



Conference report

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, meningococemia 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 (GMI¹) 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.

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. Car-

riage 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

addition, the WHO Collaborating Centres for Reference & Research on Meningococci provide laboratory services globally. Over the past 10 years, meningococcal surveillance has substantially improved in some African meningitis belt countries [43].

Nonetheless, important surveillance gaps in many countries should be addressed if we are to understand the true global burden of meningococcal disease. Knowledge of the burden of diseases is crucial for the development of appropriate strategies for prevention of meningococcal disease.

4. Characteristics of current global vaccines

Until the last decade, licensed meningococcal vaccines consisted primarily of purified polysaccharide products against 1–4 of the meningococcal serogroups: A, C, W-135 and/or Y. Now monovalent serogroup A and C as well as quadrivalent A, C, W-135 and Y polysaccharide–protein conjugate vaccines are available. Conjugate vaccines generate T-cell-dependent responses, which confer multiple immunologic advantages over polysaccharide vaccines, including induction of herd immunity effect, ability to stimulate immunologic memory and lack of induction of immunologic hyporesponsiveness [44]. In addition, tailor-made outer membrane vesicle (OMV)-based vaccines have been used for the control of serogroup B outbreaks. To date, no serogroup X vaccine has been developed, although vaccines that target non-polysaccharide antigens that are being developed for serogroup B could also provide protection against serogroup X [45]. The GMI reviewed recent data on select meningococcal vaccines, global meningococcal disease epidemiology and immunization strategies, and its findings and recommendations are briefly summarized below.

4.1. Polysaccharide vaccines

Both bivalent (A, C) and quadrivalent (A, C, Y, W-135) polysaccharide vaccines are licensed; in developed countries, however, use is primarily limited to the quadrivalent product [46]. A trivalent polysaccharide vaccine (A, C, W-135) is also available for use in sub-Saharan Africa to address the local epidemiology. Polysaccharide meningococcal vaccines elicit serum antibody responses primarily without T-cell help. In general, these vaccines are immunogenic in older children and adults but not in infants and young children, there are no booster or herd immunity effects and there are relatively rapid declines in serum bactericidal antibody titers in an age-specific fashion.

4.2. Conjugate vaccines

Conjugation of meningococcal polysaccharide(s) to a protein carrier results in a T-cell-dependent immune response, resulting in enhanced responses as measured by higher antibody concentrations in infants and the development of an anamnestic response at re-exposure [46]. Three monovalent serogroup C conjugate vaccines, one monovalent serogroup A conjugate vaccine and two quadrivalent conjugate vaccines are licensed and available on a country-specific basis. The three monovalent C vaccines are currently licensed in Europe, Australia, Canada and most Latin American countries [22,47,48]. Two of the vaccines are conjugated to the non-toxic CRM197, a mutant protein created from diphtheria toxin and one is conjugated to tetanus toxoid. A vaccine is also available containing serogroup C polysaccharide and Hib polysaccharide, both conjugated to tetanus toxoid [49]. Men C conjugate vaccines were first introduced in the United Kingdom in 1999 on the basis of safety and immunogenicity. These vaccines were incorporated into the routine infant immunization schedule at 2, 3 and 4 months of age, and a catch-up campaign targeting all children under the age of 18 years was undertaken in the United Kingdom.

Subsequently, Ireland, Spain, the Netherlands, Belgium, Iceland and Portugal incorporated meningococcal C conjugate vaccines into the national immunization programs with country-specific regimens. These vaccines elicited functional antibody and resulted in substantial declines in serogroup C disease. These declines were caused by both direct protection and herd immunity, which is due to reductions in meningococcal carriage. No increase in serogroup B disease was observed.

The monovalent A conjugate vaccine was prequalified in June 2010 by the WHO and is being introduced at public health scale in Burkina Faso, Mali and Niger in late 2010 [50,51].

