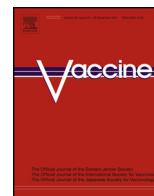




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Review

An overview of meningococcal disease in India: Knowledge gaps and potential solutions

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ABSTRACT

The Global Meningococcal Initiative (GMI) consists of an international group of scientists and clinicians, with expertise in meningococcal immunology, epidemiology, public health and vaccinology that aims to prevent meningococcal disease worldwide through education, research, cooperation and vaccination. In India, there is no national policy on routine meningococcal vaccination to control the disease. The GMI convened a meeting in India, with local medical leaders and public policy personnel, to gain insight into meningococcal disease burden and current surveillance and vaccination practices in the country. *Neisseria meningitidis* is the third most common cause of sporadic bacterial meningitis in children <5 years, with higher incidence in temperate northern versus tropical southern India. Incidence is not reliably known due to suboptimal surveillance and insufficient microbiological support for diagnosis. Since 2005, there have been a number of outbreaks, all attributable to serogroup A. Outbreak responses were ad hoc and included mandatory case reporting by hospitals in Delhi, temporary strengthening of laboratory diagnostics, chemoprophylaxis of close contacts/high-risk groups and limited reactive use of polysaccharide vaccine. Although a conjugate serogroup A vaccine (MenAfriVac™) is manufactured in India, it is not presently used in India. Epidemiological data on meningococcal disease in India are sparse. Meningococcal disease control efforts should focus on establishing systematic surveillance and educating physicians and officers of the Immunization Division of the Ministry of Health on the importance of *N. meningitidis* as a cause of morbidity and mortality. Conjugate vaccine should be used for outbreak control and the immunization of high-risk persons.

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Abbreviations: CSF, cerebrospinal fluid; GMI, Global Meningococcal Initiative; Hib, *Haemophilus influenzae* type b; IAP, Indian Academy of Pediatrics; IDSP, Integrated Disease Surveillance Project; NCDC, National Centre for Disease Control; NGOs, nongovernmental organizations; PBM, Pediatric Bacterial Meningitis; PCR, polymerase chain reaction; RT-PCR, real-time polymerase chain reaction.

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1. Introduction

Meningococcal disease is caused by *Neisseria meningitidis*, of which humans are the only known reservoir [1]. Meningococcal disease may present as pyogenic meningitis and/or a rapidly progressive septicemia. It has a high case-fatality rate unless promptly diagnosed and appropriately treated. Among those who recover, permanent brain damage and physical disability may occur. *N. meningitidis* may colonize the upper airways without invading the mucosa. Individuals in whom this occurs serve as a reservoir for the bacterium. Whether or not disease manifests in carriers of *N. meningitidis* is dependent upon microbial, environmental, and host genetic and behavioral factors [2]. Of the 12 *N. meningitidis* serogroups, six cause the majority of disease: A, B, C, W, X and Y. Globally, the epidemiology of meningococcal disease is highly variable and dynamic, with differences seen in the relative distribution of bacterial serogroups in both time and place [2]. In general, the largest burden of meningococcal disease is borne by infants and young children [2,3].

In an effort to prevent meningococcal disease worldwide, the Global Meningococcal Initiative (GMI) was formed in 2009. It consists of a multidisciplinary group, whose mission is to bring about change through education, research and international cooperation. As part of its efforts, the GMI has published global recommendations aimed at reducing the burden of meningococcal disease (Table 1) [3]. In recognition of geographic disparities in disease epidemiology, surveillance, vaccine availability and resourcing, the GMI has convened roundtable meetings with local representatives in Latin America and in India to tailor its global recommendations to local needs. The outcomes of the Indian meeting are here presented.

2. Methods

A roundtable meeting was held in Gurgaon, National Capital Region, India, in January 2012, with seven local experts and five GMI members. Indian participants included pediatricians and physicians from selected institutions in Mumbai, New Delhi and Vellore; the Ministry of Defense; and the National Centre for Disease Control (NCDC). They presented on different aspects of meningococcal disease in India, including existing surveillance, outbreaks and outbreak management and immunization practices. Following a discussion of this information, the group developed country-specific recommendations.

