk of transmissions such as kissing, sharing food, and accommodation areas.²⁹

The high population of young individuals in India, high student population, high air pollution, and tobacco use are documented risk factors prevalent in India. Air pollution causes acute respiratory tract infections, asthma, and chronic obstructive pulmonary disease.³³ It is estimated that 12.5% of the total deaths in India, in 2017, were due to the air pollution.^{34, 35} In addition, upper respiratory tract infections may pave the way for meningococcal invasion. It is shown that exposure to smoke and respiratory tract infections multiply the risk of disease: OR 2.10 (95% CI, 1.00, 4.39) and OR 3.13 (95% CI, 2.02, 4.86) respectively.²⁷ The Indian population is generally young: nearly half (47.9%) of the population is younger than 21 years (2011 Census data).³⁶ The risk of (meningococcal) disease is highest between 3 and 11 months of infancy, and teenagers are the second most at-risk age group; in adulthood the risk generally declines.²⁰ Teenagers and young adults are the most common carriers.^{20, 37–39} Therefore, young adults play a significant role in its nasopharyngeal carriage, especially in the settings of crowded conditions. The meeting experts

noted that during outbreaks, adolescents and young adults are more prone to contract the disease, but not in endemic settings when the pediatric population aged <5 years is more vulnerable. And, in reality, younger patients have a poorer prognosis since they are more likely to be admitted to a hospital with septicemia, whereas older patients are more likely to be admitted with meningitis, which is generally associated with a better prognosis.

Carriage prevalence is higher among males than females, and in smokers.¹⁹ As published information is sparse, increased nasopharyngeal carriage in the community was questioned as a potentially widespread risk factor in India. While in certain populations, like in the Indian army, it was reported to be as high as 11.9%,⁴⁰ and in a study conducted in Kashmir on college freshmen, it was 1.5% among 274 fresh college recruits.⁴¹ Nevertheless, given that 9 to 10 meningococcal cases are reported per year, and some outbreaks have occurred within the Indian Armed Forces, the military is considered a high-risk group.⁴² The risk is higher among new recruits, probably due to the crowded living conditions and mixing individuals from different geographic areas with diverse epidemiologic profiles and *N. meningitidis* serogroups undetermined nasopharyngeal carriage.⁴²

Season is another determining risk factor that influences the spatial distribution of the disease in India. Dry and cool temperatures promote transmission.⁴³ Therefore, most cases are reported during the driest period of the year and start to decline with the onset of the monsoon season during which transmission still occurs at moderate levels.⁶ This is also evidenced by the endemic case distribution more in the northern and eastern parts of the country.⁶

Meningococcal disease is underreported

The true epidemiologic picture of meningococcal disease in India is unknown due to inadequate surveillance infrastructure.⁵ The disease is notifiable in India,⁴⁴ however, only passive disease surveillance is performed,⁴⁵ and cases are underreported to the Integrated Disease Surveillance Program.^{6, 46}

One process of reporting cases involves the network of government health centers, which, on a monthly basis, send their cases to state ministries and from there to the central Ministry of Health.⁴⁵ This process excludes the cases among the population attending private hospitals.⁴⁵ Diagnostic specificity is better through the second available surveillance process that develops via the regional sentinel hospitals.⁴⁵ However, only a few sentinel hospitals have the ability to coordinate diagnostic procedures, with specific laboratories, either in-house or externally.⁴⁵

Apart from poor surveillance, additional multi-layered reasons lead to scant meningococcal disease epidemiologic information. Delay in seeking medical care,⁴⁷ unsuspecting physicians, difficulties in establishing the diagnosis in the laboratory, and a general lack of awareness of reporting obligations among healthcare providers are examples of such reasons.^{5, 6} The commonly employed diagnostic measures include microscopy, latex agglutination for antigen detection, bacterial culture, and polymerase chain reaction (PCR).^{48, 49}

