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- 1 **The Global Meningococcal Initiative: global epidemiology,**
- 2 **the impact of vaccines on meningococcal disease and the**
- 3 **importance of herd protection**

1 **Abbreviations**

2	cc	clonal complex
3	CoMO	Confederation of Meningitis Organisations
4	EPI	expanded program of immunization
5	FDA	US Food and Drug Administration
6	fHbp	factor H-binding protein
7	GMI	Global Meningococcal Initiative
8	ISPCH	Instituto de Salud Pública de Chile
9	MATS	Meningococcal Antigen Typing System
10	MCV4	quadrivalent meningococcal (ACWY) conjugate vaccine
11	MD	meningococcal disease
12	Men	<i>Neisseria meningitidis</i> serogroup
13	MLST	multi-locus sequence typing
14	MPSV4	quadrivalent meningococcal polysaccharide vaccine
15	MRF	Meningitis Research Foundation
16	NadA	<i>Neisseria</i> adhesin A
17	NHBA	Neisserial heparin-binding antigen
18	NIHR HPRU	National Institute for Health Research Health Protection Research Unit
19	NIP	National Immunization Program
20	OMV	outer membrane vesicle
21	PCR	polymerase chain reaction
22	PSV	polysaccharide vaccine
23	SIREVA II	Sistema de Redes de Vigilancia de los Agentes Responsables de
24		Neumonias y Meningitis Bacterianas
25	ST	sequence type
26	WGS	whole-genome sequencing
27	WHO	World Health Organization

28

1 **Abstract**

2 **Introduction:** The 2015 Global Meningococcal Initiative (GMI) meeting discussed the global
3 importance of meningococcal disease (MD) and its continually changing epidemiology.

4 **Areas covered:** Although recent vaccination programs have been successful in reducing
5 incidence in many countries (e.g., *Neisseria meningitidis* serogroup [Men]C in Brazil, MenA
6 in the African meningitis belt), new clones have emerged, causing outbreaks (e.g., MenW in
7 South America, MenC in Nigeria and Niger). The importance of herd protection was
8 highlighted, emphasizing the need for high vaccination uptake among those with the highest
9 carriage rates, as was the need for boosters to maintain individual and herd protection
10 following decline of immune response after primary immunization.

11 **Expert Commentary:** The GMI Global Recommendations for Meningococcal Disease were
12 updated to include: a recommendation to enable access to whole-genome sequencing as for
13 surveillance, guidance on strain typing to guide use of subcapsular vaccines, and recognition
14 of the importance of advocacy and awareness campaigns.

15
16 **Keywords:** epidemiology; Global Meningococcal Initiative; meningococcal disease; MenW;
17 *Neisseria meningitidis*; outbreaks; prevention; serogroups; surveillance; vaccination

1. Introduction

Meningococcal disease (MD) has a rapid onset with potentially life-changing consequences. MD is fatal in as many as 50–80% of untreated cases [1], and case fatality rates even in treated individuals are ~10–15% [2,3]. In addition, MD causes great morbidity, with 12–20% of survivors suffering significant clinical sequelae (e.g., paralysis, deafness, mental impairment, amputations, and seizures) [2,4–8]. According to the World Health Organization (WHO), there are no accurate estimates of the global burden of MD, a situation that is due to inadequate surveillance in many parts of the world. However, MD is often considered as endemic globally, although epidemics occur frequently in the meningitis belt in sub-Saharan Africa, as will be discussed further in this paper. Prevention strategies, in particular vaccination, have been shown to be extremely effective in controlling MD [9].

The most common presentations of invasive MD are meningitis and sepsis [10]. Localized and chronic infections resulting in pneumonia, endophthalmitis, arthritis, pericarditis, or myocarditis may also occur [3,10]. Although MD affects individuals of all ages, the highest rates of disease are found in infants <1 year old [1,11]. Peaks in incidence are also seen in adolescents as well as the elderly in some countries [12–16].

The causative agent in MD is the bacterium *Neisseria meningitidis*. In a phenomenon known as carriage, *N. meningitidis* usually colonizes the mucosa of the human upper respiratory tract without resulting in MD. Carriage is frequent and involves ~10% of the general population [17], although rates are variable by age and setting, it is highest in adolescents and young adults (e.g., ≤27%), but far lower in older adults (e.g., ≤8%) and infants (<5%) [18,19]. Transmission of the bacterium from an infected individual to another person occurs via direct contact with droplet respiratory secretions [20].

1 Genetic analysis of carriage strains has revealed a diverse range of organisms, with only a
2 few of these found to be linked to MD [20,21]. Twelve serogroups of *N. meningitidis* have
3 been identified, with six of these – *N. meningitidis* serogroups (Men) A, B, C, W, X, and Y –
4 being responsible for virtually all invasive disease [1,11]. The epidemiology of MD is
5 dynamic, with continuing changes in incidences of *N. meningitidis* serogroups and the
6 emergence of new strain variants [1,22].

7

8 Although acquisition of meningococci usually results in asymptomatic carriage, local
9 inflammation occurs in some cases along with invasion of mucosal surfaces, which provide
10 access to the bloodstream [23] and can result in invasive MD (e.g., fulminant sepsis and/or
11 meningeal inflammation) [23]. Additionally, a number of environmental factors such as
12 exposure to cigarette smoke [24], that can cause inflammation of the nasopharyngeal
13 mucosal surfaces, have also been associated with increased risk of invasive MD.

14

15 Vaccination remains the key method for prevention of MD, and various vaccines and vaccine
16 strategies have been developed. The key desired effects of vaccination are to protect those
17 vaccinated from invasive MD when they are exposed, as well as to reduce acquisition and
18 carriage, particularly of hyperinvasive isolates, and onward transmission. The coverage of
19 the various types of anti-MD vaccines are summarized in Table 1. Polysaccharide vaccines
20 (PSVs) have been available for >40 years and variously cover one or more of serogroups
21 [1]. Protein-conjugate capsular vaccines are available [25], and when possible, these
22 vaccines should be used in preference to the polysaccharide form, as they are more
23 immunogenic, provide longer-lasting immunity and a stronger response to booster
24 vaccination (i.e., more immune cell activity and antibody production) and do not induce
25 hyporesponsiveness (i.e., show a poor or absent immune response) upon repeated use [11].
26 Combination conjugate vaccines are also available [26]. Vaccines using outer membrane
27 vesicles (OMVs) have been used in outbreak control against specific strains since the 1980s

1 [27]. In addition, two vaccines designed to offer broad protection against MenB are available
2 and were developed using subcapsular meningococcal antigens [28,29].

3

4 The Global Meningococcal Initiative (GMI) was established in 2009 to promote the
5 prevention of MD worldwide through education, research, international cooperation, and
6 vaccination [11]. The GMI is an international group of clinicians and scientists with expertise
7 in MD immunology, microbiology, epidemiology, public health, and vaccination. Since its
8 inception, several global and regional meetings have been held and these have resulted in
9 the publication of recommendations, including the GMI Global Recommendations for
10 Meningococcal Disease (Table 2), as well as regional situation reports [11,30–33].

11

12 In November 2015, the GMI convened an Expert Meeting in London, UK, titled ‘Prevention of
13 Meningococcal Disease – Importance of Herd Protection’. The objectives of this meeting
14 were to discuss the importance of herd protection and the potential impact this may have on
15 MD; provide an update on surveillance, epidemiology, prevention, and control strategies
16 from around the globe; highlight the lessons learned and experience gained from
17 immunization strategies used in other countries; examine the health economics aspects of
18 meningococcal vaccination strategies; and emphasize the critical need for disease
19 awareness and advocacy with regard to MD prevention and control.

20

21 **2. Methods**

22 Participants included over 20 clinicians and scientists with expertise in various aspects of
23 MD. The experts represented institutions in Africa, the Asia-Pacific region, Europe, Latin
24 America, and North America. The meeting content comprised expert presentations,
25 workshop sessions, and roundtable discussions.

26

27 **3. Results**

1 **3.1. Surveillance, epidemiology, and control: a global picture**

2 A series of presentations were given on MD surveillance, epidemiology, and control in
3 different regions and countries from around the globe.

4
5 **3.1.1. Latin America**

6 Much of the data for Latin America are from the Sistema de Redes de Vigilancia de los
7 Agentes Responsables de Neumonias y Meningitis Bacterianas (SIREVA II) network. This
8 network includes regional reference laboratories employing deoxyribonucleic acid (DNA)-
9 based diagnostic technologies, such as PCR. Diagnostic methodologies for MD are
10 described in detail elsewhere [34].

11
12 In Chile, *N. meningitidis* is subject to laboratory surveillance and requires immediate
13 notification. Control measures implemented include vaccination (polyvalent conjugate
14 vaccine used providing protection from MenA, C, W, and Y (note: other MD vaccines are
15 licensed in Chile, but currently only the MenACWY conjugate is recommended and funded
16 by the government), and the chemoprophylaxis of close contacts to prevent secondary
17 cases. According to data from the Instituto de Salud Pública de Chile (ISPCH), since its first
18 detection in 2010, the clone serogroup:serotype;subtype W:2a:P1.5,2:sequence type(ST)-11
19 has undergone aggressive expansion, displacing serogroup B as the main cause of MD, with
20 an incidence rate of >0.5/100,000 in 2014; in 2015, again according to ISPCH data, MenB
21 also appeared to be increasing, with MenW possibly decreasing. A campaign using
22 quadrivalent conjugate vaccine aimed at children aged between 9 months and 5 years was
23 launched in late 2012; in 2014, an MD vaccination program using the MenACWY conjugate
24 vaccine was included in the national immunization program (NIP) for all children aged ≥1
25 year.

