THE GLOBAL MENINGOCOCCAL INITIATIVE:

Efforts to prevent and control meningococcal disease in India

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ABSTRACT

Background: The Global Meningococcal Initiative (GMI) is led by international experts in meningococcal immunology, epidemiology, vaccinology, and public health. The goal is to prevent meningococcal disease (MD) through education, research, and vaccination.

Methods: In January 2012, the GMI met with Indian experts to review India's MD burden and to explore MD prevention/control strategies.

Results: *Neisseria meningitidis* is the third most common cause of sporadic bacterial meningitis in children <5 years, with a higher incidence in temperate northern versus tropical southern regions. Actual incidence is not reliably known, due to suboptimal surveillance and insufficient microbiological support for diagnosis. Approximately every 20 years, India experiences large MD outbreaks that are confined to the northern part of the country and are caused almost exclusively by serogroup A. The latest outbreaks, beginning in 2005, have occurred in Delhi, Meghalaya, and Tripura. Outbreaks responses were ad hoc: mandatory case reporting by hospitals in Delhi, temporary strengthening of laboratory diagnostics, chemoprophylaxis of close contacts/high-risk groups, and limited reactive polysaccharide vaccination. Although an Indian facility is manufacturing a serogroup A conjugate vaccine for use in sub-Saharan Africa, it is not presently used in India. The GMI recommends replacement of polysaccharide vaccines with conjugate vaccines, if possible. Although routine immunization is endorsed in some settings, costs and data limitations make such an intervention not presently feasible in India. To improve understanding of the true burden of MD, the GMI recommends—in addition to routine disease surveillance—(1) soliciting existing reference centers to generate diagnostic data using real-time polymerase chain reaction and latex agglutination tests to complement traditional microbiological methods and (2) initiating carriage and seroepidemiological studies. Unless robust data are available, it will not be possible to prioritize MD for routine vaccination based on epidemiological evidence.

Conclusions: MD burden in India is underestimated, and reliable surveillance data are needed. Control efforts should focus on expanding surveillance and educating physicians and officers of the National Regulatory Authority on the importance of MD as a cause of death/disability. Conjugate vaccines should be used for outbreak control and immunization of high-risk persons.

INTRODUCTION

- Meningococcal disease (MD) is caused by *Neisseria meningitidis*[1] and has a high case fatality rate. Those who recover may suffer residual brain damage.
- Of the 12 *N. meningitidis* serogroups, 5 (A, B, C, W-135, and Y) cause the majority of disease. Serogroup distribution varies in time and place.[1]
- In general, the greatest burden of MD is borne by infants and young children.[1,2]
- Vaccination is the best prevention strategy. Meningococcal vaccines—plain polysaccharide, conjugate, and serogroup B outer membrane vesicle vaccines—have been used in different countries to control outbreaks and for routine immunization.

THE GLOBAL MENINGOCOCCAL INITIATIVE

- The Global Meningococcal Initiative (GMI) was formed in 2009 and is led by a multidisciplinary group, whose mission is to effect change in MD through education, research, and international cooperation.
  - The GMI is supported by an unrestricted grant from Sanofi Pasteur.
- The GMI has published global recommendations aimed at reducing the burden of MD (**Table 1**).[2]
- The GMI convened a roundtable meeting in January 2012 in Gurgaon, National Capital Region, India, to tailor its global recommendations to local needs.
  - Participants included medical professionals from selected institutions in India, the Ministry of Defense, and the Ministry of Health (National Centre for Disease Control [NCDC], formerly the National Institute of Communicable Disease [NICD]).

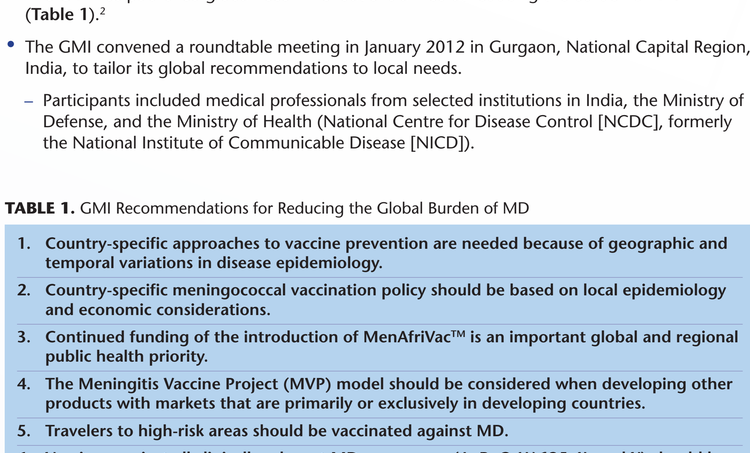
TABLE 1. GMI Recommendations for Reducing the Global Burden of MD

