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Meningococcal disease in the Middle East and Africa: Findings and updates from the Global Meningococcal Initiative

Running Title: Meningococcal disease in the Middle East and Africa

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Abstract

Preventing invasive meningococcal disease (MD) through education, research, and cooperation is the mission of the scientists, clinicians, and public health officials comprising the Global Meningococcal Initiative (GMI). The GMI roundtable meeting for the Middle East and Africa, held in Lisbon, Portugal, October 2016, produced two recommendations: vaccination of attendees should be considered for some types of mass-gathering events, as some countries mandate for the Hajj, and vaccination of people with human immunodeficiency virus, because of increased MD risk. Differences exist between Middle Eastern and African countries regarding case and syndrome definitions, surveillance, and epidemiologic data gaps. Sentinel surveillance provides an overview of trends and prevalence of different capsular groups supporting vaccine selection and planning, whereas cost-effectiveness decisions require comprehensive disease burden data, ideally counting every case. Surveillance data showed importance of serogroup B MD in North Africa and serogroup W expansion in Turkey and South Africa. Success of MenAfriVac® in the African “meningitis belt” was reviewed; the GMI believes similar benefits may follow development of a low-cost meningococcal pentavalent vaccine, currently in phase 1 clinical trial, by 2022. The importance of carriage and herd protection for controlling invasive MD and the importance of advocacy and awareness campaigns were also highlighted.

Keywords

Meningococcal disease; Global Meningococcal Initiative (GMI); Vaccination; Middle East; North Africa; Sub-Saharan Africa

Highlights

- Vaccination for some types of planned mass gatherings should be considered
- GMI recommends vaccinating HIV-positive individuals against meningococcal disease
- Improved surveillance and vaccination efforts are needed to address serogroup W outbreaks
- Targeting carriage is vital to controlling invasive meningococcal disease
- Vaccine advocacy and disease awareness campaigns are still critical

Introduction

Neisseria meningitidis is a leading causative agent of bacterial meningitis and septicemia, particularly in children <5 years old and young adults,[1] and is estimated to cause 500,000 cases and 50,000 deaths globally each year.[2] Of 12 recognized serogroups, six (A, B, C, W, X, and Y) are responsible for nearly all meningococcal disease (MD) globally.[3] It has been reported that MD causes substantial morbidity, with case-fatality ratios ranging between ~10–20%.[4–6] Most regions of Europe and North America have low MD incidence rates (e.g. ~0.14 per 100,000 US population, 2014), associated predominantly with serogroups B (MenB), C (MenC), and Y (MenY).[7,8] In contrast, the "meningitis belt" of sub-Saharan Africa has historically reported frequent epidemics of MD, but the incidence had fallen 10-fold by 2013, following the introduction of the serogroup A (MenA) vaccine in 2010; cases of MenC, W, and X are also reported in this region.[8,9] The World Health Organization (WHO) has reported 26,029 meningitis cases in the African meningitis belt in 2016 with 2080 deaths – an overall case-fatality ratio of 8.0%.[10] Only half of the laboratory-confirmed cases were caused by meningococci, while for the great majority of the samples the causative organism was not identified.

The Global Meningococcal Initiative (GMI) was established in 2009 with a goal to prevent the occurrence of MD worldwide through education, research, cooperation, and vaccination. The GMI consists of more than 70 scientists, clinicians, and public health officials globally with expertise in MD immunology, epidemiology, microbiology, public health, and vaccinology. Six global and regional GMI roundtable meetings have been held since its inception, leading to research and publications, including global and regional recommendations for MD. The objective of this regional meeting was to gain a better understanding of MD in the Middle East, North Africa, and sub-Saharan Africa. This article summarizes the discussions that took place at the meeting and outlines regional recommendations for the control and prevention of MD, based on available data and regional expert opinion.