26

1 Since 2012, a National System of Health Surveillance has been in place in Argentina, where
2 surveillance is both laboratory- and clinic-based, and a national reference laboratory
3 receives an estimated 50% of isolates. Overall disease incidence is currently low
4 (<0.7/100,000; data from the Ministerio de Salud de la Nación, Argentina); as in Chile,
5 infants and young children are most affected. Epidemiology has been dynamic in the last 5
6 years, with increased MenW circulation (W:2a:P1.5,2:ST-11 and W:2a:P1.2:ST-11
7 accounted for 78% of all isolates). In Argentina, the MenW strains are distinct from the
8 MenW strain that was first identified in Europe following the Hajj pilgrimage in 2000 (the so-
9 called 'Hajj outbreak' strain) [35], as is also the case with the strains in Chile. Argentina
10 recently announced the plan to introduce the quadrivalent conjugate vaccine for infants at 3,
11 5, and 15 months old, with an adolescent dose at 11 years.

12

13 In Brazil, MenC remains the most common cause of disease; disease due to MenW has not
14 increased as much as in Argentina or Chile, although the same MenW strain is involved [35].
15 Infant immunization with MenC conjugate vaccine follows schedule of immunization at 3 and
16 5 months, with a booster dose at 12 months, and a single dose for toddlers ages 12 to 23
17 months, but without a 'catch-up' campaign in older age groups [36]. The introduction of the
18 MenC vaccine in Brazil in 2010 provided an immediate reduction in incidence rates of MD,
19 especially in those children targeted for vaccination (Figure 1). Carriage rates in
20 adolescents, in a study performed 2 years after the initiation of the infant immunization
21 program, showed a prevalence of 10%, where serogroups were identified, serogroup C was
22 the most common (1.32%), followed by serogroups B (0.99%), E (0.74%), Y (0.49%) and W
23 (0.25%) [37]. Although plain PSVs offered protection against disease, they did not prevent
24 acquisition of carriage of MenC in the 2010 outbreaks [38], which is why only conjugate
25 vaccines are now used to control outbreaks.

26

1 In Mexico, MD is reportable through the Mexican National Epidemiologic Surveillance
2 System; however, the true burden of MD is unknown. Not all isolates are submitted to the
3 national reference laboratory, Instituto de Diagnóstico y Referencia Epidemiológicos. As a
4 consequence, a limited number of isolates receive further characterization. In general, the
5 number of reported MD cases has increased since 2002, although incidence rates are still
6 extremely low, ranging from 0.01 to 0.04 per 100,000 in the 2010–2014 period (data from the
7 Secretariat of Health, Mexico). Following the Metropolitan area outbreak in 2010, MenC has
8 emerged as the prevalent strain, with some cases of MenY and MenB. Since 2010, a
9 national response strategy has been developed that includes the availability of vaccines, but
10 they are only used in case of outbreaks and, more recently, offered for travelers to high-risk
11 countries. It is the opinion of the GMI, therefore, that *N. meningitidis* colonization in children
12 and young adults might be a better indicator to detect at-risk target populations, in addition to
13 demonstrating the presence and potential trigger of outbreaks. Such colonization data also
14 suggest that inclusion of MD vaccination in national immunization programs could be a more
15 effective protection strategy than reservation of vaccination for at-risk groups only.

16

17 *3.1.2. Asia-Pacific*

18 Approximately 4 billion people live in Asia [39], and there are two WHO regional offices
19 covering Asia, namely the South-East Asia Region and the Western Pacific Region [40]. In
20 South-East Asia, no country has been in either the WHO high (defined as >10
21 cases/100,000 per year in this region [41]) or moderate (2–10 cases/100,000 per year in this
22 region [41]) endemic rate categories for MD in the past 20 years. The true burden of MD is,
23 however, unknown in the Asia-Pacific region for several reasons, including under-reporting,
24 weak surveillance systems, lack of guidelines and standard case definitions, as well as lack
25 of awareness. In some countries in the region (such as South Korea), MD has recently
26 become a major public health issue due to more frequent outbreaks. In a move to rectify this

1 situation, a set of recommendations for surveillance, prevention, and control in the Asia-
2 Pacific region was developed at a regional meeting of the GMI in South Korea in 2014 [42].
3
4 Korea and Thailand are considered to have low endemic rates (defined for these countries
5 as <2 cases/100,000 per year [41]). On the other hand, in the Western Pacific Region, New
6 Zealand and Mongolia are considered high endemic areas, Australia is categorized as
7 moderate, and the majority of countries have low endemic rates (again defined as <2
8 cases/100,000 per year), including China, Japan, the Philippines, Singapore, and Taiwan
9 [41]. Five of the major MD serogroups (A, B, C, Y, and W) are variedly present in Asia.
10 MenA dominates in China, India, Bangladesh, Mongolia, and the Philippines during epidemic
11 years, while MenB is seen in Australia and New Zealand. MenB, as a cause of sporadic
12 cases, is seen in China, Indonesia, Japan, Malaysia, the Philippines, Singapore, Taiwan,
13 and Thailand. MenC is likewise seen in China and Singapore; MenY has been documented
14 in Japan and Taiwan and MenW in Singapore and Taiwan (2014 meeting of the GMI,
15 manuscript submitted [41]).
16
17 As with the quality of epidemiological data and vaccination programs are also variable within
18 the region [43]. Only a few countries have meningococcal vaccination in their NIPs. China
19 has routine mass countrywide immunization using PSV MenA in infants aged 6–18 months,
20 given as two doses at 3-monthly intervals, and PSV MenA and C in young children, given as
21 two doses at 3 and 6 years [44]. Comparatively, Australia uses a combined *Haemophilus*
22 *influenzae* type b and MenC conjugate (Menitorix[®], Table 1) in their NIP at 1 year [45].
23 Several meningococcal vaccines are available in the region, and the two predominating
24 types are quadrivalent meningococcal (ACWY) conjugate vaccines (MCV4) and quadrivalent
25 meningococcal PSVs (MPSV4), but the conjugate is preferred. Generally, across the region,
26 its use is only for certain conditions (e.g., asplenia, and for other persons at risk), as well as
27 for selected populations, such as those performing the Hajj pilgrimage and travelers to
28 endemic countries [43].

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Meningococcal disease is not a reportable disease in Bangladesh; therefore, there are no national data on prevalence and incidence. However, cases are captured from the ongoing surveillance at a network of multiple hospitals in urban and rural Bangladesh (Saha SK, et al, unpublished data, cited with permission). Antibiotic use prior to specimen collection presents a barrier to obtaining viable meningococcal isolates, and most cases are now detected by PCR, with only a few isolates recovered from blood samples. MenA was predominant (90%; 152/167) from 1994 to 2005. However, in subsequent years (2006–2015), MenB emerged gradually and established itself as the dominant serogroup (62%; 100/162) in Bangladesh. More than 50% of MD cases occur in the first year of life, and incidence in infants aged <1 year ranges from 18 to 24/100,000 (Saha SK, et al, unpublished data).

In Japan, cases are reported via the National Epidemiological Surveillance on Infectious Disease. The incidence of MD is low; 7–21 cases of meningococcal meningitis were reported annually between 1999 and 2012, but numbers have increased since meningococemia was added as a notifiable disease condition in April 2013. Incidence was 0.028/100,000 in 2014, and the predominant serogroup was MenY, followed by MenC and MenB. MenW is rarely reported. There have only been a few carriage studies to date; in these, an overall carriage rate of ~0.4–0.8% was observed [46,47].

Quadrivalent meningococcal vaccines have been approved in Japan since 2014 and should be available on request to anyone who qualifies for the conditions shown on the package insert; however, who should be vaccinated remains a key question, and there is a need to define high-risk populations. Indeed, there are currently no recommendations for meningococcal vaccination in Japan, except for travelers to West Africa [48].

1 3.1.3. Europe

2 Incidence of MD is currently low in many parts of Europe, with differing distributions of
3 serogroups and strains, and different vaccination policies in place. The official European
4 case definition was last updated in 2012 [49], and there is continuing movement across
5 Europe to adopt this common definition. The current clinical definition includes any person
6 with at least one of the following: meningial signs, hemorrhagic rash, septic shock, or septic
7 arthritis. The laboratory criteria must include at least one of the following: isolation of *N.*
8 *meningitidis* from a normally sterile site, including purpuric skin lesions; detection of *N.*
9 *meningitidis* nucleic acid from a normally sterile site, including purpuric skin lesions;
10 detection of *N. meningitidis* antigen in cerebrospinal fluid; and detection of Gram-negative
11 stained diplococci in cerebrospinal fluid [49].