3. Results

3.1. Surveillance

In India, disease surveillance is not enforced, as there is no public health infrastructure within the central Ministry of Health. Data on meningococcal disease stem from two main sources. The first is the network of government healthcare centers, which send case reports on a monthly basis to the central Ministry of Health via state ministries. However, because the majority of Indians use private

healthcare, the data are incomplete and poorly representative. The second is through regional sentinel hospitals. Laboratory support for the government network is fragmented. As a consequence, diagnostic specificity is low. Diagnostic specificity is better for regional sentinel hospitals. However, only a fraction have in-house laboratory capabilities or solicit the assistance of reference laboratories. Regional sentinel hospitals use definitions for both probable and confirmed cases of meningococcal disease as summarized in Table 2 [4]. According to statute, meningococcal disease is a notifiable disease in India, but reporting is not enforced (passive surveillance). The focus is more on healthcare and disease management than the deployment of staff to collect and act upon surveillance data.

3.2. Meningococcal diagnosis

In many hospitals, bacterial culture is the most commonly used diagnostic method. However, prior antibiotic use, which is prevalent in India, decreases the likelihood of isolating *N. meningitidis* via culture. Culture is generally performed in all tertiary care hospitals but is not commonly performed in the primary or secondary healthcare clinic where the diagnosis is usually restricted to clinical confirmation or at the most antigen detection. Non-culture-based methods, such as polymerase chain reaction (PCR), are used in only a few hospitals in India, primarily at the tertiary care level. Some hospitals in the private sector (and some in the public sector) employ antigen detection (e.g., latex agglutination). Multiple diagnostics kits are available. These kits lack standardization and quality control, resulting in varying specificities and sensitivities for *N. meningitidis*. Clinical samples can be sent from the private and public sectors to government reference laboratories, but because of resourcing constraints, government hospitals will not always accept them. As a consequence, data on meningococcal disease, particularly endemic disease, are sparse [5].

Serogroup A is the most common cause of meningococcal disease in India [5–9], with rare reports of disease attributable to serogroup C [5]. One fatality due to infection with serogroup B has been documented in India [10].

3.3. Epidemiology

Although many Indian outbreaks are reported in the lay press [11,12], small outbreaks, such as those in rural areas, are likely to go unreported and the true magnitude of even large-scale outbreaks is underestimated [5,7].

The existence of endemic disease is recognized [7,13,14], but much of the epidemiological data that are available were collected during outbreaks. Outbreaks have been reported more in temperate northern than tropical southern regions of the country (Fig. 1) [5]. During epidemics, case reporting and disease monitoring activities are enforced and adhered to in National Capital Region, but are discontinued once the epidemic has resolved.

Available information on the epidemiology of meningococcal disease in India has recently been exhaustively reviewed [5]. Briefly, *N. meningitidis* is the third most common cause of bacterial meningitis in India in children less than 5 years of age and is

Table 1
GMI recommendations for reducing the global burden of meningococcal disease.

1. Country-specific approaches to vaccine prevention are needed because of geographical and temporal variations in disease epidemiology
2. Country-specific meningococcal policy should be based on local epidemiology and economic considerations
3. Continued funding of the introduction of MenAfriVac™ is an important global and regional public health priority
4. The Meningitis Vaccine Project model should be considered when developing other products with markets that are primarily or exclusively in developing countries
5. Travelers to high-risk areas should be vaccinated against meningococcal disease
6. Vaccines against all clinically relevant meningococcal disease serogroups (A, B, C, W, X and Y) should be developed
7. Conjugate vaccines should replace polysaccharide vaccines whenever cost, availability, licensing and immunization policy allow
–However, polysaccharide vaccines are still recommended where conjugate vaccines are not available
8. Laboratory-based surveillance for meningococcal disease should be strengthened (or initiated) to determine the true burden of disease

Table 2
Indian case definitions for probable and confirmed meningococcal disease [4].

Probable	Suspected case of acute or bacterial meningitis AND Positivity for Gram-negative diplococci OR An ongoing epidemic OR Petechial or purpurral rash
Confirmed	Suspected or probable case of acute meningitis AND CSF-positivity for <i>N. meningitidis</i> OR Culture-positivity for <i>N. meningitidis</i> (sample derived from CSF or blood)

responsible for an estimated 1.9% of all cases regardless of age [5]. Unlike *Haemophilus influenzae* type b (Hib), *N. meningitidis* affects adults, as well as children [4,7,8,15]. This is particularly evident during outbreaks, when the mean age of cases increases [5,14,16]. The Indian Armed Forces experiences an attack rate of 9 to 10 cases of meningococcal disease per year [17] and a *N. meningitidis* carrier rate of 11.9% [18]. As a consequence, the military is considered a high-risk group in India [17]. Their risk factors include age (i.e., young adults) and living conditions that are overcrowded and poorly ventilated [19].

