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The Global Meningococcal Initiative: Recommendations for reducing the global burden of meningococcal disease

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ABSTRACT

The Global Meningococcal Initiative (GMI) is composed of an international group of scientists, clinicians and public health officials with expertise in meningococcal immunology, epidemiology and prevention. The primary goal of the GMI is the promotion of the global prevention of invasive meningococcal disease through education and research. The GMI members reviewed global meningococcal disease epidemiology, immunization strategies, and research needs. Over the past decade, substantial advances in meningococcal vaccine development have occurred and much has been learned about prevention from countries that have incorporated meningococcal vaccines into their immunization programs. The burden of meningococcal disease is unknown for many parts of the world because of inadequate surveillance, which severely hampers evidence-based immunization policy. As the field of meningococcal vaccine development advances, global surveillance for meningococcal disease needs to be strengthened in many regions of the world. For countries with meningococcal vaccination policies, research on vaccine effectiveness and impact, including indirect effects, is crucial for informing policy decisions. Each country needs to tailor meningococcal vaccination policy according to individual country needs and knowledge of disease burden. Innovative approaches are needed to introduce and sustain meningococcal vaccination programs in resource-poor settings with a high incidence of meningococcal disease.

1. Introduction

Neisseria meningitidis causes an estimated 500,000 cases of invasive meningococcal disease (including meningitis, meningococcemia and other forms of invasive disease) and 50,000 deaths annually [1]. Meningococcal disease can be rapidly progressive and fatal in previously healthy individuals [2]. Among survivors, permanent sequelae, such as limb loss, hearing loss and cognitive deficits are common [3–5]. Of 12 meningococcal serogroups, 6 (A, B, C, W-135, X and Y) cause the vast majority of meningococcal disease globally. In light of substantial progress being made with new meningococcal vaccines and with the purpose of promoting the prevention of meningococcal disease, the Global Meningococcal Initiative (GMI[1]) was established in 2009 and is composed of 25 scientists and clinicians with expertise in meningococcal disease.

The GMI is an independent, expert scientific forum consisting of 25 members from across the world that is chaired by Dr. Stanley Plotkin. It was established to promote the global prevention of meningococcal disease through education and research. The GMI is funded by an unrestricted educational grant from sanofi-pasteur.

A GMI steering group met in November 2009 to discuss the scope of the GMI. In June 2010, the first GMI summit meeting was held over 2 days to discuss issues related to the global prevention of meningococcal disease, including clinical aspects, surveillance and epidemiology. In addition, the characteristics of current meningococcal immunization policies were reviewed. The purpose of this paper is to briefly summarize issues that were discussed at this meeting and in subsequent discussions, not to provide a comprehensive review of meningococcal disease epidemiology and prevention.

2. Epidemiology of meningococcal disease

Meningococcal disease epidemiology is highly region specific. The highest incidence of disease occurs in the meningitis belt of sub-Saharan Africa, a huge area that extends from Senegal to Ethiopia, where attack rates during epidemics can be as high as 1% [6]. In countries where the disease is primarily endemic, including much of the Americas and Europe, rates of disease are much lower, ranging from 0.30 to 8.90 cases per 100,000 population [7–9].

The serogroup distribution is highly variable both geographically and temporally [10]. Over 80% of cases in the meningitis belt are caused by serogroup A strains, although disease caused by serogroups C, W-135 and X also occurs; serogroup X disease rarely occurs outside the meningitis belt. Serogroup A disease is also common in many parts of Asia and Russia but has become rare in other parts of the world, including Europe and the Americas. In China most disease is attributable to serogroups C (38%) and A (36%), with about 16% attributable to serogroup B. Serogroup Y disease has been uncommon in Europe despite recent emergence in the USA, Israel and South Africa, where it now accounts for 20% to over 30% of cases [11–13]. Serogroup C disease has declined dramatically in European countries and elsewhere that have instituted monovalent serogroup C conjugate vaccination programs, leaving many countries with a predominance of serogroup B disease. Serogroup B is

[1] See Appendix A.

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an important serogroup in many other parts of the world, including the Americas and parts of Asia.

The highest incidence of meningococcal disease in many countries occurs in infants under 1 year of age. In the European Union, the incidence in this age group is 17.0 per 100,000 with a range of 1.9 in Sweden to 88.7 in Ireland [9]. In England and Wales, 56.8% of all meningococcal disease-related fatalities in 2008 occurred in children ≤4 years of age [14].

In the 1990s, the USA, Canada and the United Kingdom experienced a second peak in meningococcal disease incidence among adolescents. In Canada and the European Union, disease incidence per 100,000 among 15–19 year olds was 1.4 and 2.3 in 2006 and 2007, respectively [8,15]. In the USA, the adolescent peak is still present but has diminished, in conjunction with the overall decline in meningococcal disease incidence [16]. Over the past 10–15 years, studies have demonstrated the importance of behavioral risk factors, such as active and passive smoking, bar and discothèque patronage and kissing, in both meningococcal disease incidence and carriage among adolescents [17,18].