Two quadrivalent conjugate vaccines are licensed, one conjugated to CRM197 (MCV4-CRM) and the other to diphtheria toxoid (MCV4-DT). MCV4-DT was licensed on the basis of safety and immunogenicity data, indicating its noninferiority to the licensed quadrivalent polysaccharide vaccine (MPSV4) in terms of percentage of adolescents and young adults who had a fourfold or greater increase in bactericidal antibody following immunization [52]. Long-term antibody persistence at 3 years post-vaccination was substantially higher among people vaccinated with MCV4-DT than people who received MPSV4. In addition, when people were revaccinated with MCV4-DT after 3 years, antibody responses were significantly higher among those initially primed with MCV4-DT, demonstrating the development of memory with primary immunization [53]. Recent preliminary data from an ongoing postlicensure study of MCV4-DT in the USA suggests that effectiveness declined from 94% (95% confidence interval [CI], 14–99%) within 1 year of vaccination to 83% (95% CI, 1–97%) 1 to <2 years after vaccination and 56% (95% CI, 74–89%) at 2 to <5 years [54].

Shortly after the introduction of MCV4-DT for use in adolescents in 2005, a cluster of cases of Guillain-Barré syndrome was identified, raising concerns about a potential link between receipt of vaccine and this syndrome. However, subsequent large studies have not demonstrated an increased risk [55].

In adolescents aged 11–18 years, serum bactericidal response to MCV4-CRM was greater for all 4 serogroups when compared to MCV4-DT [56]. The proportions of subjects with bactericidal seroresponses were statistically higher for serogroups A, W and Y in the MCV4-CRM group compared with the MCV4 group. However, the clinical relevance of these differences is not known. Safety profiles for the two vaccines were comparable.

4.3. Vaccines targeting serogroup B *N. meningitidis*

Due to the structural homology between the capsular polysaccharide and the neural cell adhesion molecule in the human fetal brain, use of serogroup B polysaccharide capsule is an unsuitable approach for vaccine development. Current efforts for vaccines that protect against serogroup B disease focus on antigenic meningococcal outer membrane proteins, which are generally found among all strains and therefore could potentially provide protection against all meningococcal serogroups. OMV vaccines are the only formulations so far to have shown effectiveness against serogroup B meningococcal disease in a variety of settings, most recently in the control of an epidemic in New Zealand [57]. A Cuban OMV-BC vaccine has been extensively used for more than 20 years and has been included in the Cuban National Immunization Program since 1991. This vaccine has controlled meningococcal disease in Cuba, with a decrease in morbidity (93%) and mortality (98%) and has also been used in other Latin American countries [58]. The strain-specific immune response to these vaccines is highly directed towards the immunodominant porin protein PorA [59]. OMV vaccines are suitable for epidemic control, but given the wide antigenic diversity of PorA in serogroup B strains causing endemic disease, they are not useful for non-epidemic settings [60].

Two vaccines that target other meningococcal outer membrane proteins are in clinical trials for protection against endemic serogroup B disease. One contains two variants of factor H binding protein (fHbp) and another contains three recombinant proteins: Neisserial adhesin A (NadA), Neisserial heparin-binding antigen (NHBA) and fHbp, in combination with the OMV vaccine previously used in New Zealand. These vaccines have been shown to be immunogenic and safe in clinical studies [61,62]. However, key unanswered questions about these vaccines include the breadth of age-specific protection against serogroup B strains, effectiveness, duration of immunity, protection against non-serogroup B strains and whether they have an impact on the acquisition of pharyngeal carriage of *N. meningitidis*.

5. Characteristics of selected current global vaccination strategies

The GMI reviewed vaccination strategies currently employed in a number of countries (Table 1).

5.1. Africa

The African meningitis belt, with its high endemic and epidemic rates of meningococcal disease, represents the most important priority to decrease the global burden of meningococcal disease. For the past 20 years, control of serogroup A meningitis epidemics in the African meningitis belt has relied on reactive immunization with polysaccharide vaccines during epidemics. This reactive strategy is logistically difficult because it relies on prompt recognition of epidemics and the ability to carry out timely vaccinations because meningococcal epidemics in this region are generally over after 6 weeks [50]. More often than not, these campaigns have had suboptimal impact.