12
13 In the UK, the introduction of MenC conjugate vaccination in 1999 through routine
14 immunization and a large catch-up campaign has resulted in significant and sustained
15 disease reduction and the induction of herd protection [50]. Routine vaccination strategies
16 have also been implemented in France, Germany, the Netherlands, and Spain, and these
17 have dramatically reduced MenC MD incidence, particularly in the countries that have
18 achieved high vaccine uptake rates among adolescents and young adults [49]. The key to
19 maintaining this success will likely be to prevent acquisition of carriage by maintaining high
20 antibody levels in adolescents. Hence, many countries, including the UK and Canada, have
21 introduced booster vaccinations in this population.

22
23 In Russia, reporting of MD is mandatory; however, there is a lack of typing facilities at the
24 local level, although the availability of PCR-based methods is increasing. Therefore, the
25 reported incidence is likely an underestimate, at 0.3–0.8/100,000 across the different
26 regions, with most cases reported in young children [51]. The known serogroups are MenA,
27 B, C, and W; MenW:clonal complex (cc)11 was first detected in Moscow in 2007, with the

1 number of cases increasing in 2014–2015 (Mironov K, unpublished data [52]). Although
2 several vaccines are licensed, including multivalent conjugate types, the national vaccine
3 strategy covers only at-risk groups, areas where the disease is endemic, and military
4 recruits. Current barriers to vaccination are reported to include the underestimation of
5 disease burden and limited pharmaco-economic data. Improved surveillance systems, better
6 physician and public awareness, and cost-effectiveness studies are also needed.

7

8 *3.1.4. Africa*

9 In South Africa, MD is endemic, with peaks in the winter and spring months. Any suspected
10 MD is notifiable, and guidelines for treatment, prevention, and control are in place. National
11 laboratory-based surveillance has been available since 1999, and enhanced surveillance
12 has been in place at 25 hospital sites since 2003. Routine vaccinations are available for at-
13 risk groups. Incidence rates in South Africa vary by province, but are currently low overall
14 (0.36/100,000 in 2014). The majority of disease is caused by MenW, followed by MenB; 67–
15 77% of disease is caused by MenA, C, W, or Y. The last peak in incidence, in 2006, was
16 attributed to MenW [53], and MenW ST-11 (related to the so-called ‘Hajj strain’) remains the
17 most prevalent, with infection rates highest in infants and young children [54]. Importantly,
18 human immunodeficiency virus infection has been associated with an increased incidence of
19 invasive MD, a higher risk of bacteremia, and a higher case fatality rate than in uninfected
20 populations [55,56].

21

22 Surveillance between 1998 and 2008 in Mozambique revealed 63 cases of MD, which were
23 serogroup A, W, and Y. Of these, MenW was again the most prevalent (38/43; 88% cases),
24 followed by MenA (3/43; 7.0% cases) [57]. As in South Africa, MenW ST-11 strains
25 appeared to be the most prevalent (as of 2005) [57].

26

1 In a number of countries worldwide, including several on the African continent, the Invasive
2 Bacterial Vaccine-Preventable Diseases hospital sentinel surveillance program [58] is
3 enabling PCR to be used for surveillance for a number of diseases, including MD.

4

5 The sub-Saharan meningitis belt has a unique MD situation and special strategies in place,
6 as discussed in Section 3.2.2.

7

8 *3.1.5. North America*

9 In North America (excluding Mexico), surveillance systems are in place and considered
10 robust; active surveillance has been in place in the USA since 1995, and surveillance has
11 been carried out in Canada since 1924 [59]. The incidence of invasive MD has remained low
12 over the past several decades, and is continuing to decline [59]. This decline is thought to be
13 multifactorial, including the introduction of mass vaccination campaigns and changes in
14 behavioral risk factors [59]. MenB and MenC are the predominant serogroups reported in the
15 region; however, localized outbreaks caused by various clones belonging to different
16 serogroups are observed [59]. Outbreaks in recent years have led to the implementation of
17 outbreak control and routine immunization vaccination programs in the USA and Canada. In
18 the USA, routine anti-MenA,C,W,Y conjugate vaccination is recommended for otherwise
19 healthy children at age 11 years, with a booster at age 16 (and catch-up program during
20 adolescence) or from infancy onwards for those with certain high-risk conditions; MenB
21 vaccination for those ages 16 through 23 is subject to individual clinical decisions [26].
22 Schedules vary across the regions and provinces of Canada, but in general anti-MenC
23 vaccination is recommended during the first year and anti-MenA,C,W,Y conjugate
24 vaccination during adolescence [60].

25

1 **3.2. Today's remaining concerns, and key prevention and control strategies**

2 *3.2.1. Prevention of carriage and the introduction of herd protection*

3 Conjugate vaccines are considered superior to plain PSVs in most aspects and also prevent
4 acquisition of carriage and promote (indirect) herd protection (Figure 2) [61,62].

5 Consequently, their use is supported by the GMI [11]. In the UK, for example, adolescent
6 boosters have been introduced to maintain herd protection that forms an integral part of the
7 MenC control strategy [63]. Additionally, in Canada, an adolescent booster dose of MenC or
8 MenACWY conjugate vaccine has been recommended in all provinces and territories [60].

9

10 In general, carriage is most frequent in young adults, with a prevalence of ~24% and
11 approaching 100% in closed or semi-closed populations, such as military recruits and
12 university students [18]. Since most transmission occurs in the carriage state, reducing
13 carriage is pivotal to effective vaccination strategies. In such situations, conjugate vaccines
14 provide herd protection by providing long-lasting protection and reducing nasopharyngeal
15 carriage [61,64,65], for example, through the presence of high levels of mucosal antibodies,
16 thus reducing total transmission in the population.

17

18 Carriage studies can support and guide the introduction of meningococcal conjugate
19 vaccines by showing which groups have the highest prevalence and are driving circulation of
20 meningococci. They can also be used to determine the impact of the introduction of
21 conjugate vaccines on carriage in vaccination programs. There are, however, few studies of
22 meningococcal carriage in some ages/populations, but those that are available provide
23 useful data. The lack of studies overall can be due to difficulties in sampling a representative
24 population. Sample sizes of several thousand or more are necessary to evaluate changes
25 when the prevalence of pathogens targeted by a vaccine is low; multicenter studies are
26 preferable, because of the variability between sites. Sample collection and transport and
27 analytical methods can all impact carriage data collection; it is also essential to have

1 rigorous quality control. Due to atypical strains, identification of *N. meningitidis* carriage
2 remains problematic, and methods need to be standardized. In general, detection and
3 characterization methods such as PCR [66], multi-locus sequence typing (MLST) [67], and
4 whole-genome sequencing (WGS) [68] appear to be the most specific.

5

6 *3.2.2. MenA and the sub-Saharan meningitis belt*

7 The sub-Saharan meningitis belt comprises 26 countries across the sub-Saharan region and
8 is characterized by very low rainfall and humidity in the dry season. Cases peak, and
9 epidemics occur more frequently, in the dry season. During the 1996–1997 MD epidemic,
10 there were >250,000 cases of MenA, prompting African governments and the WHO to
11 demand a new conjugate vaccine for Africa [69]. MenW, MenX, and MenC have also caused
12 epidemics in the sub-Saharan meningitis belt. Between 2004 and 2010, 19 sequence types
13 belonging to six clonal complexes were identified, with MenA of the ST-5 cc identified as the
14 predominant disease-causing strain, responsible for ~80% of epidemics [67,70]. The most
15 recent large-scale MenA epidemic was in 2009 [71]: during this year alone, nearly 90,000
16 cases of meningitis were reported – 50,000 of which were in Nigeria [71].

17

18 In response to the threat of MenA epidemics, MenAfriVac[®] (Table 1) was developed and
19 licensed in India and awarded pre-qualification by the WHO in 2010 [69]. The introduction
20 strategy for MenAfriVac[®] was to induce rapid direct and indirect (i.e., herd) protection by
21 vaccinating individuals aged 1–29 years in mass campaigns [72] spanning over 1–4 years,
22 and to protect new birth cohorts through a routine expanded program of immunization (EPI)
23 or follow-up campaigns. This staggered approach to vaccination was, in part, due to large
24 populations being spread over a wide area. Risk assessments were put in place [73] to
25 define priority areas and to estimate target populations before vaccine introduction, and by
26 November 2015, 237 million people had been vaccinated [74]. Enhanced surveillance and
27 outbreak response capacity are an essential part of epidemic preparedness and response,

1 enabling a quick response to new outbreaks and provision of adequate treatment and
2 containment. Case-based surveillance is being undertaken in some countries, such as
3 Burkina Faso and Niger, and uses epidemiological and laboratory data. Countries are
4 supported by the WHO and international collaborating laboratories. The incidence of MenA
5 has now dramatically decreased [65,69], and the vaccine has also had a dramatic impact in
6 reducing carriage [65]. Between 1 January and 12 May 2013, there were 9249 suspected
7 meningitis cases with a case fatality ratio of 9.3% (857 deaths) across 18 countries – the
8 lowest number of cases recorded during the epidemic season in the last 10 years [115], with
9 the majority of cases occurring during 2009 (Figure 3) [75]. Under enhanced surveillance in
10 2014, 7585 meningitis cases and 610 deaths were reported across the African meningitis
11 belt, with the WHO region-specific epidemic threshold of >100 cases/100,000 [41] crossed in
12 districts of Burkina Faso, Cameroon, the Central African Republic, Chad, Ethiopia, Gambia,
13 Ghana, Guinea, Mali, Niger, Nigeria, Senegal, South Sudan, and Sudan [76]. The WHO
14 recommendations for EPI and ‘catch-up’ schedules and dosages are being rolled out across
15 the sub-Saharan meningitis belt [72,77]. Following the introduction of MenAfriVac[®], the WHO
16 now recommends that the vaccine is incorporated into the routine EPI schedule within 5
17 years. Modeling suggests that, if routine EPI is not followed with subsequent immunization,
18 epidemics could occur within 15 years following mass campaigns [59,72].