Overview

The current regional roundtable meeting, the first to be convened for the Middle East, North Africa, and sub-Saharan Africa, was held in Lisbon, Portugal, on October 17–18, 2016. The aim of the meeting was to gain an understanding on the current MD situation in this region and to provide recommendations specific to the region. Members from countries outside the region were also invited to share their experience and specific knowledge gained from their surveillance, immunization, and outbreak programs. Regional experts did not attend from every Middle East, North Africa, and sub-Saharan Africa nation; therefore, the current article focuses on the locations represented at the Lisbon GMI Roundtable Meeting.

Objectives

The specific objectives of the meeting were to provide an update on surveillance, epidemiology, prevention, and control strategies from the Middle East, North Africa, and sub-Saharan Africa and an update from other regions and countries across the globe; discuss the issues faced regarding surveillance, prevention, and control strategies with a focus on current barriers to implementation; share lessons learned and experience gained from immunization programs used across the globe; highlight the importance of conjugate vaccines and their impact; examine the health economic aspects of meningococcal vaccination strategies; emphasize the critical need for disease awareness and advocacy for invasive MD prevention and control; and determine future GMI outputs.

Meningococcal vaccines

Meningococcal plain polysaccharide and conjugate vaccines

The first session of the meeting focused on meningococcal vaccines (those currently available and those that will become available). The relative effectiveness of polysaccharide and conjugate vaccines, and the advantages observed with conjugate vaccines were outlined. Both polysaccharide and conjugate vaccines have been shown to be effective, but in children <2 years old,

polysaccharide vaccines have poor effectiveness, while conjugate vaccines are more immunogenic, effective, and do not induce hyporesponsiveness (Table 1).[11]

It has been estimated that since its 1999 introduction to the United Kingdom, MenC conjugate vaccination has prevented >16,000 cases and >1600 deaths. The importance of indirect or "herd" protection was highlighted, using the example of MenC control in the United Kingdom (i.e. a 67% reduction in the MenC attack rate was observed in unvaccinated individuals in 2001) (Fig. 1).

In the United Kingdom, vaccination (usually multivalent) was recommended for: infant to adolescent routine vaccination, catch-up for individuals with underlying medical conditions (such as splenic dysfunction or complement disorders), first-year university students, some occupational groups (laboratory workers, military, etc), travelers to endemic destinations (Hajj pilgrimage, sub-Saharan Africa, etc), and for close contacts of a case or outbreak control. Conjugate vaccines have been preferred over polysaccharide vaccines.[12] An ACWYX conjugate vaccine is being developed by the Serum Institute of India/Program for Appropriate Technology in Health (PATH). If licensed, this will be the first vaccine to address serogroup X (MenX), making it of great interest. A further high-valency vaccine being developed is an ACWY conjugate combined with the MenB subcapsular vaccine (Bexsero®, GlaxoSmithKline, Brentford, UK). MenB vaccines were further discussed, outlining the details of the two available subcapsular vaccines, Bexsero® and Trumenba® (Pfizer, New York, NY, USA). Data from the first 10 months of the United Kingdom's implementation of Bexsero® were presented; Bexsero® was shown to have high vaccine effectiveness (83%) and no safety concerns were observed.[13] The new-generation MenB vaccines have the potential to replace outer membrane vesicle vaccines in epidemic settings.

The question of vaccinating travelers to mass-gathering events, such as the Hajj pilgrimage mentioned above, requires careful consideration. The conditions under which vaccination for mass gatherings should be recommended require further study. Factors to consider include examining the

number of attendees that defines “mass” and what risks are consequent to “gathering” (e.g. geographic spread and diversity, location of the gathering itself, duration of the gathering, homogeneity and/or diversity of the group gathered, and propensity for behavioral risk factors). To develop meaningful recommendations, research is needed to categorize gatherings by risk factors to identify those with greatest potential for life-threatening outbreak conditions and analyze the practicalities and costs for vaccination in advance of those attending such gatherings.

Surveillance/epidemiology/prevention and control strategies

N. meningitidis is usually reported to be a leading cause of bacterial meningitis in the Middle East and North Africa region[14]; however, most surveillance focuses on the Hajj pilgrimage and few other data are available. Characteristics of MD and its surveillance in specific countries of the Middle East, North Africa, and sub-Saharan Africa were discussed.