PCR is highly sensitive and specific and can be used in patients who received prior antibiotic treatment;^{48, 49} nevertheless, due to a lack of resources and infrastructure it is the least employed method in India. This further aggravates disease underreporting feeding in a vicious loop of perceived low incidence, leading to a lack of disease suspicion, diagnosis, and medical management. The available diagnostic kits for antigen detection, such as latex agglutination, have a lack of standardization and quality control, which result in variable specificities and sensitivities.⁴⁵ Moreover, due to resource limitations, reference laboratories might decline samples for analysis.⁴⁵ Overall, laboratory diagnostic facilities are scarce in most parts of the country and diagnoses in primary and secondary clinics are based on clinical presentation.^{5, 45} *N. meningitidis* culture is generally performed in tertiary hospitals, and only a few hospitals use a PCR diagnostic method.⁴⁵ Moreover, laboratory diagnoses and detection of *N. meningitidis* bacteria, if at all performed, have uncertain diagnostic specificity.⁴⁵ Culturing the organism is difficult as it is a notoriously fastidious organism, dying within hours on inanimate surfaces, that optimally grows at 35–37°C with ~5% carbon dioxide.⁵⁰ Furthermore, pre-diagnosis antibiotic therapy compromises culture diagnostic accuracy.^{49, 51} Unfortunately, empirical antibiotics are commonly used in India, and patients who present to tertiary care hospitals for meningococcal investigations have frequently taken antibiotics.^{52, 53} Therefore, detection via bacterial culture, the commonly used diagnostic method, is likely to give false-negative results and underdiagnosis.^{45, 49} However, delaying antibiotic treatment is associated with death and detrimental outcome, while antibiotic treatment should be administered not later than 1 hour after hospital admission.⁴⁹ Thus, prior antibiotic intake is like a double-edged sword that trades off better diagnosis for a better patient outcome.^{5, 6, 54}

Lastly, lack of clear reporting guidelines augments underreporting. Case reporting is enforced only during outbreaks, but once outbreaks resolve, reporting and monitoring activities are discontinued. As a consequence, endemic epidemiologic data are scarce. Small outbreaks in rural areas are often underreported, but even for large outbreaks there is inadequate epidemiologic information available.⁴⁵

Meningococcal B disease epidemiology in India

Invasive meningococcal disease (IMD) epidemiology is evolving and dynamic because it is inextricably linked to national or regional immunization programs, age groups targeted for vaccination, vaccination timing,⁴ and a variety of surveillance standards.²⁹ Globalization and ease of travel around the earth, mass gatherings, and international mass events further influence the dynamics of meningococcal epidemiology and serogroups distribution.^{4, 55}

Twelve serogroups of *N. meningitidis* have been identified, with six of them: A, B, C, W, X, and Y are responsible for most infections, and serogroups A, B, and C account for 90% of worldwide infections.^{1, 3, 4} Predominant serogroup varies by geographic region and may change in response to modifications in the immune status of the human population of the particular area.³ Therefore, MenB is prevalent in many countries and regions of the Asia, Europe, North America, and

Oceania.^{4, 31} In India, meningococcal serogroup A causes most cases, however, MenB and other serogroups (C, W, and Y) have also been documented during outbreaks and among endemic cases.^{5, 56, 57}

India, with 18% of the global total population,⁵⁸ consists of states equal to the size of big countries with vast demographic and climate diversity, and varying economic growth.⁵⁹ Therefore, the epidemiologic profile of diseases varies across India.⁵⁹ According to the National Health Profile 2019,⁶⁰ more than 3000 cases of meningococcal meningitis are reported every year in the country, with almost all states contributing to this number.⁶⁰ Serogroup classification is not available either because it was not performed or because it was not reported.