This vaccination strategy is about to change. Over the past 9 years, the Meningitis Vaccine Project (MVP), a partnership between the WHO and the Program for Appropriate Technology in Health (PATH), has developed an affordable (under US\$0.50 per dose) serogroup A conjugate vaccine called MenAfriVac™, which is manufactured at the Serum Institute of India, Ltd [63]. This vaccine has received market authorization in India and was prequalified by the WHO in June 2010; this will be introduced following the successful model used in the United Kingdom for serogroup C conjugate vaccines. Mass vaccination campaigns will be used to immunize 1–29 year olds to generate broad direct and herd immunity. Burkina Faso, Mali and Niger have all initiated campaigns in 2010. Since more than 80% of meningococcal disease in the African meningitis belt is attributable to serogroup A [64], comprehensive use of this vaccine in meningitis belt countries is expected to prevent over one million cases of meningococcal disease over a 10-year span. An important public health priority is to immunize between 250 and 300 million Africans who live in high-risk areas with MenAfriVac™. This effort is being led by the WHO and UNICEF.

Unlike countries in the meningitis belt, meningococcal disease in South Africa is endemic with seasonal increases during winter and spring months. The age group at greatest risk is children <1 year of age, although there are some differences by serogroup [65,66]. The incidence of reported laboratory-confirmed meningococcal disease ranges from 1 to 4 per 100,000 population [65,66]. Since 2003, South Africa has documented a decline in serogroup A disease and an increase in disease caused by serogroup W-135 [66]. Serogroups W-135, B and Y are currently the predominant serogroups causing disease in South Africa.

There is no routine use of meningococcal vaccines in South Africa. Two quadrivalent polysaccharide meningococcal vaccines (containing serogroups A, C, W-135 and Y) are available. Vaccina-

tion is used for at-risk populations and in response to outbreaks. No polysaccharide–protein conjugate meningococcal vaccines are registered in South Africa. In the future, conjugate vaccines will become registered and may play a role in preventing meningococcal disease in infants.

5.2. Europe

In Europe, the incidence of meningococcal disease varies by country, with rates ranging from <1 to 8.9 per 100,000 in 2006 [67]. Most cases of meningococcal disease are due to serogroups B and C (90% of cases), while cases due to other serogroups (e.g., Y and W-135) are uncommon. Up to 20% of cases are due to serogroups Y and W-135 among people over 65 years old, but these serogroups are rare in infants, in whom B strains predominate.

Many European countries (Belgium, Iceland, Ireland, the Netherlands, Spain and the United Kingdom) began to vaccinate against meningococcal serogroup C between 1999 and 2006 with a monovalent conjugate formulation, using strategies targeting infants (Ireland, Spain and the United Kingdom) or toddlers (Belgium and the Netherlands) as well as catch-up campaigns. The incidence of meningococcal disease due to serogroup C in countries with routine serogroup C meningococcal vaccination dropped from approximately 1.4 per 100,000 in 1999 to less than 0.15 per 100,000 in 2006 [67]. Infants in the United Kingdom were originally vaccinated at 2, 3 and 4 months of age, but it was found that vaccine effectiveness fell substantially after 1 year among children immunized as infants, and only 53% of infants maintained protective serum bactericidal antibody titers (1:8) by age 14 months [68]. This prompted a revision of the vaccination schedule to doses at 3, 4 and 12 months of age. Herd immunity, generated by the catch-up campaigns, was also reported in these countries and was responsible for a large reduction of the burden of the disease in unvaccinated groups [69–71].

In countries without routine serogroup C conjugate vaccination, incidence of meningococcal disease remained rather stable over the period 1999–2006 at about 0.2 per 100,000 [72]. Several of these countries (Germany, Portugal and Switzerland in 2006 and France in 2009) have now implemented routine vaccination with meningococcal C conjugate vaccine. While Portugal targeted infants, the other three countries targeted toddlers (Germany, Switzerland and France). Catch-up campaigns were recommended in France and Portugal. Moreover, Switzerland recommended a booster dose between 11 and 15 years of age. Presently, adolescents are not boosted with meningococcal C conjugate vaccine in the other countries with routine vaccination. While waning of serum bactericidal antibody titers is observed 5 years after immunization [73], reduced clinical protection has not been observed [49]. The persisting herd immunity is likely to control disease for a number of years [49]; however, boosting during adolescence will likely be efficacious in maintaining high bactericidal antibody titers.