Tunisia

In Tunisia, reporting of MD is mandatory; however, there is no national surveillance network currently operating. National data generally underestimate the actual burden. Conventional and molecular biology–based diagnosis and typing methods are available in only one hospital. Overall, 85% of cases are in children <5 years old and 38% in infants <1 year old. MenB is by far the most prevalent serogroup (80%), and case fatality ratios are around 18%. Only polysaccharide vaccine (ACWY) is available in Tunisia and is recommended for pilgrims and children with high-risk medical conditions.

Morocco

In Morocco, MD is endemic with sporadic emergence of micro-outbreaks. The incidence rate is ~2–3.6 per 100, and the case fatality ratio is 7–13%. In Casablanca, in a study using whole genome sequencing (WGS), MenB was identified in 95% of cases (2011–2015; 2% MenC, 2% MenY, 1%

MenW). Prevalence was highest in those aged 1–4 years. A single isolate of MenW was related to the Hajj strain.[15] Surveillance of invasive MD is currently underway, involving Moroccan partners with the Meningococcal Unit of the Pasteur Institute in Paris, France.

Algeria

MD is a notifiable disease in Algeria; microbiological data are collected via a network of laboratories coordinated by the Algerian Pasteur Institute. Disease is most frequent in infants <2 years old and the overall incidence reported in 2012 was 0.09 per 100,000 individuals (0.48 per 100,000 in children <5 years old).[16] In recent years, both MenB and MenW have been identified, but MenY seems to be very rare. Vaccination is not included in the national immunization program, but quadrivalent polysaccharide vaccine is recommended for pilgrims and during epidemics. The need for improved diagnosis in laboratories through the introduction of polymerase chain reaction (PCR) and blood culture, as well as improved collection and preservation of isolates was discussed.

African meningitis belt

The African meningitis belt includes parts of 26 countries; within this zone, the burden of disease is usually high, with 7,000–180,000 cases annually. There is a clear seasonal pattern and most disease occurs in the first 6 months of the year in the dry season with airborne dust and high temperatures being risk factors. Currently, two surveillance systems are operating in this region. There is an enhanced nationwide system in all these countries for the detection of outbreaks, reporting of suspected cases, and routine data aggregation and management. A case-based system located at sentinel sites monitors vaccine impact, conducts laboratory investigations, links epidemiologic and laboratory data for cases and analyses, and manages case-level data.

The case definitions employed include sudden onset of fever with meningeal signs (i.e. severe headache, neck stiffness, altered consciousness), thus overlooking cases of meningeal sepsis

without meningeal signs. It may be difficult to update these case definitions rapidly due to the lack of blood culture capability. Polysaccharide vaccine is used for the reactive programs, such as for the 2016 MenC outbreak in Niger, although vaccine shortages have been an issue. The use of conjugate vaccines seems to be typically problematic as it requires a cold chain, with MenAfriVac® being a notable exception.[17]

Rapid diagnostic tests have been employed in this region, such as Pastorex™ Meningitis (Bio-Rad, Hercules, CA, USA) for latex agglutination, as well as dipsticks; however, verification by PCR or culture is recommended before a vaccine response is triggered. Improved dipsticks are needed, in particular for detection of MenX.

Prior to MenAfriVac® vaccination (2009–2010), MenA was the predominant strain in Burkina Faso, Chad, Niger, and Nigeria.[9] Since 2011–2012, the main pathogens detected have been MenW and *Streptococcus pneumoniae* in areas where MenAfriVac® was employed; there have also been non-MenA epidemics, including MenX, MenW, and MenC.[9] The MenAfriNet program started in 2014 and is designed to obtain high-quality data and strengthen regional capacity through the use of standardized tools and databases, training, and laboratory capacity. To date, MenAfriNet surveillance operates in Burkina Faso, Chad, Mali, Niger and Togo, with the possibility to expand to other countries in the region. However, there is a need for greater national preparedness and an international emergency vaccine stockpile to ensure availability, because market availability of polysaccharide vaccine is decreasing and ACWY conjugate vaccines are currently unaffordable.

