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REVIEW

The Global Meningococcal Initiative meeting on prevention of meningococcal disease worldwide: Epidemiology, surveillance, hypervirulent strains, antibiotic resistance and high-risk populations

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ABSTRACT

Introduction: The 2018 Global Meningococcal Initiative (GMI) meeting focused on evolving invasive meningococcal disease (IMD) epidemiology, surveillance, and protection strategies worldwide, with emphasis on emerging antibiotic resistance and protection of high-risk populations. The GMI is comprised of a multidisciplinary group of scientists and clinicians representing institutions from several continents.

Areas covered: Given that the incidence and prevalence of IMD continually varies both geographically and temporally, and surveillance systems differ worldwide, the true burden of IMD remains unknown. Genomic alterations may increase the epidemic potential of meningococcal strains. Vaccination and (to a lesser extent) antimicrobial prophylaxis are the mainstays of IMD prevention. Experiences from across the globe advocate the use of conjugate vaccines, with promising evidence growing for protein vaccines. Multivalent vaccines can broaden protection against IMD. Application of protection strategies to high-risk groups, including individuals with asplenia, complement deficiencies and human immunodeficiency virus, laboratory workers, persons receiving eculizumab, and men who have sex with men, as well as attendees at mass gatherings, may prevent outbreaks. There was, however, evidence that reduced susceptibility to antibiotics was increasing worldwide.

Expert commentary: The current GMI global recommendations were reinforced, with several other global initiatives underway to support IMD protection and prevention.

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Antibiotic resistance; bacterial meningitis; conjugate vaccine; epidemiology; immunization program; meningococcal disease; Neisseria meningitidis; polysaccharide vaccine; serogroup; surveillance; vaccine

1. Introduction

Invasive meningococcal disease (IMD) results from infection with *Neisseria meningitidis* (Nm) and is associated with high case-fatality rates (CFRs) and long-term sequelae among survivors, including neurologic complications, loss of limbs, hearing loss, and paralysis [1]. The most common manifestations of IMD are meningitis and septicemia; however, other forms may arise, such as septic arthritis, pericarditis, and bacteremic pneumonia [2]. Based on the immunochemistry and genetics of the Nm capsular polysaccharides, 12 serogroups have been identified, with six (A, B, C, W, X, and Y) accounting for the majority of all cases of IMD worldwide [3,4]. The geographical distribution and epidemic potential of Nm strains differ. IMD may occur sporadically, in small clusters, as localized outbreaks, or as large outbreaks or epidemics [5]. Adequate surveillance is paramount for accurate epidemiological data and, in turn, initiation of appropriate prevention strategies [6].

2. Methods

Since 2009, the Global Meningococcal Initiative (GMI) has held various regional and global meetings in efforts to prevent IMD

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worldwide through education, research, and international cooperation [7]. In March 2018, the GMI organized a global roundtable meeting with a multidisciplinary group of scientists and clinicians representing institutions from Latin America, United States of America (U.S.A.), Canada, Europe, Russia, the Asia-Pacific region, China, East Asia, the African meningitis belt, Southern Africa, Northern Africa and the Middle East. Each delegate gave an update on IMD epidemiology and the surveillance, prevention, and control strategies in place for IMD in their region. To date, the GMI has published 10 key global recommendations for IMD (Table 1) [4,7].

The specific objectives for this meeting were to: (i) provide an update on global IMD surveillance and epidemiology, including epidemic potential of Nm strains; (ii) review current prevention and control strategies from a global perspective; (iii) share lessons learned and experience gained from IMD immunization programs used across the globe, including the use of conjugate vaccines; (iv) discuss the emergence of antibiotic resistance and its mechanisms; (v) discuss the potential risk of IMD in high-risk groups, including mass gathering attendees, and recommendations for immunization; and (vi) outline proposals for global initiatives for IMD prevention. This paper summarizes the key discussion points from the meeting to raise awareness of key challenges and to help inform global and regional recommendations for IMD prevention.

3. Results

3.1. Review of global meningococcal disease surveillance and epidemiology

National IMD laboratory-based public health surveillance enables detection of IMD and assists with a prompt and effective response, and is therefore fundamental for IMD prevention. Importantly, IMD surveillance identifies the serogroup responsible and geographical distribution, which directly informs the subsequent prevention strategies employed, including vaccination [6]. Additionally, epidemiological data post-vaccination can be used to determine vaccine impact and effectiveness [8]. The majority of countries represented at the meeting had IMD surveillance systems in place, although structures and methodologies vastly differed. The differences were predominately attributed to structural complexity (national vs. regional), necessity to report IMD cases rather than meningitis only, and laboratory capabilities (i.e. capacity and resources). In some instances, sentinel surveillance was considered adequate (e.g. Northern Africa and China) and in others, national surveillance systems were well established and included detailed laboratory analyses (e.g. United Kingdom (U.K.) and South Africa). Further, some countries implemented a regular national bulletin (e.g. some African countries and Russia) to support communication efforts between neighboring countries/regions in terms of laboratory data.

Table 1. GMI global recommendations.

1. Country-specific approaches to vaccine prevention are needed because of disease variation.
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 (MVP) model should be considered when developing other products with markets that are primarily or exclusively in low- to middle-income countries.
5. Travelers to high-risk areas should be vaccinated against MD according to recommendations by public health authorities.
6. Vaccines against all clinically relevant 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 IMD should be strengthened (or initiated) to determine the true burden of disease.
9. Local public health authorities should assess the value of issuing an advisory for those attending a planned mass gathering event to be vaccinated based on available epidemiologic evidence.
10. Vaccination of individuals who are HIV positive.

3.1.1. Incidence of meningococcal disease

Due to the diverse standards of IMD surveillance systems globally and country/regional differences in IMD epidemiology, incidence estimates for countries represented at the meeting varied drastically, particularly in terms of the time period(s) cited. Overall, current country-specific incidence levels of IMD reported during the meeting ranged from 0.01 to 0.02 cases per 100,000 persons per year in Mexico (2014–2017) [9] to 2–3.6 cases per 100,000 persons per year in Morocco (2012–2016) [7,10]. The incidence of IMD cases per 100,000 population was 0.70, 0.12, and 0.30 in Europe [11], U.S.A. [12] and Canada in 2015 [13], respectively. In China, the IMD incidence rate was 0.05 cases per 100,000 population based on data from 2006 to 2014 [14]. The incidence of IMD was reported as 0.45–1.0, 1.6, and 0.23 cases per 100,000 persons in Russia (2010–2016) [15], New Zealand (2016) [16], and South Africa (2016) [17], respectively. IMD incidence differed across East Asia, with between 0.01 and 0.03 cases per 100,000 persons per year since 2011 in Taiwan [18], and reports of between 1 and 58 cases between 2002 and 2010 in Korea ([NNDSS data collected by personal communication; unreferenced]), and between 7 and 21 cases reported annually since 1999 in Japan [19]. Further, the number of cases per 100,000 persons in 2006 was 0.01–0.08 and 0.028 in Korea and Japan, respectively [20]. The incidence of IMD in Latin America varied widely in the last decade, ranging from <0.1 cases per 100,000 persons in countries such as Bolivia, Cuba, Mexico, Paraguay, and Peru to nearly 2 cases per 100,000 persons in Brazil [21]. The meningitis belt of sub-Saharan Africa warrants a special mention given the unprecedented decline in IMD incidence levels from more than 100 cases to 0.02 cases per 100,000 population between 2011 and 2013 following the introduction of a monovalent serogroup A meningococcal tetanus toxoid conjugate vaccine (PsA-TT; *MenAfriVac*®) from 2010 [22].