19

20 Subsequent to MenAfriVac[®] introduction, MenW became the predominant strain across the
21 sub-Saharan meningitis belt. However, MenC appears to have re-emerged recently, having
22 not been responsible for outbreaks in the sub-Saharan meningitis belt since 1979 [78]; in
23 Nigeria, it increased from 452 suspected cases in 2013 to 796 suspected cases in 2014.
24 Then in 2015, the outbreak expanded rapidly, with 2845 suspected cases in Nigeria, and
25 8502 cases in the bordering country of Niger (totaling 11,347 suspected cases) [79]. This is
26 a new MenC strain (ST-10217) [79] that seems to have spread from a single source in
27 Nigeria; it is genetically unrelated to the epidemic clones found in Africa in previous decades
28 or to the rare serogroup C isolates that have circulated elsewhere in the world since the

1 1980s [80]. It probably originated from a carrier isolate that has acquired serogroup C
2 capsule and other virulence genes by recombination (Caugant DA, unpublished data, cited
3 with permission). The clone is still evolving and has now spread to neighboring countries.
4 Affected populations are unlikely to have immunity against MenC, and the prospect of a
5 major epidemic is of great concern.

6

7 **3.3. The rising concern of MenW: epidemiology and control**

8 **3.3.1. MenW epidemiology**

9 Serogroup W was discovered in 1968 and, until 2000, was responsible for a relatively small
10 number of cases worldwide. A pivotal recent event was the emergence and epidemic
11 situation of MenW in Hajj pilgrims in Saudi Arabia, the UK, and France in 2000,
12 subsequently in sub-Saharan Africa, and elsewhere globally [81,82]. The Hajj cluster of *N.*
13 *meningitidis* represents an expansion of one MenW clone within the ST-11/ET-37 complex
14 [35,83]. However, some other recent MenW outbreaks (such as seen in Brazil, Portugal
15 [84,85], Sweden [86], and Taiwan [2014 meeting of the GMI, manuscript submitted] [41])
16 have been due to other ST-11 variants. Although the hypervirulent clone W:2a:P1.5,2:ST-11
17 emerged 10 years ago in Brazil [87], incidence rates have become far higher in Argentina
18 and Chile. In Chile, for example, the MenW incidence rate had risen to >0.5/100,000 by
19 2014, compared with <0.1/100,000 in 2010 (data from the ISPCH, Laboratorio de Agentes
20 de Meningitis Bacteriana, Santiago, Chile); by 2012, 58% of MD was MenW [88]. The MenW
21 ST-11/ET37 cc now appears to be endemic in the Southern Cone region [89]. In the UK,
22 MenW has also been increasing; the new isolates belong to the ST-11/ET-37 complex but,
23 again, appear to be different from the Hajj strain, although close to the South American
24 isolates [35].

25

26 Thus, there appears to be an ongoing multifocal emergence of new MenW isolates by
27 means of an old event of capsule switching, and MenW/cc11 isolates – other than those

1 from the Hajj outbreak – have contributed to a significant proportion of MenW/cc11 cases
2 globally. Surveillance therefore needs to combine exhaustive reporting and typing and, if real
3 insight is to be gained from what is taking place with MenW, WGS typing is required. To
4 date, isolates from waves of MenW/cc11 infection have been found to have differences in
5 the genes encoding factor H-binding protein (fHbp), *fetA*, nitric oxide reductase, and nitrite
6 reductase [35,90].

7

8 3.3.2. *MenW control*

9 Vaccination strategies for controlling MenW and other *N. meningitidis* strains using
10 multivalent conjugate vaccines being rolled out in a number of countries. An immunization
11 campaign began in 2012 in Chile with the quadrivalent conjugate vaccine (MenACWY;
12 Menveo[®]; Table1), initially targeting children aged from 9 months to <5 years. The incidence
13 of MD in this age group before and after introduction of quadrivalent *N. meningitidis*
14 (MenACWY) vaccination is shown in Figure 4. Since 2012, approximately 1 million children
15 have been vaccinated, and vaccine uptake of 95% has been attained in these age groups
16 (data from ISPCH Laboratorio de Agentes de Meningitis Bacteriana). In addition, since 2012,
17 a temporary vaccination strategy was established in which children aged from 9 months to 5
18 years were vaccinated, and infants from 9 months old were given a second dose to increase
19 protection. The vaccines Menactra[®] (Table 1) and Menveo[®] have been used as part of this
20 temporary vaccination strategy. On 1 January 2014, vaccination became part of the national
21 immunization schedule and was mandatory for all children aged ≥ 1 year, with a one-dose
22 schedule of Nimenrix[®] (Table 1) implemented. Overall, however, the number of cases of
23 MenW is still increasing in Chile in children between 9 months and 5 years of age (data from
24 ISPCH Laboratorio de Agentes de Meningitis Bacteriana) (Figure 4). In Argentina, between
25 2012 and 2014, there were 848 cases of MD, with an incidence rate of 0.7/100,000
26 population; 43% of these were in infants aged <2 years [91]. Around 50% of cases were
27 MenW, and 41% were MenB [91]. Argentina recently announced the decision to implement

1 quadrivalent conjugate vaccination in infants (at 3, 5, and 15 months old). Adolescents aged
2 ≥ 11 years are to receive one dose [91]. In the UK, MenW has increased rapidly since
3 2011/2012 [92]. A vaccination program was introduced in August 2015, for teenagers and
4 university freshers, using MenA,C,W,Y conjugate vaccines, with the intention of inducing
5 direct and herd protection [63]. Although it is anticipated that conjugate vaccines will have a
6 similar effect on the carriage of W as they have had on serogroups A, C, and Y, this has yet
7 to be demonstrated.

8

9 **3.4. Decreasing the threat of MenB: implementation of MenB vaccines**

10 Capsular vaccines cannot be used for MenB due to similarities of the polysaccharide with
11 human polysialic acid on neural cell adhesion molecules; therefore, vaccines targeting MenB
12 have been developed using subcapsular proteins. Earlier vaccines based solely on OMVs
13 could only offer protection against homologous strains and needed multiple doses to induce
14 broader protection [27]. Bexsero[®], a multicomponent vaccine, was developed by reverse
15 vaccinology and comprises an OMV used in a New Zealand outbreak and three recombinant
16 proteins – the neisserial heparin-binding antigen (NHBA), the *Neisseria* adhesin A (NadA),
17 and the fHbp [29]. Clinical studies were conducted in infants, toddlers, and adolescents [93];
18 >5000 infants/toddlers and 19,000 adolescents/adults have now been vaccinated. Bexsero[®]
19 was approved by the European Medicines Agency in 2013 for individuals ≥ 2 months of age,
20 and by the US Food and Drug Administration (FDA) in 2015 for ages 10 to 25 years [94,95].
21 The vaccine is reactogenic, with transient fever seen in infants peaking ~ 6 h after
22 vaccination and resolving within 2–3 days, particularly after the primary dose; the reaction
23 can be increased by concomitant administration with other routine infant vaccinations, but is
24 manageable with paracetamol, with only 2–3% of patients requiring additional medical
25 attention [93]. A second subcapsular vaccine, Trumenba[®], contains two fHbp variants
26 [29,96], and was approved by the FDA in 2014 for use in adolescents and young adults
27 aged 10–25 years [97].

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Measurement of strain coverage with subcapsular vaccines can be complex, as they comprise multiple antigens that vary between strains and may be expressed at variable levels. The Meningococcal Antigen Typing System (MATS), which is based on an enzyme-linked immunosorbent assay, and either phenotypic or genotypic PorA typing, [98] has been used for strain characterization to evaluate potential strain coverage with Bexsero[®]. Using this method, worldwide strain coverage has been estimated at ~66–91% [92]. Some coverage of non-MenB strains by the vaccine has also been reported, with 70% coverage of MenW and MenY strains, but only ~20% for MenC. Coverage of African epidemic MenX isolates has also been suggested [99].

In 2013, MenB outbreaks occurred at two universities in the USA (Princeton, NJ and the University of California, Santa Barbara); Bexsero[®] vaccination was conducted under the FDA's expanded access investigational new-drug protocol, and approximately 5500 and 17,000 individuals were vaccinated at these universities, respectively . For the Princeton outbreak, MATS analysis showed that the strains were sufficiently reactive with the Bexsero[®] fHbp and NHBA to invoke an effective immune response, but were mismatched for the NadA and PorA antigens [102]. Vaccination uptake rates of 97% (first dose) and 92% (second dose) were achieved. Carriage was not formally assessed, but the occurrence of a ninth case in an unvaccinated Princeton student who had close contact with vaccinated undergraduates implies that the strain continued to circulate after vaccination [100,101]. Since September 2015, Bexsero has been introduced into the UK's routine infant immunization strategy [63], and enhanced surveillance – that includes genotyping and MATS – is ongoing as part of this program [103].