Turkey

Three childhood invasive infection surveillance studies are currently underway in Turkey. A nationwide bacterial meningitis study using multiplex PCR was started in 2005, a *S. pneumoniae* study was started in 2008, and a study of *N. meningitidis* bacterial isolates was started in 2013.[18,19] MD in Turkey largely affects those ≤18 years old, with estimated incidences (in 2005–2006) of

bacterial meningitis at 3.5 per 100,000 (56.5% *N. meningitidis*), meningococcal meningitis at 2.0 per 100,000, and MD at 3.5–4 per 100,000.[19] From 1985–2006, the reported incidence ranged from 1.01–5.5 cases per 100,000, indicating an intermediate level of endemic disease.[20,21] In 2005–2006, MenW (42.7% of all bacterial meningitis) and MenB (31.1%) were the most prevalent capsular group in children,[19] while in 2009–2010, the prevalence of MenA had increased (36.6%; MenW: 56.1%; MenB: 7.3%). By 2011–2012, MenW was by far the most prevalent capsular group (56.5% vs. 6.5% for MenB and 6.5% for MenA).[18] Prevalence of MenB increased in 2013–2014 (32.9% vs. 42.4% for MenW), but decreased in 2015 relative to MenW (15.8% vs. 42.1%, respectively).[22] Other data showed that relative overall prevalence of different capsular groups of MD in Turkey has been similar to that in Saudi Arabia over recent years, with MenA and MenW the most common capsular groups detected. Antibodies to the four main capsular groups have been detected in the Turkish population.[23] In a recent, multi-center study of 1518 healthy adolescents and young adults aged 10–24 years, PCR serogroup analysis indicated that the nasopharyngeal carriage rate was 6.3% and the most prevalent serogroup was W, with no serogroup C found.[24] The conjugated quadrivalent (MenACWY) vaccine is marketed in Turkey, but thus far is not included in the national immunization plan. This vaccine is recommended for those <50 years old who are travelling to the Hajj or to Umrah.[25] No recommendations for vaccination against MenB are currently available in Turkey.

South Africa

In South Africa, MD is a notifiable condition; the local health authority must be contacted by telephone if invasive MD is suspected and prophylaxis is recommended for contacts.[26] MD is endemic, peaking between May and October.[27,28] The incidence rate was 0.44 per 100,000 in 2013 and 0.36 per 100,000 in 2014. The main capsular group-causing disease is MenW (67–77% of disease is MenACWY), followed by MenB.[29] The burden of disease is highest in infants <1 year old, but the case fatality ratio is highest in adults and increases with age; in addition, human immunodeficiency virus (HIV) infection is a risk factor for contracting MD.[30] Meningococcal polysaccharide vaccines are available and the conjugate ACWY vaccine, Menactra®, has been

available since 2014.[26] Vaccination is recommended for Hajj pilgrims and travelers to Saudi Arabia, those with hazardous occupations, travelers to hyper-endemic areas, and those with certain medical conditions.[26]

Summary: surveillance/epidemiology/prevention and control

The global Invasive Bacterial Vaccine Preventable Diseases surveillance network (IBVPD)[31] has been coordinated by the WHO since 2008, using active sentinel-site, case-based, syndromic surveillance with laboratory confirmation with a range of technical and standard methodology supports, and funding opportunities. PCR and WGS help in deriving more data on MD.

Carriage and herd protection

Nasopharyngeal carriage of *Neisseria* and herd protection

Carrier studies are needed to support and guide the introduction of meningococcal conjugate vaccines by understanding the transmission of the hyper-virulent strains and to measure the indirect impact of the introduction of such conjugate vaccines in vaccination programs. Plain polysaccharide vaccines have little or no impact on carriage, give only short-term immunity, and do not provide herd protection,[32] whereas protein-conjugate polysaccharide vaccines reduce acquisition of nasopharyngeal carriage and transmission, and provide longer lasting immunity and herd protection.[33–35] Data from a number of studies have shown that conjugate vaccination, as with adolescents in the United Kingdom and also with the MenAfriVac® program, substantially reduces acquisition of carriage.