3.1.2. Serogroup distribution

Surveillance data indicated that the incidence and prevalence of Nm serogroups continually varies both geographically and temporally [23,24]. Currently, meningococcal serogroup B (MenB) is a major cause of IMD in North America, South America, Australia, North Africa, and Europe, although a decreasing incidence trend is being observed [25], which was supported by the data presented from other countries at the 2018 GMI meeting [10,11,26–30]. The incidence and prevalence of MenB naturally fluctuates over time and is currently at an all-time low; the reasons for this were unknown, but it was hypothesized that the introduction of a smoking ban in public places in some countries may have played a role.

Meningococcal serogroup C (MenC) was also reported as one of the most prevalent serogroups in Brazil [31], China [6], Russia [15,29], India [32], and Niger/Nigeria [33,34]. In India, the predominant serogroup was meningococcal serogroup A (MenA). In Japan and Southern Africa (Mozambique) meningococcal serogroup Y (MenY) [35], and meningococcal serogroup W (MenW) predominated [36], respectively. The emergence of MenW and MenY was evident in some countries worldwide [11,14,16,29,35–51].

3.1.3. Genomic alterations and epidemic potential of *Neisseria meningitidis*

The epidemic potential of a particular Nm strain may be increased by genomic alterations that infer antigenic shifts, metabolic shifts, and resistance to antibiotics [46,52–54]. The ST-11 complex (cc11) is associated with outbreaks with high CFRs, atypical symptoms (e.g. gastrointestinal findings) and a variety of serogroups (MenC, MenW, and MenB) [55–58]. The spread of cc11 has been accompanied by capsule switching and antigenic shifts, and more recently, adaptation to new niches, e.g. through the acquisition of gonococcal genes/traits, and the ability to dispense with important subcapsular vaccine antigens [37,59–62]. The MenW cc11 isolates found in South Africa likely originated from the Hajj outbreak strain of 2000/2001, which may, in turn, have originated from sub-Saharan African strains (Figure 1). MenW cc11 isolates found in the U.K. from 2009 onwards, and associated with atypical symptoms (diarrhea, vomiting, and septic arthritis), likely originated from South America, having emerged in Brazil in 2003 before spreading to Argentina and Chile [37,52,61]. The U.K. strains have since been found in France, the Netherlands, Sweden, Australia, and Canada [42,43,51,54,55,63]. Further, within the cc11 population structure, MenB and MenC cc11 isolates were highly interspersed, suggesting multiple capsule switch events [37,62].

A genetically-altered ST-11 Nm strain has recently emerged as a cause of urethritis in males, with no reported differences in clinical presentation compared with gonococcal cases [60,64]. Adaptation to the genitourinary niche was thought to be due, in part, to horizontal gene transfer of in-frame *norB-aniA* between *Neisseria gonorrhoeae* (Ng) and Nm [60,64]. The loss of the ability to express a capsule was a further gonococcal trait that was caused by the deletion of some capsular genes. Gain of *aniA* function has also been described in closely related MenC cc11 isolates from IMD cases among men who have sex with men (MSM) [65].

3.1.4. Epidemiology of recent meningococcal disease outbreaks

The magnitude, and subsequent societal and economic burden, of Nm outbreaks is often influenced by country/regional population structures, the diagnostic capacity of health-care systems and outbreak response (vaccination/prophylaxis). In the U.S.A., there have been numerous university outbreaks [12,66–70]; MenB predominated, with MenC more commonly seen in community-based outbreaks. Examples of university outbreaks between 2008 and 2017 involving MenB include Ohio University (2008–2010) [70], Princeton University (2013–2014) [67,68], and Rutgers University [69]. In Africa, the high incidence of IMD was thought to be due to the dry season and start of the Harmattan (dry and sandy east wind) in sub-Saharan Africa, which favors colonization and transmission of Nm in the pharynx [6]. Historically, >80% of Nm outbreaks in the meningitis belt were caused by MenA [6]. As noted previously, MenA IMD cases reached 100 cases per 100,000 population in sub-Saharan Africa before the introduction of the MenA-TT conjugate vaccine immunization program [22]. By 2017, MenA had significantly decreased, MenW was relatively stable and MenX and MenC had started to increase [71]. The distribution of MenX and MenC within the African meningitis belt was extensive due to cross-border spread. A novel MenC ST-10217 strain, causing epidemics of meningitis in Nigeria in 2013 and Niger in 2015 has been shown to spread over a longer period of time during the spring season, as compared with other epidemic strains in Africa [33,34,72]. Genomic analysis revealed that the strain was not genetically related to any MenC strains previously identified in Africa [33]. In April 2017, 31 IMD cases were reported, including 13 deaths, following attendance at the funeral of a religious leader in Liberia [73]. The outbreak was associated with atypical symptoms (diarrhea, vomiting, and mental confusion) and metagenomic analysis revealed the presence of a strain with 91–98% similarity to ST-10217 in six of the 10 specimens analyzed, the remaining four specimens were inconclusive [73,74]. This strain appears to be evolved and likely has the epidemic potential [75]. Outbreaks have also been reported among military personnel. Indeed, the incidence of IMD is higher among soldiers in Korea than the national average, with 2.2 cases per 100,000 persons reported per year [76]. The novel serogroup C cc4821 emerged in China in 2003 and was responsible for the outbreaks in Anhui in China from 2003 to 2005 and has rapidly spread to most provinces of China, and there was also evidence of capsular switching between MenC and MenB [77,78]. Continued epidemiological and sentinel surveillance of IMD could help determine the epidemic potential of Nm sublineages to inform future prevention strategies.

3.2. Review of current global meningococcal disease prevention and control strategies

There are marked differences in global prevention strategies, in terms of vaccination and antimicrobial prophylaxis. There are three types of vaccination: (i) polysaccharide; (ii) conjugate; and (iii) protein. In brief, polysaccharide vaccines are composed of pure bacterial cell wall polysaccharides, whereas conjugate vaccines are made by covalently bonding an antigen to an immunogenic carrier protein (e.g. tetanus toxoid, diphtheria toxoid or diphtheria toxoid variant CRM197) to enhance and maintain immunological B-cell memory [79]. This is particularly crucial for individual protection against IMD due to the generally short incubation period. Other advantages of conjugate vaccines over polysaccharide vaccines include the ability to impart herd protection by preventing the acquisition of meningococci nasopharyngeal carriage among vaccinees [80] (see Section 3.3.1), and lack of hyporesponsiveness with repeated dosing [7,79,81,82]. Several conjugate vaccines are available worldwide [83–92], with availability and licenced age differing by country. In contrast, protein-based vaccines include toxoids (inactivated bacterial toxin) and subunit or subvirion products, and are used when the use of a polysaccharide or conjugate is not possible (see Section 3.3.2).