Vaccination programs (e.g., for MenC [consisting of one to three doses of MenC conjugate vaccine in infancy, with a booster dose of MenC conjugate or MenACWY conjugate vaccine at 12–15 years old]) have been in place for a number of years in Canada; MenB, however,

1 has recently become the most prevalent serogroup in Quebec and Ontario (data from Public
2 Health Agency of Canada, 2014 shown in Figure 5) [104,105], although the reasons for
3 differences in prevalence from other provinces are unclear. Most of the isolates recently
4 characterized in Quebec have been ST-269 clones that express two variants of the antigens
5 fHbp and NHBA potentially covered by Bexsero[®] [106]. Bexsero[®] was licensed in 2013 in
6 Canada and vaccination is proposed for high-risk groups [104,107,108], with current
7 recommendations based on various criteria, including low disease burden, program cost,
8 lack of effectiveness and reactogenicity data [107,108]. In one area in Quebec, MenB MD
9 incidence reached >3.5/100,000 in the period 2006–2012, and a decision was taken to use
10 Bexsero[®] based on several strands of evidence, including phenotyping and genotyping of
11 strains. More than 50,000 people between the ages of 2 months and 20 years were
12 vaccinated on a two-dose schedule [100]. The vaccine uptake rate for one dose was 82%,
13 but this went down to 70% for at least two doses, mainly due to low uptake in older
14 adolescents and young adults [100]. Based on a modeling analysis, it was estimated that the
15 vaccination campaign reduced disease incidence by 77% [109]. In May 2014, more than a
16 year after the start of the immunization campaign, no new MenB cases had been observed
17 among vaccinees, with two cases observed among non-vaccinated adults [109]. The strain
18 therefore continues to circulate and, as in the US university outbreaks, there is no evidence
19 of indirect protection. Despite the lack of data supporting herd protection with these MenB
20 vaccines, there are data suggesting that OMV vaccines can reduce carriage [110].

21

22 **3.5. Advocacy and awareness in MD**

23 Around the world and in many different countries, many organizations play important roles in
24 raising awareness of MD and advocating for clinicians, as well as for patients and their
25 families. The Meningitis Research Foundation (MRF), for example, is a UK-based charity
26 that funds research, promotes education and awareness of MD, and provides support for
27 those affected by meningitis. For example, in the case of Bexsero[®] in the UK, following the

1 interim statement from the UK Joint Committee on Vaccination and Immunisation that
2 vaccination was unlikely to be cost-effective at any vaccine price, the MRF highlighted the
3 consequences and costs of survival with life-limiting sequelae. In addition, the MRF
4 conducted campaigns to engage with clinicians and experts in the field, as well as public
5 campaigns based on real-life personal stories in a range of settings. This coordinated
6 collective effort by parent and patient advocacy, health experts, and key opinion leaders
7 contributed to the decision to approve Bexsero[®] for use in the UK's vaccination program
8 [111].

9

10 On a global scale, another such organization, the Confederation of Meningitis Organisations
11 (CoMO) represents 45 organizations from 28 countries [112]. CoMO has a scientific advisory
12 panel comprising experts from around the globe, and uses non-government organizations
13 and 'people advocate' conferences, as well as meetings with politicians in Europe and
14 campaigning on social media. It provides a global platform for its member organizations to
15 campaign on meningitis awareness and vaccination, and organizes World Meningitis Day
16 annually in April [113]. CoMO has commissioned research into the long-term cost of
17 meningitis [114], and is currently advocating for a 'life-course' immunization initiative (for
18 infants, adolescents, and the elderly) [115].

19

20 ***3.6. The role of modeling in MD control and prevention***

21 To improve understanding of the epidemiology of an infection, make predictions about future
22 incidence under particular conditions or interventions, and identify data gaps, transmission
23 dynamic mathematical models can be developed and applied. Modeling studies of
24 meningococcal infection reinforce the importance of herd protection following mass 'catch-
25 up' campaigns and illustrate that conjugate vaccines' effect on carriage was crucial to the
26 success of the MenC and MenAfriVac[®] vaccine programs [18,72,116]. Such models are
27 used to best effect in combination with data from surveillance, clinical trials, and carriage

1 studies [61,64,65]. The clinical evidence for the impact of subcapsular vaccines (such as
2 Bexsero®) on MenB carriage is currently unclear as few data have been published [117];
3 however, models can help us to identify knowledge gaps and enable testing of how
4 hypothetical effects on carriage might impact different potential vaccination strategies.

5

6 A workshop on modeling vaccination strategies held during the meeting explored how
7 modeling can be used in combination with surveillance and vaccine information to guide
8 decision making. Transmission models should be used for MD, as the occurrence of
9 infection depends on carriage in other members of the population; risks of infection are
10 dynamic and non-linear [72,116,118]. In the UK, models have been used to synthesize
11 different types of evidence (e.g., in disease burden, natural history, and vaccine effects); to
12 make predictions about vaccine impact and also to aid optimum implementation of 4CMenB
13 vaccination; modeling has been used to evaluate factors including herd protection; to
14 compare schedules, strategies, and policy options; and to estimate the cost-effectiveness of
15 vaccination [106,116,118,119]. It was agreed by the GMI that, to predict future incidence and
16 develop a vaccination strategy during an outbreak, incidence and carriage data, and the
17 response threshold selected, are the most important factors. It was also agreed that, when
18 deciding whom to vaccinate and which vaccine to use, the availability of sufficient vaccine
19 and the vaccine's ability to interrupt carriage were the most important factors. Regarding
20 health economic analyses, it was noted that these are only reliable when working from
21 robust data. The GMI agreed that economic modeling could be conducted, but it requires
22 reliable data on the burden of the disease and should not be the sole driver of decision
23 making.

24

25 **4. Discussion**

26 The presentations on surveillance, epidemiology, and control from around the globe given at
27 this GMI meeting highlight disparities in the quality and availability of surveillance networks

1 and technologies, such as PCR and WGS. The current GMI Global Recommendations for
2 Meningococcal Disease [11] underline the need to increase the availability and quality of
3 laboratory surveillance in order to understand the true burden of MD (Table 2). The role of
4 enhanced surveillance in demonstrating the success of the MenAfriVac[®] campaigns [71] and
5 in detecting emerging MenW outbreaks in Latin America and the UK [120] illustrates the
6 importance of high-quality data that should include typing by WGS [120]. There is a need for
7 continued vigilance in the face of the emergence of new clones requiring maintenance of
8 high-level surveillance where it is already attained and improvement in countries where
9 systems are weak. Also, although vaccination programs are effective in combating MD,
10 meningococcal vaccines are still not available as part of routine childhood vaccination
11 programs in many countries.

12

13 As the GMI, we have developed a number of recommendations. First, conjugate vaccines
14 are recommended by the GMI, as in most aspects they are superior to plain PSVs (Table 2).
15 In addition, the GMI recognizes herd protection as being a significant component of control
16 in MD, with evidence presented from several studies and countries showing that adolescent
17 doses provide individual and herd protection. It is important to note, however, that a number
18 of factors, including disease prevalence, carriage rates, and vaccine type, may influence the
19 level of vaccination coverage required to attain herd immunity [121] (for example, in the
20 African meningitis belt, a vaccination rate of 70% was considered to have afforded herd
21 immunity [72]).

22

23 The success of MenAfriVac[®] in Africa and MenC vaccination in several European countries,
24 Australia, and Canada demonstrates the importance of building herd protection through
25 adolescent and 'catch-up' campaigns. It was noted that, in different countries, adolescent
26 vaccinations were undertaken at different ages (e.g., at 11 years in Argentina, but in older
27 teenagers in the UK). A number of factors seem to govern such decisions, including the
28 practicalities of timing to attain maximum vaccine uptake rates. We suggest that, as

1 socioeconomic factors – such as age, differences in levels of close physical contact, starting
2 smoking, and so on – may differ between and even within countries, local differences need
3 to be taken into account when devising vaccination strategies to ensure that herd protection
4 is optimized. Although carriage studies are complex to undertake, evaluation of the age
5 distribution of carriage, estimation of the case–carriage ratios, and identification of the clones
6 being carried are essential to fully understand the relationships between carriage and
7 outbreak strains. We also believe that MLST [67] and WGS [120] may be the most effective
8 DNA analysis methods for carriage studies.

9

10 The extensive data presented on MenW from around the globe again highlight the
11 importance of routine and ‘catch-up’ vaccination programs for both direct and indirect
12 protection. The data show that the recent expansion of MenW has been through the
13 emergence of sub-clones that are spreading globally [120]. Again, such observations
14 highlight the need for active surveillance systems that can provide accurate data through
15 WGS, for example. Intriguingly, one strain can appear to behave differently in different
16 countries; for example, the hypervirulent MenW strain that emerged in Brazil has become far
17 more prevalent in recent years in Argentina, Chile, and the UK. Yet again, such observations
18 underline the need for strong local surveillance networks and locally tailored control
19 measures. In addition, combination of WGS and new molecular techniques such as
20 proteomic gene expression analysis may provide additional detail on the biological
21 characteristics of individual strains and thus further aid our understanding of emergence
22 events [122].