In the absence of robust epidemiologic data, it is difficult to estimate the real burden of meningococcal disease in India.⁵ Trying to address this need and trying to estimate the burden of disease in the country, two research teams, a decade apart, Sinclair et al. and Dutta et al.^{5, 6} reviewed the available published literature. Sinclair et al. reported that since the first meningococcal meningitis cases were published in 1926,⁶ a number of widespread epidemics were published. The epidemics presented with a periodicity of 20 years and small outbreaks occurred in between.⁶ Until 2009, the largest epidemic occurred in New Delhi during winter in 1984.⁶ The real scale of this epidemic was unknown, as only those patients who were presented to seven major hospitals in New Delhi were recorded; in these hospitals 6133 cases and 799 deaths were recorded at the peak of that epidemic.⁶ Overall, the published data within the past 25 years from India, reported detection of *N. meningitidis* bacteria in 4.5%–23.4% of suspected cases during an outbreak and in 0.1%–7.6% suspected cases during non-outbreak periods.⁵ These wide ranges of incident cases do not offer a clear idea of the real burden of disease and are limited to suspected cases as these were defined within each respective study. Moreover, the generalizability of these estimates is limited by insufficient diagnostic facilities.⁵

In India, the burden of meningococcal disease is not limited to the pediatric population but also involves adolescents and young adults.⁵ The reported outbreaks of the past 25 years have involved increasing numbers of adolescents and young adults and has shown a shift upwards to the median age of patients.⁵ During the endemic periods, at least half of the reported cases involved adolescents and adults.⁵

Effective polysaccharide-protein conjugate vaccines are available against all major six serogroups.^{4, 61} However, such sort of MenB vaccines could not be successfully developed because the serogroup B polysaccharide proved to be poorly immunogenic while also carrying antigenic similarity to sialic acid, a component of the human cell membrane.^{62–64} As a result, developing MenB vaccines was challenging for many years until the innovative technique of reverse vaccinology was employed to identify alternative surface antigens that were sufficiently conserved throughout the MenB serogroup and highly antigenic to elicit a protective antibody response.^{64, 65} The recent licensure of two new protein-based MenB vaccines with broad coverage has provided a major boost for the fight against meningococcal disease in these countries where this serogroup is the main cause of IMD.^{66–70}

Meningococcal outbreaks are cyclical and unpredictable

The outbreaks of meningococcal disease occur with a certain periodicity. For example, in the African belt, the epidemics occur in epidemic cycles of 8 to 15 years.⁷⁰ In New Delhi, the epidemic cycle is 15–20 years.⁶ The epidemic cycle in the United States (US), before the introduction of meningococcal vaccines, was approximately 10 years.⁷¹

This periodicity and unpredictable reemergence of meningococcal epidemics further weakens an already loose surveillance while resources are diverted to more urgent needs. It also increases underdiagnoses by unsuspecting treating physicians. Nevertheless, the free circulation of pathogenic serogroup continuously threatens to give rise to a new epidemic.⁷² The interim break in disease incidence should not abstain from efforts to implement effective vaccination control that is proven to halt and alter disease burden.^{71–73}

MenB vaccination in India: an unmet medical need?

To prevent the loss of lives and morbidity associated with meningococcal disease, the focus should be on preventing outbreaks.²⁵ It was agreed by all meeting experts that vaccines are the best armamentarium in preventing outbreaks. Since serogrouping of meningococcal cases is commonly not performed in India, it becomes essential to cover all the vaccine-preventable meningococcal serogroups in circulation, namely A, C, W, Y, and B. Vaccines for four (A, C, W, Y) out of the five common disease causing serogroups (A, B, C, W, Y) exist in the country. However, protection against MenB is completely lacking. This is of high concern, considering the nature of the disease and the sociocultural demographic profile of India that creates an unmet medical need for the uncovered vulnerable population. With the advent of MenB vaccines, effective vaccines became available for the first time against most of the disease-causing meningococci. The target group for meningococcal vaccinations is decided by prevailing epidemiological factors, and each country has its unique immunisation schedule.^{29, 74} Infants, children, adolescents, and specific risk groups have all been treated differently in the various national vaccination programmes.⁷⁴ Many European Union (EU) countries and the United Kingdom (UK) have incorporated MenB vaccination in their infant immunisation schedules,^{75, 76} and the quadrivalent meningococcal conjugate vaccine serogroups A, C, W, and Y (MenACWY) is routinely recommended in adolescents in the US,^{77, 78} the UK,⁷⁶ and some of the EU countries.⁷⁵