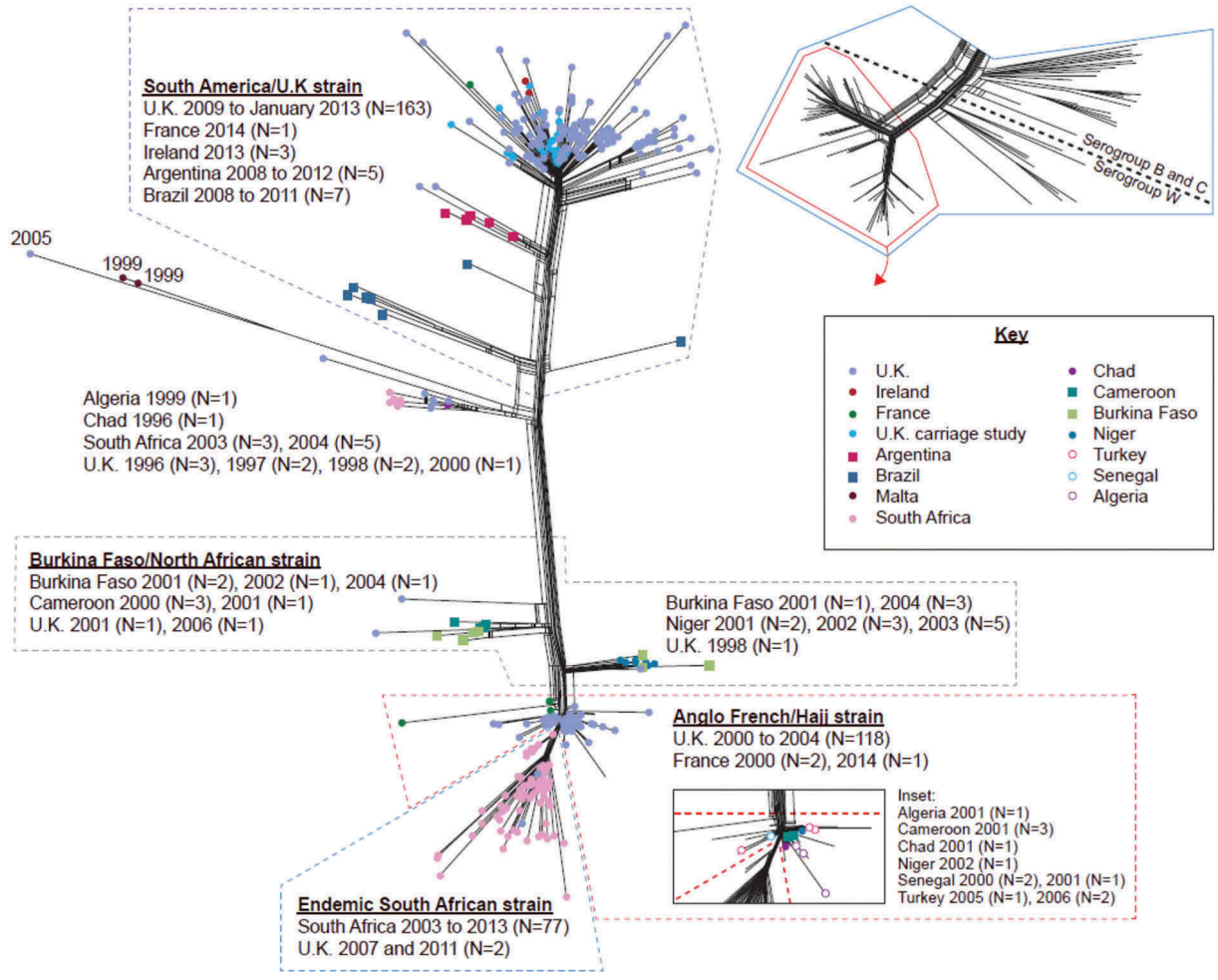

Figure 1. Geo-temporal distribution of isolates within distal sublineages of meningococcal lineage 11.1.The inset (top-right) depicts a cgMLST (1546 loci) neighbor-net phylogenetic network of all 750 geo-temporally diverse cc11 isolates and two non-cc11 isolates (cc8 and cc41/44) highlighting the distal region of lineage 11.1 that bifurcates into two sublineages. Isolates corresponding to this region underwent a separate cgMLST (1546 loci) comparison to generate the neighbor-net network in the main figure. Both sublineages contained several clusters, each relating to a noteworthy episode of MenW disease. One lineage included the strain relating to the Hajj outbreak of 2000 onwards (Anglo-French Hajj strain), the expansion of endemic MenW:cc11 disease in South Africa from 2003 (endemic South African Strain) and a period of MenW:cc11 epidemics in sub-Saharan Africa (Burkina Faso/North African Strains). The other sublineage contained clusters relating to expanding endemic MenW:cc11 disease in South America and the U.K. (the South American/U.K. strain). Dots relate to individual cases. The scale bar indicates the number of loci differing among the 1546 compared. Figure adapted from Figure 3 of Ref. [37] and reprinted from Journal of Infection, Vol 71/Issue 5, J Lucidarme, DM Hill, HB Bratcher, et al. Genomic resolution of an aggressive, widespread, diverse and expanding meningococcal serogroup B, C and W lineagep. 549, 2015, with permission from Elsevier.

Some countries provide vaccination via National Immunisation Programmes (NIPs) and others provide vaccinations to high-risk populations (e.g. conjugate MenACWY in India) or for outbreak control only (e.g. MenB vaccine in Canada; polysaccharide MenA and MenAC vaccines in Russia; polysaccharide vaccines in the African meningitis belt). The optimal approach is to include vaccination via NIPs to maximize coverage; however, this decision is often determined by cost-effectiveness analyses [7]. A number of factors influence cost-effectiveness, including variables to incorporate, how to capture benefits and uncertainty, comparators, time-period and how to value items in the future. In some countries where vaccines are not provided free of charge, patients may pay for vaccines through the private health-care sector. The prevailing factor for vaccination recommendations is the country- and serogroup-specific incidence of Nm by age group, highlighting the importance of continual surveillance to ensure vaccinations are available to those most in need in a timely manner. Conjugate vaccines, especially MenA, MenC, and MenACWY, are used in many countries, except Northern Africa, Middle East and China where polysaccharides are used [6,7,47].

In recent years, there has been increasing use of multivalent vaccines, with the polysaccharide and conjugate meningococcal serogroups A, C, W, and Y (MenACWY) vaccine the most widely implemented. In the U.S.A., the MenACWY conjugate vaccine has been recommended as part of the routine immunization program for adolescents aged 11 to 12 years, with a booster dose at age 16 years, since 2005. The U.K. switched from MenC to MenACWY in adolescents in 2015 [93], Chile included the MenACWY conjugate vaccine in the NIP in 2012, Argentina added MenACWY to their NIP in 2018, and MenACWYX is planned for widespread use across sub-Saharan Africa by 2022. Despite MenB being one of the most prevalent serogroups worldwide and some countries incorporating it into their NIP (e.g. U.K., Andorra, Lithuania,

Italy and Ireland) [94–97], there are countries that do not yet have a MenB vaccine licensed (e.g. Turkey and African countries).