Conducting carriage studies

At some time in their lives, most people will be carriers of *N. meningitidis*. Carriage is age-dependent, with a point prevalence of 10–35% in young adults in Europe[36]; in sub-Saharan Africa, it

is highest in children.[37] A number of factors affect carriage, such as contact with other carriers, age, sex, respiratory tract infections, tobacco smoke exposure, social behavior, living conditions, etc.

For a study in Burkina Faso, a timeframe before and after vaccination was chosen, with sites selected in different urban and rural settings, households randomly selected, and locations mapped by a global positioning system. Demographic and other data were collected with a specially designed questionnaire and sampling undertaken from pre-specified oropharyngeal sites. Swabs were taken, transported, and evaluated (for serogrouping, antibiotic resistance, genotyping, etc), following specified methods under monitored and quality-controlled conditions. As large numbers of samples and data were generated, well-organized data management processes were required.[34]

Careful interpretation of carriage study data is necessary as the carriage situation in a population will be temporally and geographically dynamic and can change rapidly.

Carriage, herd effects, and modeling

To understand the epidemiology of MD, an understanding of carriage is very important. Modeling can be used to explore the complex process of *N. meningitidis* transmission. It is assumed that the effects of vaccines are mediated through inhibiting individual colonization (infection), as well as MD itself. Transmission-dynamic models, allowing for dynamic carriage epidemiology, can be used to improve our understanding of the epidemiology of an infection, to make predictions about the future incidence of an infection under particular conditions, and to identify knowledge gaps where more epidemiologic data are required. Modeling was used to demonstrate the important effects of MenC vaccination – in particular, the impact of the large United Kingdom catch-up campaign on herd protection and carriage[33] – to examine carriage prevalence by age in Europe, and to explore how long herd protection might last. For rational decision-making, models are best used in combination with real-world data from disease surveillance, carriage studies, and seroepidemiology.

Modeling has been used to explore the direct effects of MenAfriVac® in Africa, such as vaccine effectiveness against MenA, and indirect effects, such as the effect of vaccination on disease risk in the unvaccinated population. Modeling requires good quality surveillance data, as was collected in Chad in 2011–2012, for example. An age-structured transmission model was used that captured all the key epidemiologic features of MenA in the African meningitis belt and a number of different vaccine strategies were modeled.[38] Modeling showed that follow-up vaccine strategies were needed to maintain protection and helped to inform current WHO MenA vaccine recommendations for sub-Saharan Africa.

Roundtable discussion: global control of MenW disease

Men W global epidemiology

From around 2000 onward, MenW started to appear at significant levels in Europe[39,40] and South Africa,[28] and eventually globally. Historically, MenW has been present (e.g. in the 1960s), with outbreaks of various clones in sub-Saharan Africa in the 1980s and 1990s. Molecular techniques, such as WGS, have now enabled precise characterization of isolates and construction of genetic lineages of the emerging MenW strains. The Hajj (or Anglo-French-Hajj) clone and other recent outbreaks of MenW had been identified by techniques such as multilocus sequence typing (MLST) as an expansion of MenW ST-11. However, it was not clear if all the outbreaks were due to the re-emergence of the same strain. WGS enabled building a high-resolution phylogenetic tree for MenW ST-11. These data suggested that an original UK strain in 2008 corresponded to a new lineage within the MenW ST-11 that was distinct from the Anglo-French-Hajj clone. Cases due to this original clone levelled off after 4 or 5 years, followed by the emergence of a new lineage in the United Kingdom in 2013, and reductions in case fatality ratios after another 3 years. In other countries, both the 2008 and 2013 strains were found; it appears that the 2013 strain is expanding rapidly (relative to the United Kingdom) in other countries.[41] The reasons for this rapid expansion are unclear and further investigation is required. In addition, a number of groups in the United Kingdom and France

have recently noted that MenW ST-11 is associated with some unusual symptoms, such as septic arthritis.[39,42] In Europe and the United Kingdom, MenW has also been found to present atypical symptoms such as diarrhea and vomiting without classic signs of meningitis or hemorrhagic rash.[43] There is a need for surveillance that combines exhaustive reporting and microbiological typing. As previous genotyping studies were unable to discriminate sporadic and epidemic MenW isolates reliably, WGS should and can be the standard typing scheme for MenW isolates given that techniques such as MLST do not provide sufficient resolution.