MCV4-CRM was recently licensed in Europe. However, there is no recommendation for routine use because of the low incidence of meningococcal disease attributable to serogroups A, W-135 and Y in Europe (<10% of cases) [67]. This vaccine is, however, recommended for travelers (e.g., pilgrims to Mecca) and other high-risk groups, such as those with splenectomy and terminal complement component deficiencies.

5.3. North America

5.3.1. Canada

Although immunization policy is province specific, the National Advisory Committee on Immunization (NACI) for Canada first recommended meningococcal C conjugate vaccine for infants, children through 4 years of age, adolescents and young adults, beginning

Table 1
Examples of current meningococcal disease vaccination programs.

Country	Vaccine	Vaccination schedule
African meningitis belt	Men AC polysaccharide, Men ACW polysaccharide (New MenA conjugate vaccine to be introduced in 2010)	Reactive vaccinations as part of outbreak management (the new Men A conjugate will be used preventively)
Argentina	MenAC polysaccharide MenC conjugate MenB	Outbreak management
Australia	MenC conjugate	12 months of age
Brazil	MenAC polysaccharide MenC conjugate	≥2 years of age 3, 5 and 12–15 months of age
Canada	MenC conjugate MenACWY conjugate	2, 4 and 12 months of age 2–55 years, if high risk
China	MenA polysaccharide MenAC polysaccharide	2 doses between 6 and 18 months Booster at 3 and 6 years
Cuba	MenBC	3 and 5 months of age
France	MenC conjugate	1 dose between 12 and 24 months (2–24 years for catch-up)
Greece	MenC conjugate	2, 4 and 15–18 months of age
Guyana	MenACWY polysaccharide	Only in high-risk or special needs groups
Italy	MenC conjugate	2 months–2 years
Japan		No routine vaccination strategy
India	MenAC polysaccharide	In epidemic areas
Mexico		No routine vaccination strategy
Mongolia	MenACWY polysaccharide	2–14 years
New Zealand	MeNZB	Routine vaccination has ceased; vaccination still available for high-risk groups
Paraguay	MenAC polysaccharide	Only in high-risk or special needs groups
Russia	MenAC polysaccharide	Contacts with the infected
Saudi Arabia	MenACWY conjugate	Healthcare workers, Hajj pilgrims and residents of the Hajj region aged 2–55 years
South Africa	MenACWY polysaccharide	Only in high-risk groups and for outbreak management
Spain	MenC conjugate	2, 6 and 15–18 months of age
United Kingdom	MenC conjugate (combined with Hib at 12 months)	3, 4, and 12 months of age
United States	MenACWY conjugate	11–18 years (2–10 years, 18–55 if high risk; 13–18 years for catch-up)

in 2001 [8]. In 2007, the recommendation was changed for high-risk individuals 2–55 years of age to receive quadrivalent conjugate meningococcal vaccine (serogroups A, C, Y and W-135), but, for the routine immunization of adolescents, meningococcal C conjugate vaccine remained the recommendation unless local epidemiology warranted use of the quadrivalent conjugate. The NACI also stated that the quadrivalent conjugate meningococcal vaccine could be considered for individuals with HIV, as well as for high-risk individuals who are ≥56 years of age and who had close contact with people with invasive meningococcal disease (caused by one of the serogroups covered by quadrivalent conjugate meningococcal vaccine).

In 2009, the NACI recommended immunization with quadrivalent meningococcal conjugate vaccine in early adolescence (rather than meningococcal C conjugate vaccine), even if previous meningococcal vaccination had been completed as part of an infant or toddler vaccination program. In addition, some of the provinces/territories changed their recommendation for the 12-month dose of meningococcal C conjugate vaccine to the quadrivalent conjugate vaccine. The rationale for the adolescent dose was to ensure that circulating antibodies were present because this age cohort exhibits a second peak for meningococcal disease (after infancy) and has the highest meningococcal carriage rate. The NACI also recommended that children aged 2 years or older, with

immunodeficiency states defined by abnormal humoral function, should receive the quadrivalent conjugate meningococcal vaccine. Children between 2 and 10 years of age should receive a dose of meningococcal C conjugate (with a minimum of a 1-month interval between vaccines).