1.	**Country-specific approaches to vaccine prevention are needed because of geographic and temporal variations in disease epidemiology.**
2.	**Country-specific meningococcal vaccination 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 (MVP) 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 MD.**
6.	**Vaccines against all clinically relevant MD serogroups (A, B, C, W-135, 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 MD should be strengthened (or initiated) to determine the true burden of disease.**

SURVEILLANCE

- MD is a notifiable disease in India, but reporting is not enforced, as the health system is focused more on healthcare than the deployment of staff to collect surveillance data.
- In most Indian hospitals, bacterial culture is the most commonly used detection method, but cultures are often negative (**Figure 1**)—a consequence (at least in part) of prior antibiotic use, which is rampant in India.
  - Non-culture-based polymerase chain reaction (PCR) is not used in any hospital in India.
- In the private sector, some laboratories use latex agglutination kits for determining the etiology of bacterial meningitis, but quality control is lacking and different kits have varying specificities and sensitivities for *N. meningitidis*.

FIGURE 1. Total Number of Clinical Samples Tested and Positive by Bacterial Culture or Latex Agglutination for *N. meningitidis*



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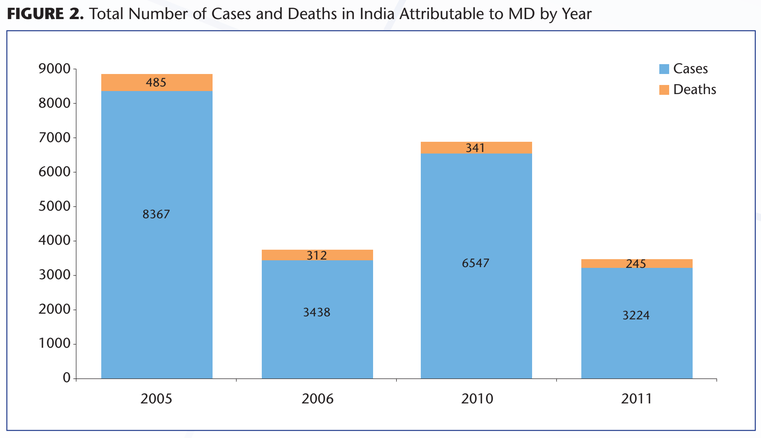
- During epidemics, case reporting and disease monitoring activities are enforced in National Capital Region, but are discontinued after the epidemic has resolved.
- Consequently, data on MD in India—particularly endemic disease—are sparse.
  - Small outbreaks are likely to go unreported and the magnitude of even large-scale epidemics is underestimated.

EPIDEMIOLOGY

- Endemic disease is recognized in several regions of the country (**Figure 2**).[4]

FIGURE 2. Total Number of Cases and Deaths in India Attributable to MD by Year



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- Outbreaks occur at approximately 20-year intervals and are more common in temperate northern versus tropical southern regions of the country.[5] However, there is no clear association between climate and demographics in some parts of the country.
- *N. meningitidis* is the third most common cause of bacterial meningitis in India—responsible for 1.9% of all cases.[5]
  - Unlike *Haemophilus influenzae* type b, *N. meningitidis* affects children, as well as adults.[6]
  - The Indian Armed Forces is a high-risk group, experiencing 9–10 cases of MD per year.[7]
- Serogroup A is the most common cause of MD in India,[5,6] with rare reports of serogroup C.[5]
- Since 2005, there has been an increase in the number of MD outbreaks in India, with epidemics in New Delhi (2005–2009), Meghalaya (2008–2009), and Tripura (2009).[4]
  - The distribution of MD cases over time for the New Delhi outbreak is depicted in **Figure 3**.
  - The distribution of MD cases by location for the Tripura outbreak is presented in **Figure 4**.