Since 2005, there has been an increase in the number of meningococcal disease outbreaks reported throughout India: New Delhi (2005–2009) [4,8,13–16,20], Meghalaya (2008–2009) [14] and Tripura (2009) [14,21] (Fig. 2). In these outbreaks, adolescents and young adults were predominately affected. There was also a high incidence of meningococemia [8,14], which at one New Delhi hospital represented 40% of cases [20].

3.4. Outbreak identification and management

Despite lack of routine surveillance, the NCDC and the Municipal Corporation of Delhi do receive case reports of meningococcal disease from major healthcare institutions. Based on these reports, an outbreak is declared if:

- Attack rate is ≥ 5 -fold higher than that seen in previous years in the same area, or if no data are available for that same area, an attack rate that is ≥ 5 -fold higher than that seen in similar areas.
- Attack rate (probable and confirmed cases) is > 5 cases/100,000 over a 3-month period.
- Incidence (probable or confirmed cases) increases for 3 consecutive weeks in the same area.
- Attack rate of > 3 cases of meningococcal disease in < 3 months among persons residing in the same area (community) who are not close contacts of each other, with a primary disease attack rate of > 10 primary cases/100,000 [22].

When there is an outbreak, immediate action is taken by the government. However, in remote areas of the country, more time may be needed before remedial action can be expected. A rapid response team typically composed of an epidemiologist, medical professionals and a microbiologist is deployed to identify individuals exposed to meningococcal disease and to assist in the management of those who are ill [23]. If diagnostic facilities are not available locally, as is typical for remote areas of the country, patient samples are sent to the NCDC for diagnostic testing [14]. During the recent outbreaks,

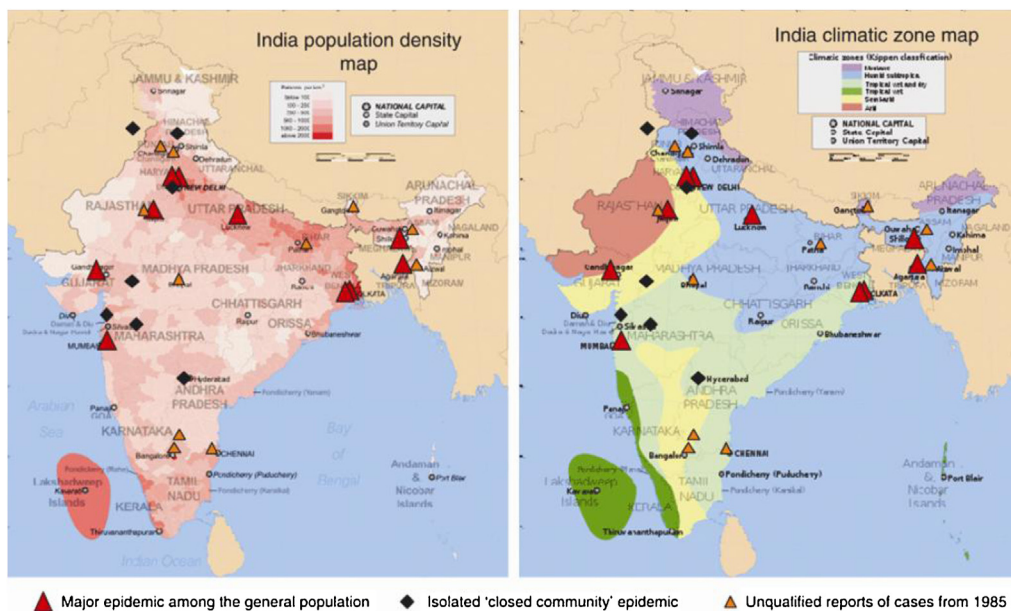


Fig. 1. Overlay of meningococcal disease incidence with (left) population density and (right) climate in India [5].