5.3.2. United States

In the USA, a bivalent polysaccharide AC vaccine was available in 1976, which was superseded by the quadrivalent polysaccharide A, C, Y and W-135 vaccine in 1981, that, until recently, was used universally in military recruits. By 1986, meningococcal quadrivalent polysaccharide vaccine was recommended for children 2 years and older with functional or anatomic asplenia and complement or properdin deficiencies, as well as for control of outbreaks due to vaccine serogroups, and for international travelers [52]. In 2000, the American College Health Association recommended immunization for all college students, and the American Academy of Pediatrics and Advisory Committee on Immunization Practices (ACIP) recommended the education of students and parents about the risk of meningococcal disease and immunization at the request of the student.

MCV4-DT became available in 2005 and is now licensed for people between 2 and 55 years of age. Routine immunization is recommended for all adolescents 11–18 years old, those children

2 years and older at increased risk of meningococcal disease (such as children with terminal complement or properdin deficiencies or anatomic and functional asplenia), persons older than 2 years with HIV infection, children and adolescents who travel or reside in countries where meningococcal disease is epidemic, laboratory workers exposed to live *N. meningitidis*, college freshmen living in dormitories and military recruits. The ACIP also recently recommended a booster at 16 years for adolescents vaccinated at 11 years of age due to waning antibodies and evidence for declining vaccine effectiveness over 5 years [52]. MCV4-DT is also indicated for control of outbreaks caused by vaccine-preventable serogroups. More recently, MCV4-CRM was licensed in the United States for persons between 11 and 55 years of age and can be used interchangeably with MCV4-DT in this age group [52,53]. At the October 2010 ACIP meeting, it was recommended that the current recommendations for MCV should be changed to include a booster dose given 3–5 years after initial immunization (dependant on age of initial immunization) based on the declining effectiveness of MCV-DT with time after administration [54].

5.4. Latin America

In many Latin American countries, polysaccharide vaccines, the serogroup B OMV plus a serogroup C polysaccharide Cuban vaccine, meningococcal C conjugate vaccine, and quadrivalent (A, C, W-135, Y) meningococcal conjugate vaccine are available through private markets, with generally poor vaccine coverage, or in public markets for selected high-risk groups and/or control of outbreaks [22].

In the late 1980s, Cuba implemented a mass vaccination campaign with the serogroup B OMV plus a serogroup C polysaccharide vaccine targeting all persons less than 19 years of age and, since 1991, this vaccine has been routinely used in their childhood immunization schedule [58]. Brazil is the only country in the region that has begun to introduce the serogroup C conjugate vaccine into the routine immunization schedule. Infants receive two doses at 3 and 5 months, with a booster dose at 12–15 months, while toddlers between 12 and 23 months of age receive one dose. No catch-up campaigns in older age groups are currently planned [22].

5.5. Asia

In China, polysaccharide (A, A+C, and A+C+W-135+Y) and conjugate (A+C) vaccines are available. Two doses of polysaccharide A vaccine are administered to children at 6 and 18 months. Two doses of polysaccharide A+C vaccine are administered to children at 3 and 6 years. In areas where children <2 years have been vaccinated, decline in disease incidence has been observed, whereas regions that have not implemented vaccination campaigns continue to experience meningococcal outbreaks. In China, the current challenges are to strengthen surveillance, improve the sensitivity of case reporting, decrease mortality rates and expand immunization to the whole country.

Bivalent (A+C) polysaccharide meningococcal vaccine is used in India for vaccination during epidemics.

5.6. Pacific

In 2004, New Zealand initiated a serogroup B meningococcal vaccine campaign to control an epidemic dominated by serogroup B:4:P1.7b,4, with a peak incidence of 17.4 cases per 100,000 in 2001 [74]. The vaccine, called MenZB™, was tailor-made to control the epidemic strain using an OMV approach. The effectiveness of this vaccine was demonstrated by a 3.7-fold decreased risk of serogroup B disease among vaccinated versus unvaccinated individuals [75]. The Meningococcal B Immunization Programme was terminated in 2006 [76]. Disease incidence remains relatively low,

with 2.6 cases per 100,000 individuals in 2007 [10]. New Zealand public health officials continue to actively monitor the incidence of disease following the termination of the program.