3.3. Lessons learned from immunization programs and research worldwide

3.3.1. Importance of conjugate vaccines in the prevention of meningococcal disease

Implementation of the MenC conjugate vaccine into the NIP and the accompanying catch-up campaign in the U.K. in 1999 [98], significantly reduced the incidence of IMD and carriage of MenC [80]. Due to vaccine effectiveness waning rapidly in young children, as indicated by poor persistence of MenC antibodies, the introduction of a 'booster' in adolescents in the U.K. in 2013 was intended to maintain antibody levels and hence, offer continued protection against IMD and MenC carriage. In response to an unexpected rise in MenW cases in the U.K., Public Health England introduced the MenACWY conjugate vaccine into the routine adolescent school program in 2015. The vaccine was administered to adolescents aged 14 and 15 years old, as well as students attending university for the first time (Figure 2, [99]). However, despite 71% vaccination coverage with the MenACWY conjugate vaccine at one university, a cross-sectional study showed that carriage of MenW increased substantially in first-year university students [100]. Additionally, the introduction of a monovalent MenA conjugate vaccine in Africa successfully reduced invasive disease and carriage rates by inducing direct and indirect (herd) protection, respectively [101–104]. As mentioned previously, multivalent vaccines are being used more frequently with the aim of providing broader protection against IMD than monovalent vaccines. However, it is important to acknowledge that we still need more evidence to understand the true impact of multivalent conjugate vaccines against other serogroups.

3.3.2. Importance of MenB protein vaccines

Polysaccharide-based MenB vaccines do not exist. The alpha-2 linked polysialic acid of MenB is identical to that found on the surface of human neuronal cells, and thus, such vaccines would be poorly immunogenic and could potentially evoke an autoimmune response [105]. The approach was therefore to identify non-capsular antigens that are surface-exposed, conserved and can induce serum bactericidal antibodies. Outer membrane vesicle (OMV) vaccines were used in countries such as Norway, Cuba, Brazil, Chile, France, to control clonal MenB outbreaks in the 1980s, and also in New Zealand from 2004 to 2008 [106]. OMV vaccinations are still used in Cuba; they can provide protection when an IMD outbreak shares similar (not necessarily identical) PorA to that included in the vaccine [107]. Following the publication of the first meningococcal genome, reverse vaccinology was used to develop a vaccine comprising three primary recombinant antigens: (i) factor H-binding protein (fHbp); (ii) *Neisserial* adhesin A (NadA), and (iii) Neisseria Heparin-Binding Antigen (NHBA). In addition, it includes the OMV expressing PorA from the New Zealand strain, PorA P1.4 [108–110]. Since the introduction of the 4CMenB vaccine (*Bexsero*®) in 2015 in the U.K., three million doses have been administered and there has been a significant decline in the number of MenB cases among infants and toddlers [111]. A reported two-dose vaccine effectiveness of 82.9% (95% CI 24.1—95.2) was reported against all MenB cases during the first 10 months of the program [111]. This was equivalent to a vaccine effectiveness of 94.2% against the highest predicted MenB strain coverage of 88% [111]. Current published data suggest that the 4CMenB vaccine has limited, if any, effect on the carriage of MenB [112]. Although the 4CMenB vaccine is reactogenic [113], recent surveillance data do not support initial concerns with respect to increased risk of Kawasaki disease and seizures [114]. The 4CMenB vaccine has the potential to offer protection against meningococci belonging to other serogroups.

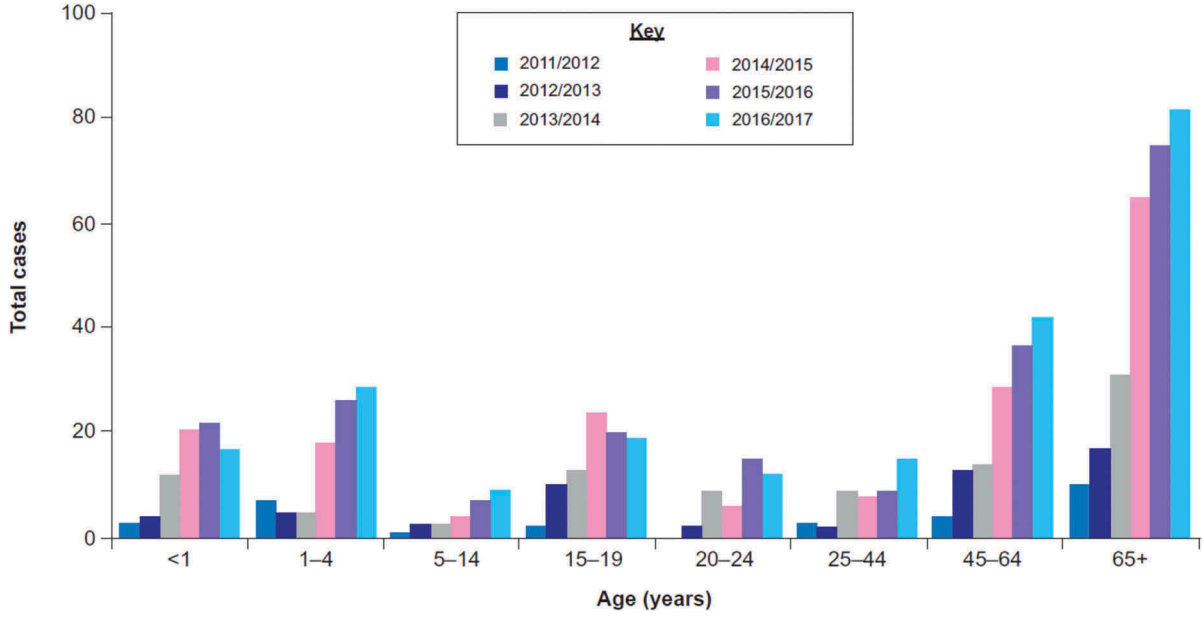

Figure 2. Incidence of MenW in the U.K. from 2011/2012 to 2016/2017 [99].