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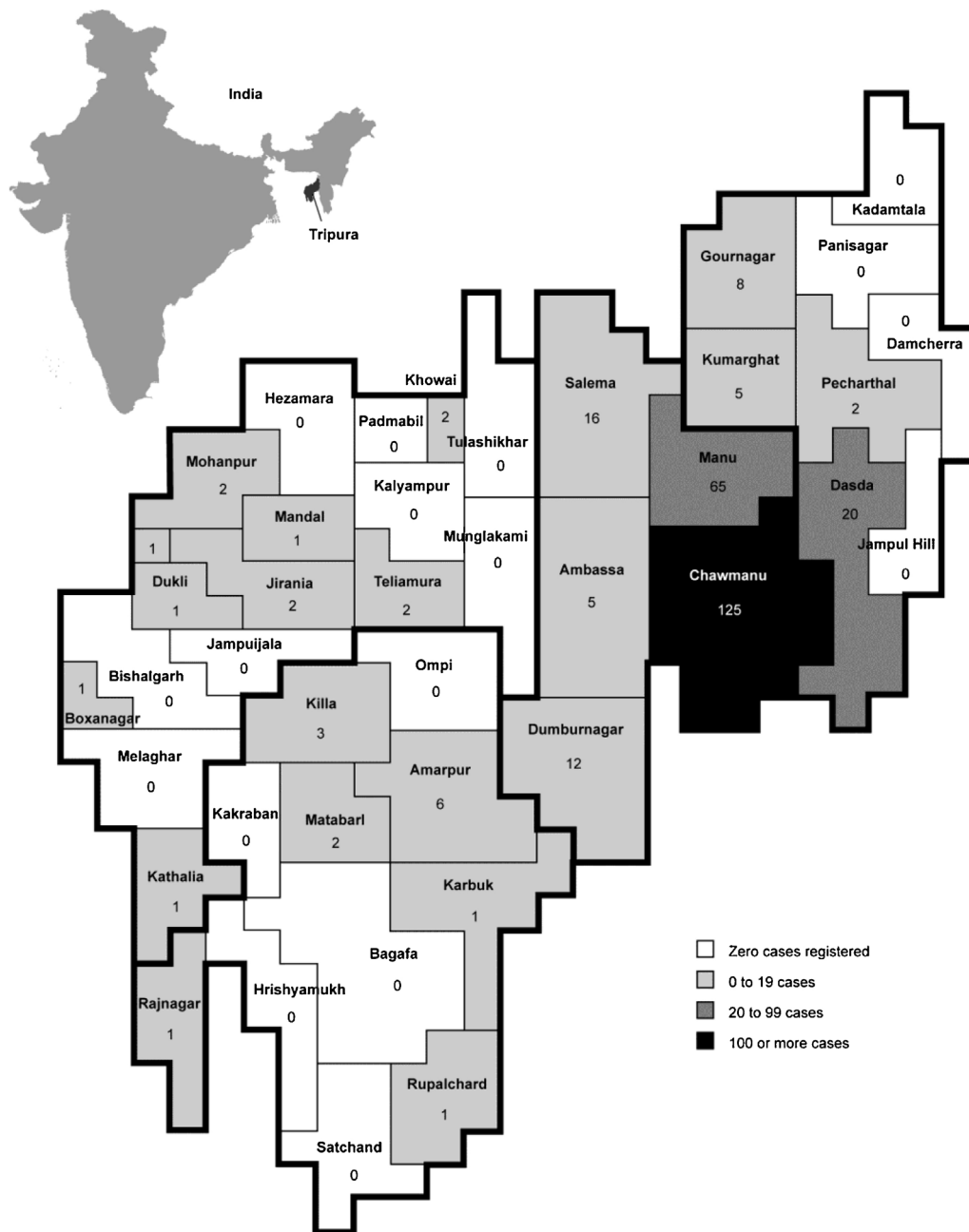


Fig. 2. Distribution of meningococcal disease cases in Tripura during the 2009 outbreak [21]. Reproduced with permission. The boxes represent Blocks in Tripura State.

microscopy, culture and latex agglutination tests were employed for diagnosis [16,20,21]. PCR was also used to investigate the epidemic in New Delhi [9,20].