23

24 The report presented on the outbreak of MenW at the 2015 World Scout Jamboree in Japan
25 [86] illustrates the ever-present risk and need for preventive measures such as vaccination
26 for participants in events where large numbers young people are gathered. It also underlines
27 the importance of maintaining immunity in adolescents and young adults.

28

1 Subcapsular MenB vaccines are now available and have been used effectively in outbreak
2 control [100,102,109], and are also now included in routine infant vaccination
3 recommendations in the UK. To evaluate the level of coverage provided by these vaccines,
4 such as in an outbreak situation, accurate data on presence and expression of the various
5 vaccine-related antigens in the active strain are required. For this, again, good-quality
6 surveillance with access to MATS and DNA analysis technologies, especially WGS, are
7 required. There is still uncertainty about the ability of these vaccines to eliminate MenB
8 acquisition/carriage, and further data are needed in this area.

9

10 The importance of raising awareness and of advocacy in promoting the prevention and
11 control of MD was highlighted by the work of the MRF and the CoMO. Indeed, these
12 organizations continue to play an important role in activities to support the introduction and
13 expansion of vaccination and surveillance programs.

14

15 As noted above, modeling can be used to help us understand the impact of
16 carriage/acquisition reduction on indirect protection and to enable longer-term predictions.
17 The GMI agreed that models are used to best effect in combination with data from various
18 sources, including disease surveillance, clinical trials, and carriage studies.

19

20 **5. Summary**

21 During the 2015 GMI meeting, presentations showed how vaccination programs have been
22 successful in reducing MD incidence in many countries; however, it was also described how
23 new MenW clones present a threat, as does the emergence of a new MenC strain in the
24 African meningitis belt. As a result of the findings presented, the GMI recognized the
25 importance of ongoing vigilance and called for continued support and expansion of
26 vaccination and surveillance programs. The importance of building herd protection and
27 stopping acquisition for the prevention of transmission of MD was also discussed. The GMI

1 agreed that vaccination of those age groups with the highest carriage rates (particularly
2 adolescents) is important for this. With this in mind, the GMI also called for vaccination
3 programs for protection during large gatherings of young people in close contact.
4 Presentations from the MRF and the CoMO showed how such organizations are key to
5 ensuring continuation and growth in all of these areas.

6

7 Updates to the GMI Global Recommendations for Meningococcal Disease were determined
8 during the meeting based on the findings presented (Table 3). The GMI agreed that there is
9 a need for a recommendation to enable access to WGS as part of surveillance programs
10 and also for DNA sequence data to be publicly available. It was also agreed that guidance
11 on the antigen expression criteria that indicate use of subcapsular vaccines should be
12 included in the recommendations. Finally, the GMI agreed that support for MD advocacy and
13 awareness campaigns should be included in the GMI Global Recommendations for
14 Meningococcal Disease.

15

16 **6. Expert commentary**

17 MD remains an important health concern in many regions across the globe, particularly
18 Africa, where morbidity and mortality rates are still high, as well as in Asia, where the true
19 burden of MD is uncertain. However, health policy leaders, scientists, and clinicians in these
20 regions (and individual countries) can learn from the experiences, insights, and strategies of
21 others from across the globe where MD has been prevented and controlled with great
22 success. Indeed, much can be learnt from the Latin American experience and control of
23 MenW, as well as from the control of MenA in the African meningitis belt, of MenC in
24 Australia, Brazil, Canada, and Europe, and of MenB in the UK and Canada.

25

26 Since the introduction of meningococcal vaccines, the world has seen a substantial
27 reduction in the burden of MD. Outbreaks continue to occur in many areas of the world. The

1 reasons for this are multifactorial and include: relatively low vaccination uptake rates; poor
2 surveillance and control systems; lack of standardized case definitions and diagnostic
3 assessments; lack of herd protection; failure to vaccinate those currently at risk; strain
4 changes; rise of serogroup(s) not covered by currently used vaccines; and the general
5 unpredictability of MD epidemiology.

6

7 Moving forward, a key strategy to further reduce/interrupt MD transmission, beyond the
8 levels noted today, would be to induce herd protection in populations where it is currently
9 lacking. Data suggest that herd protection can be achieved with conjugate vaccines by
10 immunizing those who are most likely to be carriers and thus targeting the driving force of
11 transmission (i.e., adolescents and young adults), as opposed to immunizing those in whom
12 only direct protection is gained (i.e., infants and young children). Some countries are
13 currently implementing (or at least recommending) such strategies (e.g., the USA and UK).
14 Of course, achieving and sustaining herd protection will be a challenge in itself and is likely
15 to require high vaccination uptake rates in populations where vaccine uptake is currently low.
16 While the experience in many countries, both developed and developing, proves that
17 decreasing the overall incidence of MD and control of outbreaks is possible, coordinated,
18 sustained, and long-term strategies will be required in each country in order to reach the
19 goals of lowering mortality and morbidity due to MD.

20

21 **7. Five-year view**

22 In the next 5 years, the epidemiology of MD will most likely continue to be dynamic and
23 change across the globe, as enhanced surveillance systems and prevention and control
24 strategies are being implemented. Furthermore, it is likely that localized outbreaks that are
25 potentially controllable through vaccination programs will continue to occur in places where
26 systems are weak or lacking. In addition, the emergence of new strains is likely to be an
27 issue, such as the ST-10217 in Nigeria and Niger and the variants of ST-11/ET-37 cc MenW,

1 and the spread of other hypervirulent strains. Constant vigilance and high-quality MD
2 surveillance will be needed.

3

4 New multi-omic technologies and bioinformatics tools continue to develop, with genetic
5 techniques such as real-time PCR and WGS, as well as gene expression methods such as
6 transcriptomic and proteomic analyses, which enable even more in-depth strain
7 characterization, becoming more widely available. Such techniques could become more
8 accessible to surveillance laboratories at least on a regional level, if not nationally, within the
9 next 5 years, and should improve not only surveillance but also understanding of emergence
10 of particular strains. It would be hoped that availability of higher-quality epidemiological data
11 from such sources could be used as a driver for implementation of effective routine and
12 emergency vaccination programs. In parallel, the increasing availability of carriage data,
13 together with the availability of new DNA technologies and modeling data, should enable
14 effective targeting of age groups and populations in whom carriage is greatest, and where
15 immunization would be best employed to develop effective herd protection. The GMI agrees
16 that vaccination of the age groups with the highest carriage rates (particularly adolescents) is
17 important for this, and should be implemented, or at least recommended, in more countries
18 in the next 5 years.

19

20 The GMI recognizes the importance of ongoing vigilance and has called for continued
21 support and expansion of vaccination and surveillance programs. Organizations such as the
22 MRF and the CoMO will be key to ensuring the continuation and growth of surveillance and
23 vaccination programs during the coming years.

24

25 When employed in organized vaccination programs, new vaccines, such as the quadrivalent
26 MenACWY conjugate vaccines and the MenA conjugate MenAfriVac[®], have already made
27 dramatic contributions to the control of MD through providing direct protection and,
28 potentially, herd protection. It is anticipated that, if such programs are continued and

1 expanded, impact on MD will also continue. The new MenB vaccine Bexsero[®] has also now
2 shown effectiveness in real-world outbreak situations and, within the next 5 years, its effects
3 within a national infant immunization program and on carriage should be better understood.

4

5 Finally, availability of high-quality surveillance data in the future is also necessary so that a
6 state of preparedness is maintained and suitable vaccines are available, or can be rapidly
7 made available should newly emergent strains become a threat (e.g., MenC in the sub-
8 Saharan meningitis belt).

9

10 All of these points are covered by the GMI Global Recommendations for Meningococcal
11 Disease. If they are implemented, through a combination of improved disease surveillance,
12 the availability of conjugate vaccines, and advocacy to build disease awareness, it might be
13 possible to have a substantial impact on the incidence of MD globally within the next 5 years.

14 **8. Key issues**

- 15 • The GMI is an international group of clinicians and scientists with expertise in MD
16 immunology, microbiology, epidemiology, public health, and vaccination; it was
17 established to promote the prevention of MD worldwide through education, research,
18 international cooperation, and vaccination.
- 19 • The GMI has previously produced a set of Global Recommendations for Meningococcal
20 Disease (Table 2).
- 21 • More than 20 clinicians, scientists, and public health experts representing institutions in
22 Africa, the Asia-Pacific region, Europe, and Latin America convened in November 2015
23 to discuss topics including herd protection, surveillance, epidemiology, prevention, and
24 control strategies.
- 25 • Although vaccination programs have been successful in reducing MD incidence in many
26 countries, it was agreed that new MenW sub-clones present a threat, as does the
27 emergence of a new MenC strain in the sub-Saharan meningitis belt.

- 1 • The GMI recognizes the importance of ongoing vigilance in the face of this dynamic
2 disease and called for continued support and expansion of vaccination and surveillance
3 programs.
- 4 • Building herd protection and stopping carriage are important, as they prevent
5 transmission of MD; therefore, vaccination of those age groups with the highest carriage
6 rates (particularly adolescents) is necessary, as are vaccination programs for protection
7 during large gatherings of young people in close contact.
- 8 • A number of additions to the GMI Global Recommendations for Meningococcal Disease
9 were agreed:
- 10 ○ There is a need for a recommendation to enable access to WGS as part of
11 surveillance programs, and also for DNA sequence data to be publicly available.
- 12 ○ Guidance on the antigen expression criteria that indicate use of subcapsular vaccines
13 should be included in the recommendations.
- 14 ○ The GMI recognizes the importance of MD advocacy and awareness campaigns and
15 agrees that support for such activities should be included in the GMI Global
16 Recommendations for Meningococcal Disease.