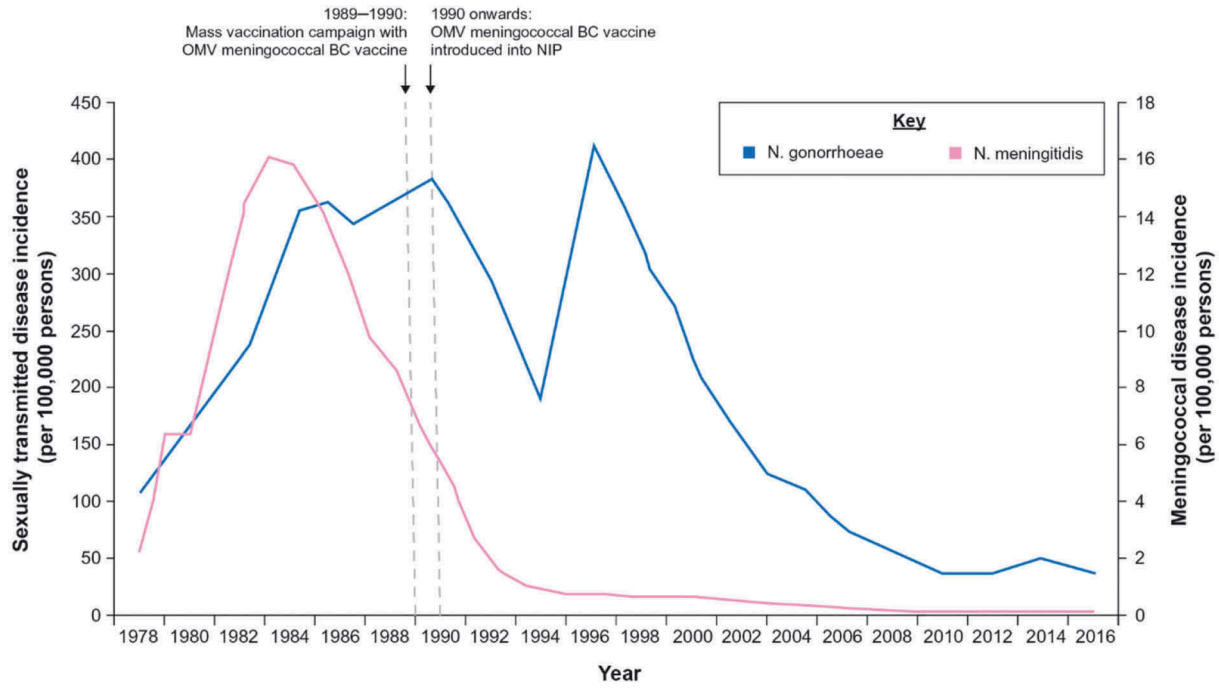

Figure 3. Incidence of *N. gonorrhoeae* vs. *N. meningitidis* in Cuba (1978–2016) [130].

Interestingly, infants that received the 4CMenB vaccine showed serum bactericidal antibody activity against the hypervirulent MenW ST-11 strain [115], which is in line with the observed reduction in MenW cases among infants [116]. The Cuban OMV meningococcal BC vaccine (*VA-MENGOC-BC®*) has been used effectively in Cuba, and other Latin American countries [117,118], to control MenB disease [119–125]. Over 30 years, ~60 million doses of the Cuban OMV vaccine have been administered demonstrating a good safety and tolerability profile with a significant decrease in the incidence of IMD post-vaccination [117,118,120].

Given that Nm and Ng belong to the same genus, there are considerable structural similarities between the PorB protein found in Nm and Ng [126]. Further, the genes encoding fHbp and NHBA may also be found, and the corresponding proteins expressed, in Ng [127]; although, fHbp is not surface-expressed in Ng [128], and there are differences in the nucleotide and amino acid sequences between the two species [127]. Data, albeit limited, showed that meningococcal recombinant protein and OMV-based vaccines may provide protection against Ng in Canada and Cuba (Figure 3) [129,130], following a similar observation in New Zealand. An ecological study in Saquenay-Lac-St-Jean, Quebec, suggested that the 4CMenB vaccine may offer some protection from Ng infection among individuals aged 14–20 years [131]. More in-depth analyses are ongoing to fully establish the nature of the relationship between the 4CMenB vaccine and Ng infection rate.

3.3.3. New approaches for vaccination strategies

The use of additional multivalent polysaccharide vaccines, as well as concomitant administration of multivalent vaccines with protein-based vaccines, to provide broader protection against IMD, are being considered and actively researched. Evidence to date does not indicate any major safety signals for the multivalent MenACWY vaccines; however, there was a significant association between Bell's palsy and MenACWY-CRM when administered concomitantly with other vaccines. Further, there was no association when the vaccine was administered alone [132], thus highlighting the need for further investigations. The immunogenicity of co-administration of MenC-CRM and 4CMenB has also been studied with no immediate safety or effectiveness concerns [133]. New multivalent vaccines are being developed, including a pentavalent MenACWYX vaccine for Africa, which is currently being studied in clinical trials.

3.3.4. Use of meningococcal modeling in outbreaks and persistence of vaccine protection

A useful tool for informing IMD control strategies is transmission modeling, which can be used to predict IMD epidemiology, including the impact of proposed vaccination programs. Models should ideally incorporate data from disease surveillance, carriage studies, and seroepidemiology. As models are, by definition, simplifications of real-world scenarios, they should be considered an additional, rather than a definitive, tool for decision-making. Nevertheless, they have been used to inform vaccination programs. For example, modeling for the conjugate MenC vaccine in the U.K. showed the significant decline in IMD cases when herd immunity was taken into consideration [134]. Modeling of PsA-TT used an age-structured transmission dynamic model to capture key epidemiological features of MenA in the African meningitis belt, including periodic epidemics, seasonality, varying sizes of epidemics, variable risk of disease age, carriage by age, immunity from the carriage, and transmission between asymptomatic carriers [135]. Ultimately, the model highlighted the importance of the introduction of the vaccine into routine Extended Program on Immunization (EPI) or periodic mass

vaccination in 1– 4-year-olds to avoid resurgence of MenA approximately 10–20 years after the initial mass campaign in 1– 29-year-olds [135]. Additionally, modeling for the introduction of the 4CMenB vaccine into the U.K. suggested that, if herd effects are assumed, long-term protection would be expected by vaccinating adolescents [136]. However, in the absence of herd effects, vaccination during infancy would be preferable, and since herd effects for meningococcal protein-based vaccines are unclear, this debate is ongoing [136].

IMD modeling may be used to better understand the importance of particular assumptions, such as the persistence of protection of a vaccine, which can determine the need for, and timing of, booster vaccinations. For example, if the duration of protection is short (e.g. 5 years), booster vaccinations in those immunized at younger ages may be warranted to prevent resurgence. In fact, the aforementioned PsA-TT model demonstrated that resurgence of MenA occurs earlier and with higher incidence if persistence is assumed to be five rather than 10 years [135]. Strategies such as catch-up campaigns and the routine immunization of older children could be considered if the duration of protection is known to be short.

Due to the low incidence of IMD, it is not feasible to conduct efficacy studies for the licensure of meningococcal conjugate vaccines. These vaccines have been licensed on the basis of safety and immunogenicity data. This therefore requires surrogates of protection. Surrogates of protection, which are required for IMD modeling, are unknown for MenA. The use of human complement serum bactericidal assay (hSBA) may not be an appropriate correlate of protection for MenA and utilization of different MenA strains in rabbit complement serum bactericidal assay (rSBA) yield different lengths of protection [137]. Based on serogroup A-specific immunoglobulin G (IgG), a booster campaign would be required after 3 years for children aged 1−4 years following the PsA-TT campaign [138]. In contrast, a booster campaign would be required after 8 years for children aged 1−4 years following the PsA-TT campaign based on strain, A3125, and antibody persistence remains high, even 5 years following primary vaccination based on strain F8238 [139]. As such, further understanding of the correlates of protection is needed.