FIGURE 3. Distribution of MD Cases Reported by Hospitals in Delhi During 2006-2010

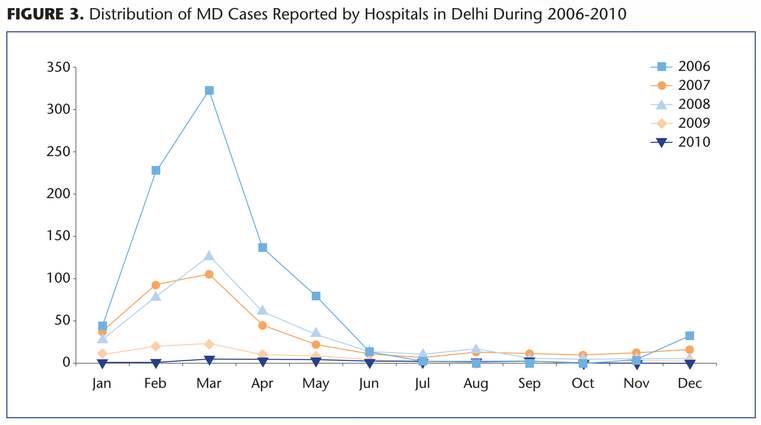

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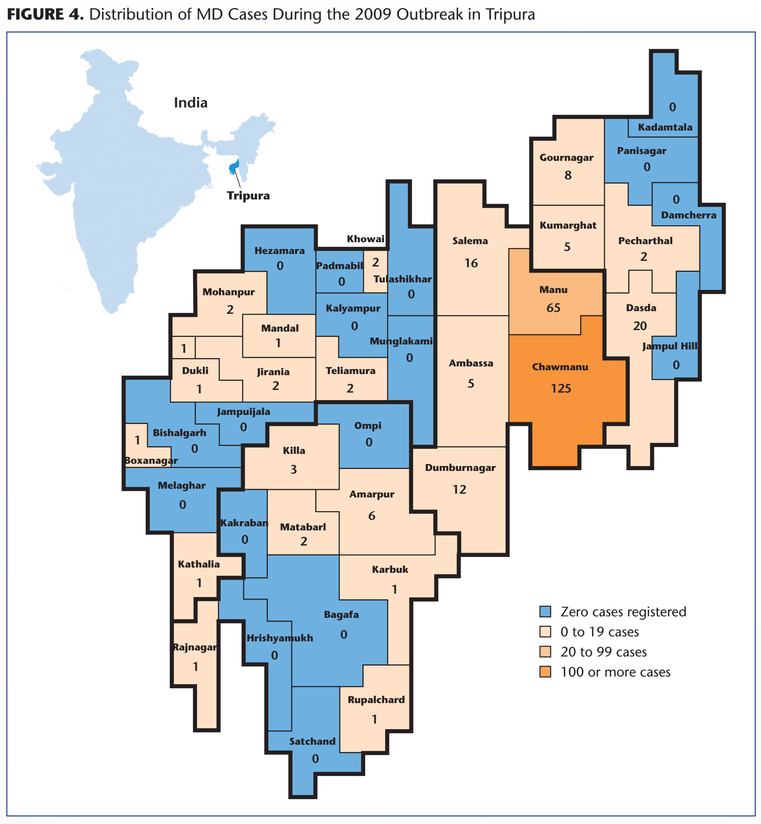
FIGURE 4. Distribution of MD Cases During the 2009 Outbreak in Tripura



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OUTBREAK IDENTIFICATION AND MANAGEMENT

TABLE 2. Situations in Which Outbreaks Are Declared in India

- **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 population over a 3-month period**
- **Incidence (probable or confirmed cases) increases for 3 consecutive weeks in the same area**
- **Single case in an epidemiological setting (eg, nurseries, hostels, barracks, jails)[4] occurs**
- **Attack rate of >3 cases of MD 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[10]**