Current barriers to routine MenB immunization in India, include the perceived low disease incidence and the relatively high cost of the vaccines. MenB vaccination would particularly benefit certain vulnerable population groups who are either more prone to suffer from a severe form of disease or more prone to acquire the disease.⁷⁹ Prioritizing high-risk populations, MenB vaccinations should be provided to the army/military recruits, college students living in dormitories, immunocompromised populations, travelers to the endemic zones of the world, and other at-risk groups.^{5, 25} Nonetheless, protein-based MenB vaccines also provide cross immunogenicity to other *Neisseria* species, including *N. meningitidis* serogroups A, B, C, and Y as

well as *Neisseria gonorrhoeae*, because the included protein antigens are well conserved across the *Neisseria* genus.^{80–82} However, individual vaccines are recommended to better protect against the other *Neisseria* diseases. The MenB vaccines also have the potential to already be co-administered and in the future combined with available MenACWY to provide broad protection against five major serogroups that are responsible for nearly all IMD globally.^{83, 84} Moreover, although MenB vaccine shows activity against *Neisseria gonorrhoeae* the clinical data are not yet solid enough to assure protection against gonorrhoea, hence not yet.⁸¹ Sexually transmitted infections involve 6% of the Indian population, and therefore, they constitute an important public health problem.⁸⁵ Evidence shows that 3%–19% of these infections are due to gonorrhoea.⁸⁶ Sharma et al. reported “alarming resistance” of their *N. gonorrhoeae* cases toward antibiotics threatening to become untreatable.⁸⁶

Ways forward recommendations

In summary, the evidence discussed in the meeting clearly described that India has an abundance of risk factors for disease transmission and outbreaks and frequently suffers meningococcal disease outbreaks. However, the overall disease burden and serogroup distribution are unclear due to the high rates of underdiagnosis and underreporting, creating a setting of general disease negligence and unawareness. It is evident that wider vaccination coverage should be considered to prevent outbreaks and recommendations should be made for selectively prioritize vaccination for higher-risk groups. Meningococcal disease is also difficult to identify in its early stages due to its insidious onset, with early signs and symptoms that are very similar to those of flu or flu-like illness, limiting disease detection, diagnosis, reporting and early treatment.

The meeting experts wrapped up the meeting by discussing the ways to move forward in meningococcal disease characterization and management in India. Experts recommended that to overcome the current situation of underreporting and disease negligence the scientific community and health authorities in India would need to undertake the following initiatives:

- To conduct prospective multicenter nasopharyngeal studies to map the carriage rate and the different serogroups in the country.
- Strengthen microbiological labs across the country with good diagnostic technologies to isolate meningococcal serogroups.
- Educate and develop better disease awareness among physicians regarding sample collection, preservation, and transfer for laboratory diagnostic procedures.

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Authors' contributions

SA was in charge of supervision and project administration and performed data curation and investigation. All authors participated in the discussion and the development of this manuscript and gave final approval before submission.

Availability of data and materials

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Abbreviations

CI	confidence interval
CFRs	case fatality rates
EU	European Union
GSK	GlaxoSmithKline
IMD	invasive meningococcal disease
MenACWY	quadrivalent meningococcal conjugate vaccine serogroups A, C, W, and Y
MenB	meningococcal serogroup B
OR	odds ratio
PCR	polymerase chain reaction
UK	United Kingdom
US	United States

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