5.7. Destination-specific vaccine strategies for travelers

Vaccination against meningococcal disease is not a requirement for entry into any country, except for Hajj/Umrah pilgrims to Saudi Arabia, for whom the quadrivalent meningococcal vaccine (polysaccharide or conjugate) is a visa requirement. Proof of immunization is needed for all Hajj and Umrah visa applicants [77].

Meningococcal vaccination is recommended for travelers to the meningitis belt in sub-Saharan Africa, particularly during the dry season (December to June). Travelers should be advised to receive a meningococcal vaccine that covers all four vaccine serogroups. Refugee settings in Africa present a particular potential but undocumented higher risk for meningococcal disease because of overcrowding.

Vaccination should be advised for travelers to other areas that are actively experiencing outbreaks or epidemics. Up-to-date information is available at www.cdc.gov/travel/diseases/menin.htm or at www.who.int/csr/disease/meningococcal/en/.

Students who travel overseas for the purpose of entering universities may be at modestly elevated risk of meningococcal disease in some countries based on observations in the USA and United Kingdom [52,78]. They should be advised about the local immunization recommendations and follow local recommendations and regulations. Children from countries with routine immunization programs traveling to hyperendemic countries are advised to complete their vaccination schedule before departure as conjugate vaccines may not be available at the destination country. If they only received the serogroup C conjugate vaccine, depending on the epidemiology of meningococcal disease in the destination country, it is important that children also receive coverage against the other serogroups with currently available quadrivalent vaccines.

6. Summary of GMI recommendations

At the inaugural meeting of the GMI, the complexity of meningococcal disease epidemiology was reviewed. Because of huge regional and temporal differences in epidemiology, it is obviously not possible to formulate global vaccination recommendations. As a consequence, future GMI meetings will be regionally focused, with the intention of developing country-specific recommendations. However, the GMI endorses the following general principles:

1. The striking regional variability in disease incidence and serogroup distribution underscores the need for country-specific approaches to vaccine prevention of meningococcal disease. There is a need for each country to assess the health economics of routine meningococcal immunization because the current disease incidence is at a nadir in some countries.
2. Country-specific meningococcal policy should be based on local epidemiology and economic considerations.
3. The GMI strongly supports the rapid introduction of MenAfriVac™ to African meningitis belt countries as the surest strategy to rapidly decrease the global burden of meningococcal disease. Continued funding of the introduction of this affordable vaccine is an important global as well as regional public health priority.
4. The MVP model that resulted in the rapid development of a new and affordable serogroup A conjugate vaccine specifically designed to meet an African problem 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. Information about meningococcal vaccines for travel can be found at www.cdc.gov/travel/diseases/menin.htm and www.who.int/csr/disease/meningococcal/en/.
6. While substantial progress has been made in the area of meningococcal vaccines during the past 10 years, additional vaccine development is needed. Ultimately, vaccines covering all relevant serogroups that cause disease globally, including A, B, C, W-135, X and Y, should be developed. Current broad-coverage serogroup B vaccines that are in development may provide some protection against all meningococcal serogroups because the vaccine targets (including fHbp, NadA and NHBA) are serogroup-independent.
7. Because of the limitations of polysaccharide antigens, conjugate vaccines should replace polysaccharide vaccines whenever possible as allowed by cost, availability, licensing and immunization policy. However, polysaccharide vaccines are still recommended where conjugate vaccines are not available.
8. Laboratory-based surveillance for meningococcal disease should be strengthened to determine the true disease burden, particularly in countries that have substantial disease and are considering meningococcal immunization programs. Countries lacking adequate surveillance should consider studies to measure disease burden for meningococcal disease, as well as other vaccine-preventable invasive bacterial diseases, such as *Haemophilus influenzae* type b and *Streptococcus pneumoniae*.

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