- Rapid response teams—typically composed of an epidemiologist, medical professionals, and a microbiologist—are deployed to outbreak areas to identify exposed individuals and to assist in disease management.[11]
- Disease surveillance temporarily increases during outbreaks, with samples often sent to the NCDC for diagnosis.[4]
  - During the recent outbreaks, microscopy, culture, and latex agglutination tests were employed for diagnosis.[9,12]
  - PCR was also used in New Delhi.[13]
- The NCDC does not consider mass chemoprophylaxis to be epidemiologically appropriate or cost effective.
- Mass reactive vaccination is instituted when disease incidence exceeds 10 cases/100,000.[4]
  - For the first time in India's history, mass immunization with bivalent (A+C) polysaccharide vaccine was undertaken to control the Meghalaya and Tripura outbreaks.[4]

VACCINATION

- Only polysaccharide meningococcal vaccines are available in India: bivalent (A+C) and quadrivalent (A+C+W-135+Y).[4]
- A monovalent conjugate vaccine against serogroup A (MenAfriVac™) is being manufactured by the Serum Institute of India for use in sub-Saharan Africa.[14] Not presently licensed for use in India, it may soon be made available to the Indian public.[7]
- Given the perceived low incidence of MD, meningococcal vaccines are not routinely administered.
  - The lower incidence may be artefactual, the consequence of disease under-reporting, disease misdiagnosis, and rampant antibiotic use.
- The Indian Academy of Pediatrics (IAP) recommends—in an attempt to avoid hyporesponsiveness—that individuals (even those who maintain a lifelong risk of MD) receive only a single booster dose with a polysaccharide meningococcal vaccine.[10]
  - The IAP prefers conjugate to polysaccharide meningococcal vaccines.[10]

TABLE 3. Summary of MD in India

- **Disease is prevalent, but of a low priority due to:**
  - **Competing infectious disease interests**
  - **Lack of systematic disease surveillance**
  - **Inadequate laboratory diagnostic support services, even in hospitals.**
- **Outbreaks create crisis situations that are managed *ad hoc*.**

PROPOSED RECOMMENDATIONS FOR THE PREVENTION OF MD IN INDIA

Surveillance

- Vaccination strategies are best guided by robust epidemiological data. The GMI thus recommends:
  - Establishing routine surveillance for bacterial meningitis,
  - Standardizing protocols for laboratory diagnosis, including use of latex agglutination tests and real time-PCR (RT-PCR),
  - Initiating nasopharyngeal carriage and seroepidemiological studies in India.
- In 2004, the NCDC launched the Integrated Disease Surveillance Project (IDSP), which seeks to strengthen surveillance for epidemic-prone diseases, so that outbreaks can be detected early and timely action can be taken.
  - Introduction or expansion of multiplex RT-PCR would allow established IDSP-affiliated laboratories to simultaneously test for multiple agents, including *N. meningitidis* and its serogroups.

Immunization

- Reactive vaccination against MD in India is restricted to outbreak control,[4,15] a strategy marked by limitations:
  - Some outbreaks have an abrupt onset and are of relatively short duration,
  - Immunological delay, with protective adult antibody titers not typically achieved until 7–10 days post-vaccination,[1]
  - Substantial proportion of MD cases can occur before vaccination campaigns are initiated,
  - Access to and mobilization of life-saving vaccines may be impaired.
- Polysaccharide vaccines have a favorable safety and tolerability profile, but relative to conjugate vaccines are associated with immunologic shortcomings:
  - Poor immunogenicity in children <2 years of age,
  - Inability to generate immunologic memory,
  - Provision of only transient and incomplete protection against carriage and thus no substantial contribution to herd immunity,[1]
  - Induction of hyporesponsiveness.
- Therefore, the GMI, like the IAP and the Association of Physicians of India,[15] prefers conjugate meningococcal vaccines.
  - Conjugate vaccines should be the vaccines of choice for outbreak control and immunization of high-risk persons.
- Until robust surveillance data are available, the GMI recognizes that India is not ready to implement routine vaccination against MD.
  - To provide broad serogroup coverage, a quadrivalent conjugate vaccine should be considered.
- Local delegates believe that if recommendations existed, private practice physicians would immunize against MD. The GMI supports the immunization of high-risk individuals either with a quadrivalent or monovalent serogroup A conjugate meningococcal vaccine.

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