3.4. Emergence of antibiotic resistance

Increased use of antibiotics worldwide for various bacterial infections has had a detrimental impact on antimicrobial resistance in bacteria. Nm is still susceptible to most antibiotics that are used for treatment and prophylaxis of IMD; however, the incidence of strains with reduced susceptibility to penicillin (as indicated by increased minimum inhibitory concentrations [MIC] toward the standardized breakpoint of non-susceptibility) is increasing worldwide [140]. Non-susceptibility (or resistance) to penicillin arises from modifications in bacterial penicillin-binding proteins (PBPs); enzymes that are involved in peptidoglycan biosynthesis, which bind to penicillin and other beta-lactam antibiotics [140]. Alterations in the PBP2 protein encoded by the *penA* gene led to modifications of the bacteria's peptidoglycan structure, as well as a 10-fold reduction in its affinity for penicillin [141], thereby reducing its susceptibility to the agent [140,142]. Alterations of the *penA* gene most likely occurred through horizontal gene transfer from other species of the genus *Neisseria* (*Neisseria perflava, Neisseria mucosa,* and *Neisseria cinerea*), producing a *penA* allele that has a mosaic structure. Of concern, isolates harboring the allele *penA327* showing reduced susceptibly to penicillin and third-generation cephalosporins were identified in 2012 [141]. The allele was found to originate from Ng [141]. The *penA1C* allele is currently only found in Ng, but carries a high level of resistance to penicillin and third-generation cephalosporins. *penA1C* differs from *penA327* by only one nucleotide, thus there is a risk that isolates with antibiotic resistance (rather than reduced susceptibility) may emerge in the future. Encouragingly, isolates resistant to rifampicin and ciprofloxacin are rare and heterogeneous [143]. Resistance to rifampicin arises from alterations in the *rpoB* gene, which lead to marked increases in the MIC of the isolates (>1.0 mg/L) [143]. Isolates that harbor a modified *rpoB* gene are rare and have only been identified in Europe [143], but they remain a concern, especially in countries that use rifampicin as the first-line antibiotic for prophylaxis. Ciprofloxacin resistance involves mutations in the *gyrA* gene [144]. Isolates resistant to ciprofloxacin have been identified in France, India, Italy, Spain, and Sweden, and in 2009, an outbreak of resistant isolates was reported in the U.S.A. [144,145]. Ciprofloxacin-resistant isolates have also been reported in Argentina and, in China, more than 70% of Nm strains are non-susceptible [46,146]. Different Nm strains in China have shown non-susceptibility to ciprofloxacin [146], as well as nalidixic acid [6]. Specifically, molecular profiling indicated a high prevalence of Nm quinolone non-susceptibility in Shanghai, which was associated with hyper-virulent IMD lineages cc4821 and cc5, giving rise to two quinolone-resistant strains; cc4821-R1-C/B and cc5-R14-A [147]. Further, the MIC values of several antibiotics used in China to treat Nm have increased, and some ciprofloxacin-resistant strains obtained from healthy carriers possessed identical *gyrA* sequences to those obtained from individuals with IMD [146]. Global antibiotic resistance surveillance is therefore warranted to monitor changes in antibiotic susceptibility of Nm and to ensure IMD cases, including epidemics, are treated effectively.

3.5. IMD in high-risk groups

Country or region-specific immunization programs generally target populations considered most at risk of IMD or carriage. The incidence of IMD is highest among children <1 year and adolescents/young adults [148]. In addition to age, there are other populations considered at high risk of IMD, including individuals with functional or anatomic asplenia, complement deficiency and human immunodeficiency virus (HIV) [12,149–151]. Indeed, individuals with complement deficiency and HIV have an approximately 1000-fold and 10-fold increased risk of IMD, respectively [82,152–154]. Unvaccinated and vaccinated patients taking eculizumab for paroxysmal nocturnal hemoglobinuria (PNH) or atypical hemolytic uremic syndrome (aHUS) have a markedly increased risk for IMD. There is varied guidance on the use of antibiotic prophylaxis in such patients [12,155]. MSM is also considered a high-risk group [154], with a high incidence of MenC in both outbreak and non-outbreak settings. The cc11 strain was responsible for IMD outbreaks among MSM [156], and HIV infection is likely responsible for most of the increased risk among MSM. Following genomic analysis of the new clone of MenC identified in MSM, the strain was found to have acquired

the capacity to spread via sexual transmission, as well as via respiratory droplets [65]. Additionally, numerous laboratory-acquired IMD cases have occurred, with half of the cases resulting in death [157]. As such, it is also important to offer laboratory workers meningococcal vaccines and to ensure all safety procedures are followed.

There has been an increased incidence of IMD during some mass gatherings. With the exclusion of the Hajj and Umrah, the IMD burden at mass gatherings was 66 per 100,000 persons based on 13 studies published between 1991 and 2015 [158]. Such events often involve international travel, crowding and engagement in social behaviors that increase the likelihood of Nm transmission (e.g. smoking, kissing, sharing of food/drink) [37,52,159]. Historically, the Hajj has been associated with local and international outbreaks of IMD, but the last major outbreak occurred in 2000 [160–164]. Consequently, a number of preventative measures are in place, including vaccination with a quadrivalent MenACWY vaccine for all national and international pilgrims, residents of Mecca and Medina, Hajj workers and personnel working at ports of entry. Ciprofloxacin is given as chemoprophylaxis to pilgrims arriving from the African meningitis belt and there are awareness campaigns on IMD and preventative measures available. IMD outbreaks have been associated with the Norwegian 'russefeiring' since the 1990s, an event involving 60,000 adolescents partying for several weeks [165]. In 2011, there were four cases that were attributable to MenY. Since 2011, vaccination with the tetravalent MenACWY conjugate vaccine and a MenB vaccine has been recommended for those aged between 16 and 19 years. Six cases of IMD, confirmed as MenW: P1.5,2,36-2: F1-1: ST-11 (cc11), occurred among Scottish and Swedish individuals associated with the World Scout Jamboree (WSJ) in 2015, an international mass gathering, held in Japan, where 33,000 teenagers of 14–17 years gathered from 162 countries. The novel MenW strain was found to have descended from the aforementioned MenW cc11 South American strain sub-lineage [52,166]. In addition, the probable transmission of MenW from Scouts to passengers seated nearby during an international flight was reported, but the incident did not fulfill European Centre for Disease Control and Prevention (ECDC) criteria for flight contact [166,167]. All the aforementioned examples of outbreaks reported during mass gatherings stimulated a debate around the definition of a mass gathering and the control strategies that should be implemented. The World Health Organization (WHO) defined a mass gathering as a high concentration of people, at a specific location, for a specific purpose, over a set period of time, which has the potential to strain the planning and response resources of the country or community; however, the WHO does not currently recommend routine immunizations for mass gatherings, other than the Hajj and Umrah. Sports events (e.g. the Olympics), music festivals, high-profile funerals, and military camps may also be rated as mass gatherings, but reports on subsequent IMD are scarce [168]. Irrespective of the definition, there are wider considerations regarding the association of IMD clusters within international mass gatherings, including markers of known risk factors, increased carriage/disease incidence, viral illness, close living, close contact, sharing food/drink, and air travel.