The measures used to prevent and contain meningococcal disease outbreaks in India are summarized in Table 3. Chemoprophylaxis, the intention of which is to eliminate nasopharyngeal carriage, is given to close contacts, preferably within 24 h of contact with a primary case [4]. Ceftriaxone or ciprofloxacin is typically used for chemoprophylaxis, with the latter being the antibiotic of choice given the need for only a single oral dosage [24,25]. It must be emphasized, however, that mass chemoprophylaxis is not considered to be epidemiologically appropriate or cost effective. Alarmingly, ciprofloxacin-resistant *N. meningitidis* was detected during an outbreak in New Delhi that began in 2005 [25] and was imported into Italy. Importation of this ciprofloxacin-resistant

strain was assumed given the patient's travel history to Chennai and New Delhi and multilocus sequence typing [24]. This event underscores how in the era of increasing globalization, health policy decision makers must consider disease not only in their own borders, but elsewhere.

Table 3
Outbreak prevention and control actions in India [14].

- Active case surveillance
- Early diagnosis and prompt treatment
- Chemoprophylaxis of close contacts (household members, healthcare professionals)
- Fostering disease awareness within the community, including the need to seek medical help and to avoid crowded places
- Respiratory isolation of patients for 72 h
- Reactive vaccination of high-risk groups

Reactive vaccination may also be employed and is implemented via public outreach and the establishment of immunization clinics. Whether mass or targeted immunization is initiated depends on the geographic distribution of cases, age-specific disease incidence and resourcing [14,26]. For example, mass reactive vaccination in India is instituted when disease incidence exceeds 10 cases/100,000 in a given district [4,14]. For the first time in India's history, mass public immunization with bivalent (A+C) polysaccharide vaccine was undertaken to control the Meghalaya and Tripura outbreaks [14]. While targeted vaccination may be operationally more feasible, especially in light of potentially limited vaccine supplies and manpower, the identification of high-risk groups (e.g., healthcare workers) and an understanding of transmission dynamics are critical to maximizing the effectiveness of targeted immunization campaigns. Such knowledge can only be obtained through robust surveillance.

3.5. Vaccination

In India, only polysaccharide meningococcal vaccines are available: bivalent (A+C) and quadrivalent (A+C+W+Y) [14]. A monovalent conjugate vaccine against serogroup A (MenAfriVac™) manufactured by the Serum Institute of India for use in sub-Saharan Africa [27,28] is licensed but not yet available in India. This vaccine has been shown in a Phase I clinical trial to be well tolerated and immunogenic in healthy Indian adults aged 18–35 years [29] and in those 2–29 years of age in sub-Saharan Africa [30]. In December 2010, immunization of the whole 1- to 29-year-old population of Burkina Faso was performed to achieve a reduction in the circulation of the serogroup A meningococcus nationwide and to directly protect the age group at highest risk of meningococcal disease [31]. Initial results from Burkina Faso have shown that MenAfriVac has been highly effective at preventing invasive serogroup A meningococcal disease, reducing serogroup A disease by nearly 100%, eliminating district level serogroup A outbreaks [32] and also in causing a rapid reduction in carriage of serogroup A meningococci [33]. In Burkina Faso, during the 2011 meningitis season, the incidence of suspected bacterial meningitis was reduced in all age groups, including those too young or too old to have been vaccinated, suggesting the induction of herd protection. In the 2 years following the introduction of MenAfriVac there have been no cases of invasive serogroup A meningococcal disease in vaccinated individuals [34].

Both meningococcal polysaccharide (bivalent and quadrivalent) and conjugate (monovalent and quadrivalent) have been demonstrated to have excellent safety profiles [2,29,30] and MenAfriVac has, by December 2012, been administered to over a 100 million persons [35]. A novel benefit of MenAfriVac is that it is approved to be kept outside the cold chain for up to 4 days at up to 40 °C, in a controlled temperature chain. MenAfriVac was the first vaccine intended for use in Africa approved for this type of use, potentially setting a regulatory path that other heat-stable vaccines can follow. Vaccine cost is a further potential barrier to countries initiating vaccine introduction or vaccination campaigns. MenAfriVac, with its associated low cost, less than fifty US cents per dose, makes it possible for the African countries themselves to purchase vaccines for future birth cohorts [36]. However the cost of distribution and administration of the vaccine continues to have the greatest impact on the overall cost of immunization campaigns.