Best strategies to control serogroup W disease

Following the Hajj outbreak in 2000, MenW persisted in Saudi Arabia[44] and a quadrivalent polysaccharide vaccine was introduced and deployed in children <5 years old in the early 2000s (two doses for those <2 years old and one dose for those ≥2 years old); however, only the older children had a serum bactericidal antibody response.[45] Three quadrivalent ACWY conjugate vaccines are now available. In Chile, MenW cases increased rapidly and a conjugate quadrivalent vaccine was introduced in 2012 for children <4 years old, with two doses for those <2 years old and one dose for those 2–4 years old. The estimated coverage for one dose was 84% but only 69% completed the full two-dose regimen. In 2014, the schedule was changed to a single dose at 1 year old and the program has reduced mortality; however, the percentage of MenW is continuing to increase in the unvaccinated population.[46] A carriage study in Chile found a low carriage rate overall (0.2%); however, ST-11 is known to have a low carriage rate but to cause severe disease.[33,47] UK data for MenC show the importance of reducing carriage on the overall disease burden. In the United Kingdom, MenW affects all age groups, including older patients, thus differing from MenC in the 1990s, which largely affected teenagers and young adults. The increase of MenW was considered a public health emergency and a strategy of vaccinating adolescents (aged 14–18 years) with quadrivalent conjugate vaccine was adopted in 2015.[48] To date, direct protection has been reported and it is hoped that herd protection will follow. Thus, programs targeting young children give direct protection, but are time-limited as antibody persistence is poor; however, programs targeting

adolescents and carriers can induce herd protection and antibody persistence is good. MenW cases in the elderly remain a concern and it is not yet known whether they will be covered by herd protection through immunizing adolescents.

Roundtable discussion: cost-effectiveness assessment in decision-making about vaccines

Cost-effectiveness analyses have become increasingly important in decision-making.[49–51] For example, in the United Kingdom, new vaccines cannot be recommended for introduction by the Joint Committee on Vaccination and Immunization (JCVI) unless they are deemed cost-effective. A cost-effectiveness analysis compares both the costs and health effects of an intervention to an alternative to determine the extent to which the intervention provides "value for money." Cost-effectiveness evaluations for vaccines can be more complex than for other interventions as benefits are accrued over a long time, most recipients are young children, there may be direct and indirect effects (such as transmission and herd protection), and the vaccines available may have different valences. A workshop was held to explore scenarios of cost-effectiveness, in which participants considered the healthcare and societal costs and wider societal benefits of different scenarios. Several factors need to be considered when planning analyses, including the choice of what costs to include (the perspective), how to capture benefits, what comparisons to make, how to capture uncertainty, how to value items in the future (discounting), and the time period (time horizon) to be considered. The benefit measured needs to be selected according to the type of intervention or illness. Inclusion of discounting in analyses has a greater impact on interventions that have lifelong effects, compared with short-term interventions, so cost-effectiveness analyses of vaccination can be particularly affected by the choice of discount rate used. Discounting is highly controversial and countries have their own guidelines on the levels of discounting employed. Participants indicated that cost-

effectiveness analyses are used in France, Norway, South Africa, Switzerland, and Turkey. The JCVI has allowed representatives from other countries to observe cost-effectiveness presentations.

MenAfriVac® immunization program, learnings, and future activities

Where do we go from here?