Interestingly, an adolescent peak has not been seen in all countries. Interepidemic and epidemic meningococcal disease in the African meningitis belt is characterized by high incidence rates in individuals up to 20 years of age [19,20]. In Brazil, where most cases are sporadic, meningococcal disease incidence progressively declines from infancy through adulthood. However, during recently reported outbreaks in Brazil, the majority of them associated with serogroup C, a shift in the age distribution of meningococcal disease has been observed, with increased numbers of cases seen among adolescents and young adults [21,22]. In China, the highest incidence also occurs in infancy followed by a progressive decline in older age groups. The reasons for the adolescent peak in some countries and not others are not known, although an adolescent peak has been associated with the introduction of new clones [23]. In the African meningitis belt, climatologic factors are important because meningococcal disease occurs exclusively during the hot, dry and dusty season from January to April/May, but cases promptly cease with the first rains [24].

The reported incidence of meningococcal disease in Latin America varies widely, from fewer than 0.1 cases per 100,000 inhabitants in Mexico and Cuba to almost 2 cases per 100,000 inhabitants per year in Brazil; this likely represents an underestimate of true disease burden. The highest age-specific incidence of meningococcal disease is consistently observed in infants <1 year old. Most cases of meningococcal disease are sporadic but outbreaks, mostly caused by serogroup C, occur at irregular intervals. Most cases are caused by serogroups B and C but some countries have recently experienced the emergence of disease caused by serogroups Y and W-135 [22,25].

As with many infectious diseases, meningococcal disease incidence increases in the elderly; the reasons for this increase are multifactorial and likely include immune senescence, a high prevalence of chronic medical conditions and relative crowding that is associated with long-term care facilities.

In China, reported incidence varies across the country from 0.01 to 0.70 per 100,000. Although the completeness of surveillance in China is unknown, it is in the process of being strengthened throughout the country [26].

In Bangladesh and India, recent epidemics of meningococcal disease have occurred, predominantly caused by serogroup A [27,28]. Disease incidence is seasonal and greater during the first half of the year, dropping off after June, which coincides with the start of the rainy season [29]. Little is known about the epidemiology of meningococcal disease in India during interepidemic periods.

N. meningitidis is a successful human commensal organism that is commonly found in the human pharynx. A high proportion of carried strains are unencapsulated and therefore not virulent. Carriage rates vary substantially over time and geography, with the highest rates generally found in adolescents [30].

2.1. Travel-associated meningococcal disease

International dissemination of *N. meningitidis* has been demonstrated in a series of outbreaks during the Hajj; most recently a serogroup A outbreak in 1987 [31] and subsequent serogroup W-135 outbreaks in 2000 and 2001 [32,33]. During the 1987 outbreak, the risk to US pilgrims was estimated to be 640 per 100,000 pilgrims [34]. No major outbreaks have occurred since 2002 since the quadrivalent (serogroups A, C, W-135 and Y) meningococcal vaccine became a Hajj visa requirement [35].

The risk for international travelers depends on the epidemiology in the destination country, trip duration, and traveler behaviors, including extent of contact with the local population. During the 1982–1984 outbreak in Nepal, six travelers acquired meningococcal disease, which resulted in two deaths, and all had close contact with the local population [36,37]. Despite the high incidence of meningitis in the African meningitis belt, there are only a few reports of travelers to this region affected by meningococcal disease [37].

3. Problems with diagnosis and surveillance

The development of country-specific meningococcal immunization policy requires comprehensive laboratory-based surveillance data. Traditionally, there has been heavy reliance on culture-based surveillance, which has the advantage of allowing determination of serogroup and other characteristics of the meningococcal isolate. However, bacterial culture generally leads to an underestimation of disease burden. Therefore, some countries have also included PCR-based approaches to surveillance. PCR has the advantage of providing a diagnosis in the setting of culture-negative meningococcal infection, which is common in places in which antimicrobial administration before initiation of therapy is frequent and/or microbiology services are suboptimal [38,39]. Although the meningococcal isolate is not available in culture-negative, PCR-positive cases, molecular approaches can be used to determine the capsular group and other microbial characteristics. In the United Kingdom, 58% of laboratory-confirmed meningococcal cases were confirmed by PCR alone [40]. In Brazil, use of PCR increased the yield by 92% over what was estimated by culture alone [41]. However, PCR should not replace culture. Additional non-culture methods are being developed and additional approaches are likely to be available in the future.

Surveillance for meningococcal disease in some parts of the world is based on clinical case definitions, particularly in resource-poor countries [10]. In settings in which laboratory resources are limited, clinically diagnosed cases may account for the majority of those reported. As an example, surveillance in the African meningitis belt is based in part on a case definition that can be used in any type of healthcare setting [42]. During epidemics, which are generally caused by a single strain, laboratory confirmation of a small number of cases is often used to make decisions about reactive community-based immunization programs.

The GMI encourages the use of culture supplemented by non-culture laboratory approaches to surveillance to ensure accurate estimates of meningococcal disease burden in all countries wishing to develop meningococcal immunization policy. Partnerships between resource-rich and resource-constrained regions are encouraged to overcome obstacles to laboratory-based surveillance in developing countries. As an example, the European Meningococcal Disease Society (EMGM) provides reference laboratory services not only for Europe, but also for parts of Africa and Latin America. In