Given the perceived low incidence of meningococcal disease, meningococcal vaccines are not routinely administered in India, with immunization during inter-epidemic periods reserved for high-risk groups, such as children living in orphanages, prisoners, soldiers or travelers to areas where the disease is endemic or where an outbreak is ongoing [14,26]. In accordance with the policy of the Kingdom of Saudi Arabia Ministry of Health, a single dose of quadrivalent polysaccharide vaccine is given to Indians

10–14 days prior to Hajj travel [14,26]. As mentioned, the Indian Armed Forces is at higher risk for meningococcal disease than other population cohorts [17,19]. Military personnel serving abroad are immunized according to international health advisories or other country/region-specific requirements. Presently, all new cadets and recruits are being vaccinated on a trial basis with a meningococcal quadrivalent polysaccharide vaccine. It remains to be determined whether this vaccination program will continue over the long-term.

Meningococcal vaccination recommendations have also been published by scientific societies such as the Indian Academy of Pediatrics (IAP). Like the NCDC, the IAP recommends use of meningococcal vaccines for those ≥ 2 years of age in certain high-risk groups (e.g., those with asplenia or complement deficiencies), but advises, in an attempt to avoid hyporesponsiveness, that individuals (even those who maintain a lifelong risk of meningococcal disease) receive only a single booster dose with a meningococcal polysaccharide vaccine [22]. The IAP prefers meningococcal conjugate vaccines to polysaccharide formulations [22].

3.6. Healthcare in India

The current state of healthcare in India is of genuine concern and is negatively impacted by a number of factors. First, most medical facilities are found only in cities and richer districts [37,38], with the majority (66%) of healthcare professionals located in urban areas [38]. Yet, more than 70% of Indian's population (700 million people) live in rural villages [39], and transport and proper roads to urban centers are nonexistent in some places [37]. Second, medical buildings are often in dilapidated conditions, lack sufficient electricity and sometimes house nonfunctional equipment. Third, shortages in equipment, supplies and staff exist, with less than one nurse and one doctor per 1000 patients [38]. Last, the brunt of healthcare costs (69%) is borne by the patient, with federal, state and local governments contributing only 24%, a reflection of the fact that only 5.2% of India's Gross Domestic Product is spent on healthcare [38].

4. Discussion

4.1. Surveillance

The attendees of the GMI India Roundtable Meeting identified the need for and potential benefits of a surveillance system that integrates disease reporting from both the public and private sectors. Recognizing that vaccination strategies are best guided by robust epidemiological data, the GMI recommends (1) supplementing bacterial culture with laboratory diagnostics (e.g., real time-PCR [RT-PCR] and latex agglutination tests) allowing the identification of at least the five major serogroups, (2) establishing routine surveillance for bacterial meningitis and septicemia and (3) initiating nasopharyngeal carriage and seroepidemiological studies in several parts of the country. Such an undertaking is not unprecedented in a low resource setting. The Pediatric Bacterial Meningitis (PBM) surveillance network, which was initiated in Africa in 2001, collects data on laboratory-confirmed bacterial meningitis cases in children <5 years from sentinel hospitals located throughout the continent [40]. Because of the data amassed, many African countries began to vaccinate against Hib and pneumococcal and meningococcal diseases [40,41]. This effort was facilitated by exploiting existing infrastructure: the PBM forged a partnership with the Network for Surveillance of Pneumococcal Disease in the East Africa Region (netSPEAR), sharing staff and laboratory equipment [40].

India has its own surveillance success story: the NCDC launched the Integrated Disease Surveillance Project (IDSP) in 2004. The IDSP

seeks to strengthen surveillance for epidemic-prone diseases, so that outbreaks can be detected early in their course and appropriate and timely public health responses can be taken. Under the IDSP, state and district level surveillance units are coordinated by a central facility in Delhi. Currently, the IDSP receives weekly epidemiological reports from 85% of the country's districts [42]. PCR is not performed in the IDSP as it is not mandated by their guidelines to confirm a case. The district and state surveillance is largely deficient currently, but many measures are currently underway to strengthen the IDSP. The current strategy planned is to develop 50 priority district labs in 35 states. To provide access to diagnostic facilities for epidemic prone diseases during outbreak situations to the remaining districts, state based referral lab network are being piloted in nine states. This referral laboratory plan, currently being piloted, aims to utilize the laboratory infrastructure and expertise available at medical colleges to diagnose and identify outbreaks in linked districts not having access to functional district public health laboratories. Introduction or expansion of multiplex RT-PCR would allow established laboratories to simultaneously test for multiple agents, including *N. meningitidis* and its serogroups [42]. Action should thus be focused on establishing a network for bacterial surveillance. Indian efforts to enact virological surveillance during the 2009 influenza pandemic could be looked to for inspiration [43].