17

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25

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2 Papers of special note have been highlighted as either of interest (•) or of considerable
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1 Tables

2 **Table 1.** Meningococcal disease vaccine coverage and manufacturers

Vaccine	Coverage	Manufacturer
	(<i>N. meningitides</i> strain)	
Polysaccharide vaccines		
Various	One or more of A, C, W, and/or Y	Various (available for >40 years)
Protein conjugate vaccines		
Meningitec [®]	C	Nuron Biotech Inc, Exton, PA, USA
Menjugate [®]	C	GlaxoSmithKline Biologicals SA, Rixensart, Belgium
NeisVac-C [®]	C	Pfizer Inc, New York, USA
MenAfriVac [®]	A	Serum Institute of India Ltd, Pune, India
Menactra [®]	A, C, W, Y	Sanofi Pasteur SA, Lyon, France
Menveo [®]	A, C, W, Y	GlaxoSmithKline Biologicals SA, Rixensart, Belgium
Nimenrix [®]	A, C, W, Y	Pfizer Inc, New York, USA
Combination conjugate vaccines		
Menitorix [®]	C + <i>Haemophilus influenzae</i> type b	GlaxoSmithKline Biologicals SA, Rixensart, Belgium
MenHibrix [®]	C, Y + <i>Haemophilus influenzae</i> type b	GlaxoSmithKline Biologicals SA, Rixensart, Belgium
Subcapsular meningococcal antigen vaccines		
Trumenba [®]	B	Wyeth Pharmaceuticals Inc. (a subsidiary of Pfizer Inc.), Philadelphia, PA, USA,
Bexsero [®]	B	GlaxoSmithKline Biologicals SA, Rixensart, Belgium

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1 **Table 2.** The GMI Global Recommendations for MD [33].

1	Country-specific approaches to prevention of MD by vaccination 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 model should be considered when developing other products with markets that are primarily or exclusively in developing countries.
5	Travelers to high-risk areas should be vaccinated against invasive MD.
6	Vaccines against all clinically relevant serogroups (MenA, B, C, W, X, and Y) should be developed.
7	Conjugate vaccines should replace PSVs whenever cost, availability, licensing, and immunization policy allow. However, PSVs are still recommended where conjugate vaccines are not available.
8	Laboratory-based surveillance for MD should be strengthened (or initiated) to determine the true burden of disease.

2 GMI: Global Meningococcal Initiative; MD: Meningococcal disease; PSV: Polysaccharide
3 vaccine.

4 Adapted from Vaccine, Vol 33, Marco Aurélio P. Sáfaci, Miguel O’Ryan, Maria Teresa
5 Valenzuela Bravo, Maria Cristina C. Brandileone, Maria Cecília O. Gorla, Ana Paula S. de
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7 Borrow, on behalf of the Global Meningococcal Initiative. The current situation of
8 meningococcal disease in Latin America and updated Global Meningococcal Initiative (GMI)
9 recommendations, Pages No. 6529–6536, Copyright (2015), with permission from Elsevier.

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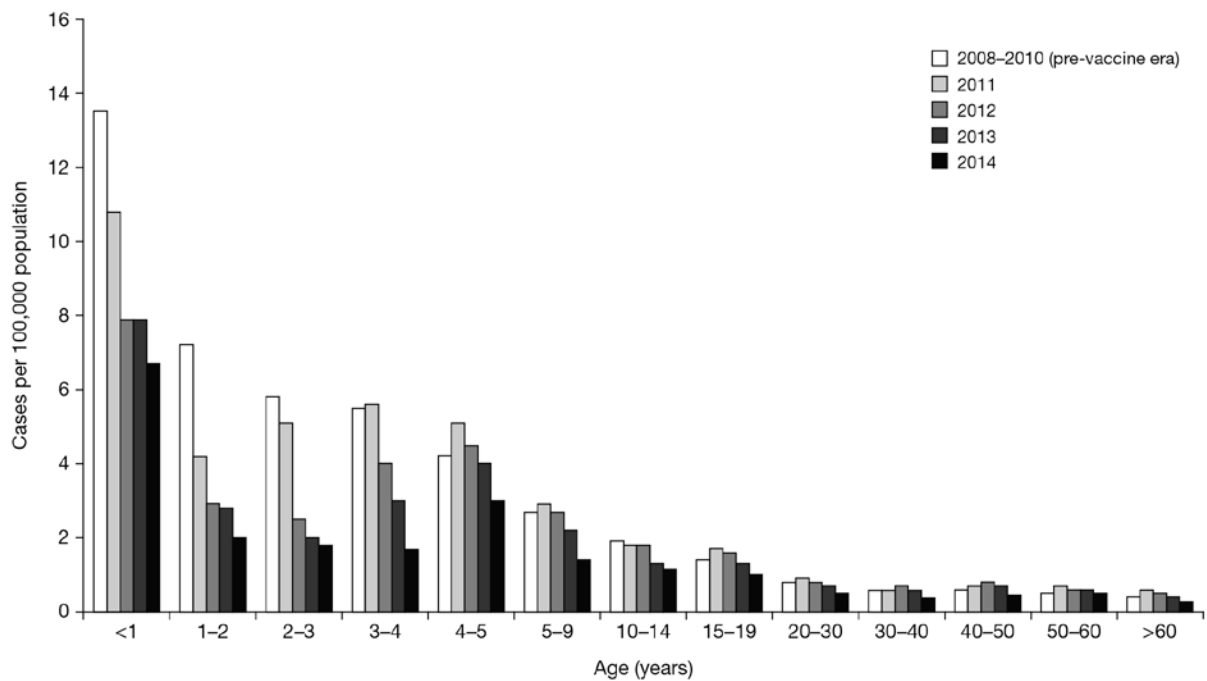
- 1 **Table 3.** The GMI Updated Global Recommendations regarding strategies for the
 2 prevention of MD and the importance of herd protection.

1	The GMI advocates WGS and/or collaborations enabling WGS, as well as the sharing of sequence data in the public domain.
2	The GMI recommends vaccination of those attending large and prolonged events such events such as the World Scout Jamboree, given the increased risk of contact with the pathogen.
3	The GMI recognizes the importance of ongoing vigilance in the face of this dynamic disease and calls for continued support and expansion of vaccination and surveillance programs.
4	Building herd protection and stopping acquisition are important, as they prevent transmission of MD; therefore, the GMI recommends vaccination of those age groups with the highest carriage rates (particularly adolescents).
5	The use of subcapsular vaccines (e.g., MenB vaccines) should be based on molecular typing and/or local data of strain coverage.
6	The GMI recognizes the importance and impact of MD advocacy and awareness campaigns and strongly supports such activities.
7	The GMI underlines the need for promoting modeling studies to help the decision-making process.

- 3 GMI: Global Meningococcal Initiative; MD: Meningococcal disease; WGS: Whole-genome
 4 sequencing.