3.6. Global initiatives for IMD prevention

Despite meningitis and neonatal sepsis (which is almost indistinguishable from meningitis in neonates) together being the second biggest infectious killer of children under 5 years of age globally [169], many of the major global strategies for health do not refer to meningitis as an issue warranting prioritization. This is in contrast to diseases such as malaria, rabies, and cholera that now have global action plans to 2030. A meeting organized by the Meningitis Research Foundation (MRF), in collaboration with the WHO, was held in the U.K. in 2017 with diverse representation, including the African meningitis belt health ministries, patient groups, pharmaceutical companies, researchers, the Bill & Melinda Gates Foundation and Public Health England to address this gap. Specific calls to action arising from the meeting, included to: (i) protect at-risk populations globally through routine and catch-up immunization programs, outbreak strategies, development of new rapid diagnostic tests, and continued research into pathogens that cause meningitis; (ii) maximize benefit of existing vaccines by developing targeted campaigns, a new multivalent conjugate vaccine and strengthening the capacity of networks and laboratories working within the African meningitis belt; and (iii) provide a step-change in support available to meningitis survivors and their families, working with national and regional health-care systems to promote information to populations, making meningitis education a routine part of health information campaigns, and establishing national and international networks of best practice to raise disease awareness. The WHO is currently developing proposals and seeking funding to create a global roadmap for meningitis through to 2030. The MRF is working on 4 initiatives that will help underpin the new global roadmap, including a global data paper and meningitis impact portal, a global meningococcal genome library, rapid diagnostics tests and a research network.

4. Discussion

A relatively large proportion of the meeting focused on IMD surveillance, epidemiology, prevention and control strategies worldwide. Of note, MenB and MenC are still a major cause of IMD worldwide, with the emergence of MenW and MenY in recent years. Further, cc11 has spread internationally, accompanied by the ability of cc11 strains (e.g. MenC) to adapt to new niches, acquire gonococcal genes/traits (including antibiotic resistance) and dispense with important subcapsular vaccine antigens [37,59–62]. Additionally, MenX and MenC have spread extensively within Africa due to cross-border transmission. Importantly, the GMI stressed that experiences with the ST-10217 in Nigeria and Niger and ST-11 MenW in the U.K. can further knowledge on the evolution of Nm strains. Ongoing surveillance and genomic analyses are therefore crucial in the prevention of IMD.

The magnitude and social and economic impact of an outbreak varied considerably between high-income and low- to middle-income countries and was influenced by many factors, such as country/regional population structures, diagnostic capacity of health-care systems and outbreak response (vaccination/prophylaxis). Although individual capacity varies

considerably, countries and health organizations can continue to learn from the experiences and strategies of others across the globe where IMD has been prevented or controlled. Indeed, such lessons were a focus of this meeting and have fed into the existing GMI recommendations (Table 1).

The success of a MenC conjugate vaccination program in the U.K. and elsewhere was used to reinforce the vital role of herd protection in preventing the spread of IMD, and the development of new multivalent vaccines, as well as co-administration of vaccines may provide broader protection against MD. An update on the surveillance of OMV-based vaccination in infants and toddlers in England suggested that the 4CMenB vaccine provided protection against a hypervirulent MenW strain [115]. Data presented, albeit limited, showed that OMV-based vaccines against MenB may provide protection against Ng in Canada and Cuba [129,130]; however, it was emphasized that further analyses were needed. Finally, transmission models were highlighted as a useful tool to predict MD epidemiology and support control strategies, including the need for, and timing of, booster vaccinations. However, the GMI cautioned that models were simplifications of real-world scenarios so should be considered as an additional, rather than definitive, tool for decision-making.

Although the GMI affirmed that Nm was susceptible to the antibiotics that were currently used for treatment and prophylaxis of IMD, it was cautioned that there was evidence that reduced susceptibility to antibiotics is increasing worldwide [140,143]. Antibiotics are undoubtedly one of the most important tools used in the prophylaxis and treatment of IMD to prevent related fatalities and sequelae. The identification of several strains of Nm that have shown non-susceptibility to select antibiotics adds to the concern that antibiotic resistance may emerge in the near future and cause a substantial setback in the progress of the global management of IMD. Clearly, global antibiotic resistance surveillance is imperative to ensure the continued efficacy of all IMD treatments.

IMD outbreaks during the Hajj, the WSJ in Japan in 2015 and the Norwegian 'russefeiring', prompted discussion around the definition of a mass gathering and the control strategies that should be implemented. The WHO does not currently recommend routine immunizations for mass gatherings, other than the Hajj and Umrah. It was debated whether sports events (e.g. the Olympics), music festivals, high-profile funerals, and military camps should be included.

Patient populations at high risk of IMD were each discussed in turn, and included individuals with asplenia, complement deficiencies, and HIV. Interestingly, administration of eculizumab to a vaccinated patient with PNH, who later died, raised the question whether better guidance was needed on the use of vaccines and chemoprophylaxis in such patients [12,155]. MSM and laboratory workers were also flagged as high-risk groups.

To date, vaccination programs have been effective in substantially reducing the incidence of IMD in many countries across the world (e.g. the control of MenA in the African meningitis belt since the phased introduction of PsA-TT in 2010). It is crucial that countries continue to be reactive to the changing epidemiology of IMD moving forward, and regularly update routine and emergency vaccination programs to ensure a quick and effective response following the inevitable emergence of new Nm strains. A key strategy to reduce the carriage and incidence of IMD would be to induce herd protection in populations where it is currently lacking. The targeted immunization of high-risk patient populations, other than children and adolescents, may directly prevent outbreaks and significantly reduce IMD transmission. Of course, achieving and sustaining herd protection worldwide will be challenging given diverse standards in IMD management. Worldwide coordinated, sustained and long-term strategies, alongside vigilant surveillance is urgently required in all countries to continue to lower IMD-related morbidity and mortality.

5. Summary

Based upon the data presented, it is clear that the epidemiology of IMD is constantly evolving, highlighting the need for surveillance and policies for prevention and control. Increasing application of genomic analyses worldwide has accelerated knowledge around the local evolution of all hypervirulent Nm lineages, including the accumulation of genetic changes. Therefore, genomic analyses are needed to determine the epidemic potential of sublineages, and for reliable tracking of meningococcal strains and initiation of appropriate vaccination programs.

Conjugate vaccines are generally superior to polysaccharides. They can also prevent the acquisition of meningococci pharyngeal carriage among vaccinees, which proved to be crucial for the success of the immunization programs with the MenC and MenA conjugate vaccines. However, revaccination is needed in some populations that remain at risk. Such policy decisions can be informed by mathematical modeling. Vaccination of high-risk populations and attendees at mass gatherings associated with an increased risk of IMD is warranted; however, the definition of a mass gathering may need to be revisited given that IMD outbreaks have been associated with sports events, festivals, high-profile funerals, and military camps. Although Nm is still susceptible to antibiotics used for treatment and prophylaxis of IMD, reduced susceptibility to antibiotics continues to be a concern. As such, global antibiotic resistance surveillance is recommended. Both the MRF and WHO have initiatives in development, including the development of a new task force and roadmap for meningitis to 2030.