4.2. Immunization

In India, vaccination against meningococcal disease is reactive and limited to outbreak control [14,26]. This strategy is marked by a number of limitations: (1) some outbreaks are abrupt in onset and of relatively short duration, (2) there is immunological delay after meningococcal vaccination, with protective antibody titers in adults not typically achieved until 7–10 days post-vaccination [2], (3) a substantial proportion of meningococcal disease cases can occur before vaccination campaigns are initiated and (4) access to and mobilization of life-saving vaccines may be impaired. The initiation of immunization campaigns after an outbreak has begun is estimated to prevent fewer than 70% of epidemic-associated cases of meningococcal disease, even under ideal circumstances [44].

Only meningococcal polysaccharide vaccines have been available in India until recently [14]. Although polysaccharide vaccines have a favorable safety and tolerability profile, they are associated with a number of immunological shortcomings that are largely overcome by conjugate vaccine formulations. First, polysaccharide vaccines are poorly immunogenic in children <2 years of age, unlike conjugate vaccines, which are immunogenic in infants. Second, polysaccharides do not stimulate T cells, and as a consequence, immunological memory is not induced. Third, polysaccharide vaccines provide only transient and incomplete protection against carriage [2]. Conjugate vaccines have been shown to reduce acquisition of bacterial carriage among the immunized, interrupting bacterial transmission and contributing to the generation of herd protection within a population [45]. Antibody titers wane over time with both polysaccharide and conjugate meningococcal vaccines [2,46,47], necessitating revaccination. However, polysaccharide vaccines may induce hyporesponsiveness, a phenomenon by which antibody titers upon revaccination are lower than those obtained after initial vaccination [48]. In contrast, booster dosing with conjugate vaccines tends to elevate antibody titers [47,49,50] and can overcome (at least partially) polysaccharide vaccine-induced hyporesponsiveness [51,52]. For these reasons, the GMI, like the IAP and the Association of Physicians of India [26], prefers conjugate meningococcal vaccines.

Routine immunization against meningococcal disease is not being considered in India because meningococcal disease is regarded as having a lower background incidence than either

Streptococcus pneumoniae or Hib [5]. However, this lower incidence may be artificial, and the consequence of disease under-reporting, disease misdiagnosis and rampant antibiotic use. Although recruits to the Indian Armed Forces are routinely immunized with a meningococcal quadrivalent polysaccharide vaccine, at least on a trial basis, military authorities may want to consider the eventual need for booster dosing in light of waning immunity and the issue of hyporesponsiveness intrinsic to polysaccharide formulations.

Until robust surveillance data become available, the GMI recognizes that India is not ready to implement routine vaccination against meningococcal disease. While quadrivalent conjugate vaccines provide broad serogroup coverage, most outbreaks (and possibly endemic disease) in India are limited largely to serogroup A. There is thus strong support for the introduction of a monovalent serogroup A conjugate vaccine. However, informed decisions on the preferential use of monovalent versus quadrivalent conjugate vaccines require better understanding of meningococcal disease in India. Local delegates in attendance at the meeting believed that if recommendations existed, private practice physicians would immunize their patients against meningococcal disease. To this end, the GMI supports the immunization of high-risk individuals either with a quadrivalent or monovalent serogroup A conjugate vaccine.

5. Summary

Although meningococcal disease surveillance in India is not routine and data on endemic disease are lacking, the country is known to experience occasional outbreaks—most recently in 2009—due to serogroup A. These outbreaks can be large in magnitude and are controlled using chemoprophylaxis and/or reactive vaccination. Only polysaccharide meningococcal vaccines are presently available in India. To improve surveillance, and thus understanding of the true burden of meningococcal disease, the GMI recommends (1) strengthening surveillance, (2) expanding use of latex agglutination tests and RT-PCR and (3) initiating carriage and seroepidemiological studies in several parts of the country. Without robust epidemiological data, it will be difficult to assess the need for routine immunization against meningococcal disease in India. Until such time, the GMI recommends the replacement of polysaccharide vaccines with conjugate vaccines, without necessarily changing current indications.

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