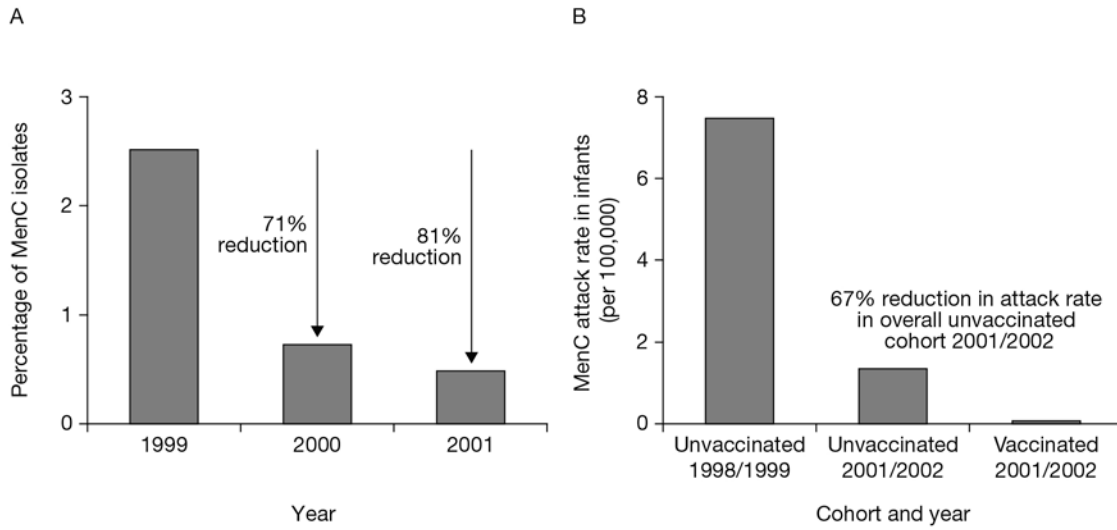
1 Figures

2 **Figure 1.** Incidence rates before and after routine MenC vaccination in Brazil, 2008–
3 2014. Adapted with permission from Safadi MA, Berezin EN, Arlant LH.
4 Meningococcal Disease: Epidemiology and Early Effects of Immunization Programs.
5 *J Pediatric. Infect Dis Soc.* 3(2), 91-93 (2014). Supplemented with unpublished data
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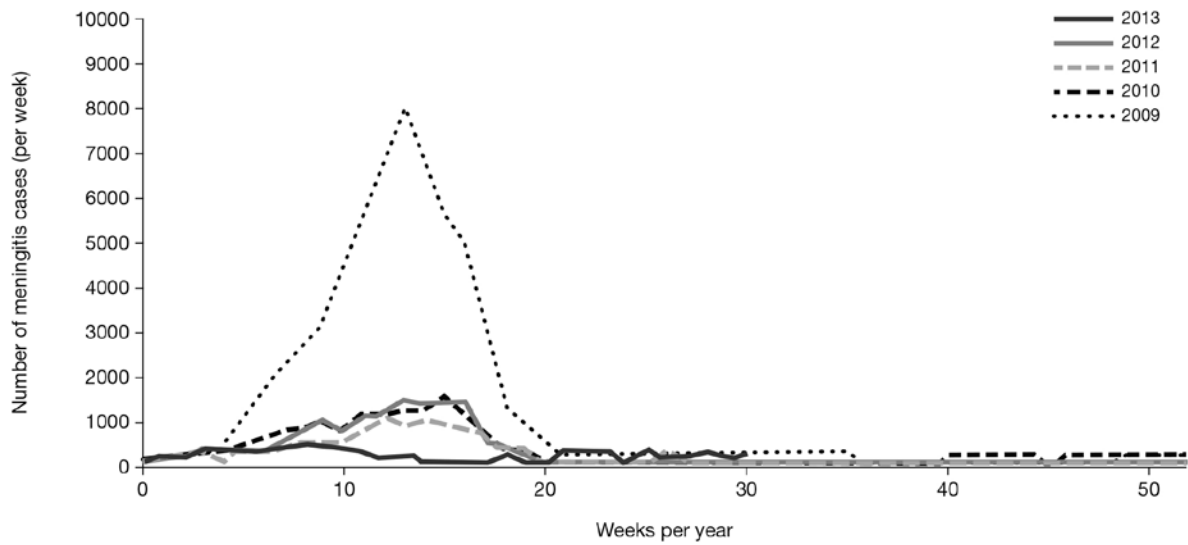
1 **Figure 2.** Impact of MenC conjugate vaccines in reducing carriage, leading to herd
2 protection in the UK. (A) Reduction in MenC carriage [61] (immunized individuals
3 aged 15–19 years). (B) Direct and herd protection [62] against MenC (attack rates in
4 infants and overall attack rate reduction in age group 2 months to 18 years)



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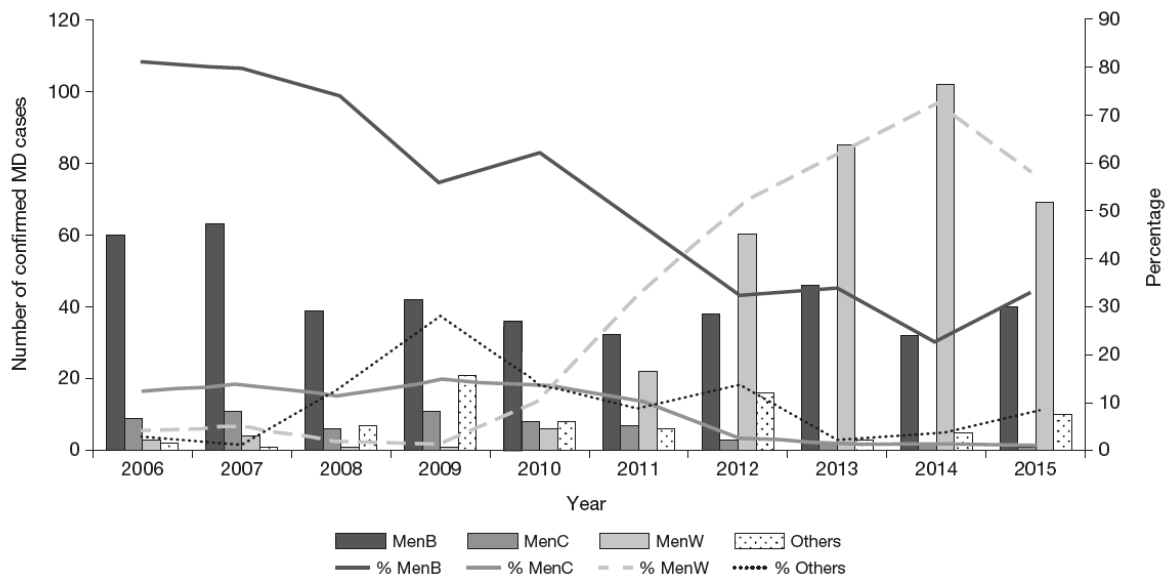
6

1 **Figure 3.** Effect of MenAfriVac[®] vaccination on number of meningitis cases (data for
2 African countries under enhanced MD surveillance) [75].
3 Reproduced with permission from WHO surveillance bulletins. [http://www.meningvax](http://www.meningvax.org/epidemic-updates.php)
4 [org/epidemic-updates.php](http://www.meningvax.org/epidemic-updates.php) (2016) <http://www.meningvax.org/epidemic-updates.php>,
5 last accessed October 4, 2016.



1 **Figure 4.** Incidence of MD in Chile in children between 9 months and <5 years of
 2 age before and after introduction of quadrivalent *Neisseria meningitidis* (MenACWY)
 3 vaccination in 2012 (unpublished data from Instituto de Salud Pública de Chile,
 4 Laboratorio de Agentes de Meningitis Bacteriana, Santiago, Chile).
 5 MD: meningococcal disease; Men: *Neisseria meningitidis* serogroup.

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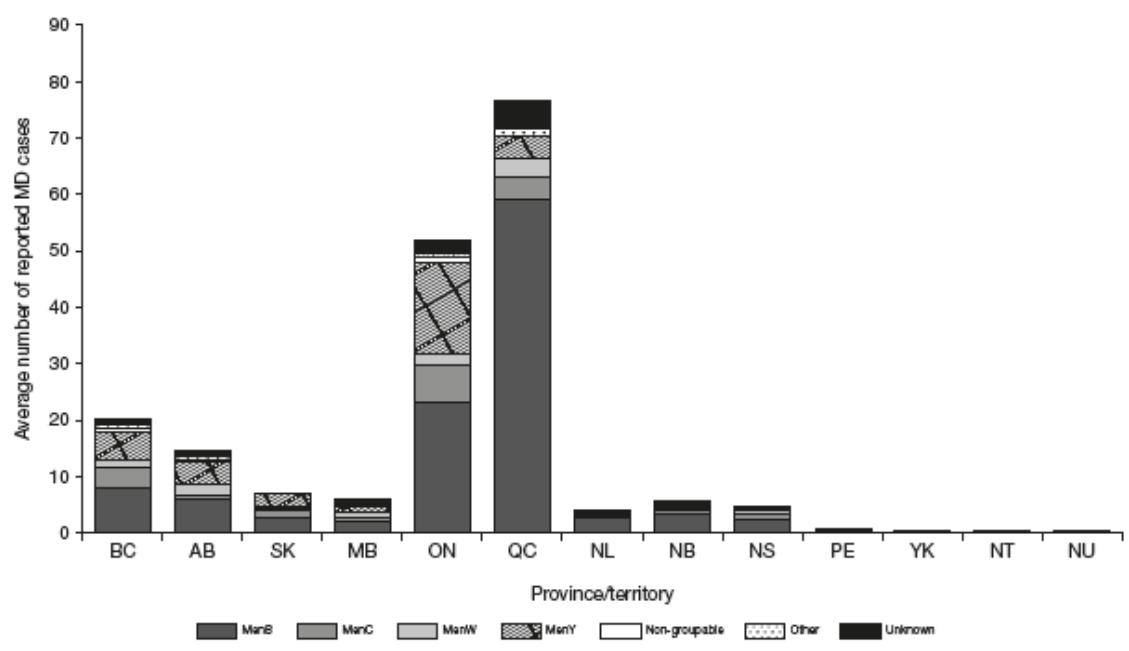
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1 **Figure 5.** Average annual number of invasive MD cases reported in Canadian
 2 provinces, 2007–2011. © All rights reserved. The Recommended Use of the
 3 Multicomponent Meningococcal B (4CMenB) Vaccine in Canada: Common
 4 Guidance Statement. Public Health Agency of Canada, 2014. Reproduced with
 5 permission from the Minister of Health, 2016.

6 http://publications.gc.ca/collections/collection_2014/aspc-phac/HP40-103-2014-
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 9 AB: Alberta; BC: British Columbia; MB: Manitoba; MD: meningococcal disease; NB: New
 10 Brunswick; NL: Newfoundland and Labrador; NS: Nova Scotia; NT: Northwest Territories;
 11 NU: Nunavut; ON: Ontario; PE: Prince Edward Island; QC: Quebec; SK: Saskatchewan; YK:
 12 Yukon.

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