6. Expert commentary

IMD is an important health concern with outbreaks occurring in many areas of the world, particularly in low- to middle-income countries where morbidity and mortality rates remain high. MenB and MenC remain a major cause of IMD worldwide; however, MenA, MenW, MenX, and MenY, predominate in a number of different countries. In order to reduce the global incidence of IMD, it is imperative that countries and health organizations continually learn from the experiences and effective strategies implemented by other countries. Of note, the induction of herd protection following the implementation of conjugate vaccines into the NIP together with catch-up campaigns, as well as the observed potential for protein-based vaccines to offer

protection against multiple serogroups (e.g. 4CMenB may protect against MenB and MenW) and Ng (e.g. protein – and OMV-based vaccines may provide protection against Ng in Canada and Cuba, respectively).

Currently, vaccines and antimicrobial prophylaxis are the mainstays of IMD prevention and have significantly reduced the incidence of IMD in many countries worldwide. To continue to reduce the incidence levels of IMD, there are a number of key issues that need to be addressed. Evidence gathered to date regarding the ability of Nm to adapt genetically, implies that new hyper-virulent strains may emerge. Further, the imminent emergence of an antibiotic-resistant strain of Nm is a valid and growing concern. As antibiotics are undoubtedly one of the most important tools used in the prophylaxis and treatment of IMD, an antibiotic-resistant strain could cause a substantial setback in the progress of the global management of IMD. Ongoing vigilance and genomic analyses will ensure the prompt determination of the epidemic potential of Nm strains, to inform the rapid development and implementation of appropriate control strategies. At every opportunity, lessons should continue to be learned from the emergence of new strains, and the spread of other hyper-virulent strains to increase knowledge on the evolution of such strains. Moreover, global antibiotic resistance surveillance is imperative to ensure the continued efficacy of all IMD treatments.

Many steps are being taken to prevent outbreaks of IMD; however, outbreaks still occur and therefore continued efforts are needed. The observed increase in the incidence of IMD following some mass gatherings and other highly-attended events (e.g. sports fixtures and music festivals) highlights the need to target such events to help control the international spread of IMD. As a first step, revisiting the definition of mass gathering may prompt initiation of preventative measures for IMD to help mitigate the risk of international spread. Additionally, the targeted immunization of high-risk patient populations may also prevent IMD. Of course, achieving and sustaining IMD protection worldwide will be challenging given diverse standards in IMD management; however, continued country- and regional-specific efforts that underpin the GMI ethos for international cooperation will help drive an overall reduction in the incidence of IMD.

7. Five-year view

In the next 5 years, the epidemiology of IMD will most likely continue to vary both geographically and temporally due to many competing factors. With the implementation of enhanced protection and control strategies, the world will likely see a decreasing trend in the overall incidence of IMD; however, factors such as differing country/regional surveillance systems and the evolution of new hyper-virulent Nm strains may pose a threat and lead to an increase in the incidence of IMD.

The identification of several strains of Nm that have shown non-susceptibility to select antibiotics adds to the growing concern that antibiotic-resistant strains of Nm will emerge in the coming years. The GMI recognizes that epidemiological surveillance is essential to determine the epidemic potential of Nm strains and inform future prevention strategies. In particular, the update of routine and reactive vaccination programs with suitable vaccines is necessary for a quick and effective response should newly emergent Nm strains become a threat.

The clinical development and subsequent licensing of two pentavalent vaccines, MenABCWY and MenACWYX, are likely within the next 5 years. Once added to NIPs, these vaccines are expected to play a significant role in the global management of IMD through direct and indirect (herd) protection.

Currently, the prevailing factor for vaccination recommendations is the country-specific incidence of respective Nm serogroups across age groups; however, the application of protection strategies to other high-risk groups, such as individuals with asplenia, complement deficiencies, and HIV, persons receiving eculizumab, MSM and travellers to epidemic areas, differs between countries. The GMI agrees that targeted routine and catch-up vaccination programs for high-risk patient populations is important for this reason, and should be implemented into the country and region-specific immunization programs within the next 5 years. Further, following several IMD outbreaks during events, such as festivals and high-profile funerals, the GMI recommend that the definition of mass gathering be revisited and adequate preventative measures and control strategies put in place prior to any event with the potential to increase the rate of Nm carriage or incidence of IMD.

The GMI postulates that coordinated, sustained and long-term surveillance/vaccination strategies, such as those discussed herein are required to improve the management of IMD and lower associated mortality and morbidity. The WHO and MRF initiatives to create a global roadmap for IMD through to 2030 are currently in development and will be key to ensuring the continued growth of management strategies worldwide.

Key issues

- In March 2018, the GMI met with a group of multidisciplinary scientists representing institutions from several continents across the globe to discuss IMD epidemiology, surveillance and protection strategies, with a focus on emerging antibiotic resistance and the protection of high-risk populations.
- IMD outbreaks continue to occur in many areas of the world; the magnitude and subsequent societal and economic burden varies considerably between high income and low- to middle-income countries, and is determined by factors such as country/regional population structures, diagnostic capacity of health-care systems and outbreak response (vaccination/prophylaxis).
- Transmission modeling can be used to inform IMD control strategies and predict IMD epidemiology, including the impact of proposed vaccination programs.
- The incidence and prevalence of IMD continually varies worldwide, and the epidemic potential of a particular Nm strain may be increased by genetic alterations that infer antigenic and metabolic shifts, and antibiotic resistance.

- MenB is a major cause of IMD in America, Australia, and Europe and a decreasing trend is currently being observed worldwide, whereas there is an increasing incidence of MenW globally.
- Although vaccination programs have been successful in reducing IMD incidence in many countries, the emergence of the new MenC strain (ST-10217) and variants of ST-11 (cc11) in several serogroups (MenB, MenC, and MenW), and also unencapsulated urogenital cc11 strains, may pose a threat and require close surveillance.
- The GMI recognizes that genetic analyses of IMD cases, together with continued epidemiological surveillance of the disease, are needed to determine the epidemic potential of Nm strains and inform future prevention strategies.
- There are marked differences in prevention strategies, in terms of vaccination and antimicrobial prophylaxis across the globe.
- Several conjugate vaccines are widely available to provide direct protection against MenA, MenC, MenW, and MenY, that afford many advantages over and above those offered by polysaccharide vaccines, such as the ability to impart herd protection via the prevention of the acquisition of carriage among the vaccinated population.
- To date, Nm is susceptible to antibiotics used in the treatment and prophylaxis of IMD; however, several Nm strains in China have shown non-susceptibility to select antibiotics raising the concern that strains with antibiotic resistance may emerge elsewhere in the future.
- The incidence of IMD is highest among children <1 year and adolescents/young adults; however, there are other populations considered to be at a high risk of IMD, including individuals with hereditary or acquired complement deficiencies, persons receiving eculizumab, those with HIV, MSM, laboratory workers, and travelers to epidemic areas and some mass gatherings.
- The GMI calls for the continued and regular update of routine and reactive vaccination programs with appropriate vaccines, including conjugate vaccines, as well as the implementation of targeted immunization of high-risk patient populations into country and region-specific immunization programs.
- The GMI continues to drive efforts to prevent IMD worldwide through education, research, and international cooperation.

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