MenAfriVac® was the outcome of a Meningitis Vaccine Project (MVP; lead by WHO-PATH), involving international cooperation and technology transfers. It was licensed by the Indian National Regulatory Authority in December 2009 and pre-qualified by the WHO in June 2010.[17] It was first introduced in Burkina Faso, Mali, and Niger in Q4 2010 as a 10-dose vial. New dosage presentations were developed for use in the routine infant schedule from 2015, and it remains an affordable vaccine for developing countries. The vaccine gives direct protection and reduces carriage.[34] The WHO MenA strategy induced herd protection through mass vaccination campaigns, targeting 1 to 29 year olds. More recently, MenAfriVac® MenA conjugate vaccine was introduced into the routine immunization schedule (for infants aged 9–18 months), thus protecting birth cohorts. As well as this, surveillance and epidemic response were strengthened.[52] By August 2016, 265 million people had been vaccinated in 19 countries (Benin, Burkina Faso, Cameroon, Chad, Democratic Republic of Congo, Ethiopia, Gambia, Ghana, Guinea, Guinea Bissau, Ivory Coast, Mali, Mauritania, Niger, Nigeria, Senegal, South Sudan, Sudan, and Togo); around 30 million are still to be vaccinated in the remaining seven countries (Burundi, Central African Republic, Eritrea, Kenya, Rwanda, South Sudan [second phase], and Tanzania). In 12 countries, vaccination programs were prioritized and introduced following risk assessment using a standard tool based on risk indicators, mapping information, and local expert opinion.

This was the first vaccine to be deployed locally using a controlled temperature chain (CTC) rather than needing a cold chain[53] and, in 2016, >2.5 million people were vaccinated using the CTC method. Wastage was low, high coverage was achieved, there were no serious adverse events after vaccination, and the CTC protocol was well understood and accepted. Carriage of MenA was substantially reduced in areas where vaccination had been introduced (by 98% in Chad).[35] In addition, MenAfriVac® uses tetanus toxin as a carrier, and some serologic data have suggested protection against tetanus.[54]

In 2010–2012, MenW disease reemerged in Burkina Faso.[55] MenC emerged in northern Nigeria in 2013 and western Niger in 2015, resulting in the largest post-MenAfriVac® outbreak and the largest MenC outbreak on record, and it has now spread into neighboring countries. The outbreak was large, rapid, and attack rates were high; it was found to be caused by a previously unrecorded MenC clone. It appeared to have emerged in Nigeria before the MenAfriVac® campaign and was not likely to be associated with the elimination of MenA epidemics following the vaccine's introduction.[56] All the MenC strains isolated were ST10217, they belong to an unassigned clonal complex, and all have the same molecular profile.[56,57] They are genetically unrelated to the epidemic clones causing disease in Africa in the past decades, or to the rare MenC isolates that have circulated since the 1980s.[58]

A further outbreak of MenW occurred in Togo in 2016 and also in northern Ghana. In the past 16 years, there have been a number of non-MenA outbreaks in the region and MenA is still circulating at a low level, although the vaccine failure rate is very low.

The success of MenAfriVac® to date needs to be sustained, with rollout into other countries, continuing introduction into routine programs, and ongoing surveillance to monitor long-term impact, effectiveness, failure, and non-MenA serogroups. There are a number of challenges to overcome for MenAfriVac®, such as bridging the gap between campaign and routine vaccinations, with a need for

further catch-up vaccinations. Finally, there needs to be clear communication about the new dose sizes available, and vaccine supply must be maintained and programs financially enabled.

A new initiative was started by the United Kingdom Department for International Development in 2008 in partnership with PATH and the Serum Institute of India to develop an affordable thermostable pentavalent ACWYX vaccine.[59] Clinical development will be mainly in Africa (with some trials in India and in the USA), with immunoassays undertaken by Public Health England and initial licensing planned for export from India. The vaccine is currently in phase 1 clinical trial, and it is hoped that it will be available for use in 2020–2022.

Meningococcal vaccination and HIV

A number of recent studies have shown that the risk of MD is higher in individuals with HIV.[60–64] In the past, some studies have looked at all types of meningitis rather than purely MD, and findings have been unclear; some of the older studies were also conducted before the introduction of highly active antiretroviral HIV therapy. However, results of surveillance data analysis from 2003–2007 in patients of all ages conducted in South Africa showed that HIV was associated with a higher incidence of MD and higher case fatality ratios.[30] Other recent studies, including two from the United States from the 2000s, have found a 13-fold and 10-fold greater risk of MD for those with HIV,[65] although the findings on case fatality ratios were less clear. Importantly, patients in these recent studies were receiving antiretroviral therapy and a good standard of healthcare.

The responses to vaccination in people with HIV have been shown in immunogenicity studies; however, two doses of vaccine are required.[66,67] Some countries now have recommendations for vaccination with the MenACWY conjugate vaccine, for example, in the United States, where the Advisory Committee on Immunization Practices has proposed that children ≥2 years old with HIV who have not been previously vaccinated should receive a two-dose primary series of MenACWY (at ages 0–2 months), and a multi-dose schedule for children <2 years old.[68] Individuals with HIV who

have been previously vaccinated with one dose of MenACWY should receive a second dose at the earliest opportunity, and continue to receive boosters at the appropriate interval.[60] Current booster recommendations are 3 years if <7 years at previous dose and at 5 years if ≥7 years at previous dose.

An important issue with such recommendations, however, is the cost of the conjugate vaccine, particularly in low-/middle-income countries with high rates of HIV. There also have been recent outbreaks involving two ST-11 strains of MenC in several countries among men who have sex with men (regardless of HIV status), and this group may need to be included in immunization recommendations.[69]

Advocating for vaccines

Advocating for vaccines needs to be contextually sensitive, and therefore can have different objectives by region and country. Defining clear objectives from the outset is vital as subsequent actions undertaken may be radically different dependent on the setting. For example, the MVP used a combination of country visits, workshops, a website, the mass media, and vaccination champions to achieve its mass vaccination goals at international, national, and sub-national levels, whereas the Confederation of Meningitis Organizations (CoMO), which exists to help patient groups meet their goals, supported a campaign in Spain to make the MenB vaccine available through pharmacies by advising on use of a targeted letter to the appropriate health authority (eg, Minister of Health, Surgeon General, etc) in that country. CoMO also holds conferences and provides a website to help share advocacy tools (http://www.comomeningitis.org/). The Advocacy for Immunization website developed by the PATH campaign with Johns Hopkins University also provides a set of useful tools and guides to advocacy.[70] The MenB campaign of the Meningitis Research Foundation (MRF) in the United Kingdom had two objectives: to get the vaccine introduced into the national immunization program and to make the decision-making framework fair. Before the vaccine was available, a

multifaceted campaign to support meningitis vaccination began, including petitions, cost evaluations, evidence to support more favorable parameters for cost effectiveness evaluation, letters to the appropriate health authority (eg, Minister of Health) from clinicians, scientists, and professional medical bodies (e.g. the Royal Colleges), events for members of parliament, use of social media, etc. Following recommendation by the United Kingdom's JCVI, advocacy continued until the vaccine was introduced for infants <1 year old. An online petition to the United Kingdom government with >800,000 signatures was made to expand the age range for MenB vaccination, which led the MRF to act with press releases, develop a 10-point action plan for the government (with Meningitis Now, UK),[71] and take various other measures. The petition and campaign resulted in a parliamentary select committee hearing, a debate in the United Kingdom parliament, a ministerial commitment to fund a national study of the MenB vaccine's impact on carriage in teenagers, and a ministerial commitment to publish findings of the cost-effectiveness working group. This work is ongoing, especially to make sure that the decision-making framework is fair.

A number of approaches can be successful in this regard, as shown in Fig. 2. There are challenges to successful advocacy campaigns, including vested interests affecting decision-making frameworks, political will, actual resource (human and financial), the need for collaborative working, and the need to work with the media to simplify complex issues.

Updates to the GMI recommendations

Two proposals for updates to the GMI recommendations were considered during the meeting:

- A recommendation that local public health authorities should assess the value of issuing an advisory for those attending a planned mass-gathering event to be vaccinated. This proposal follows the model adopted in several countries with respect to the Haj pilgrimage and the experience of outbreaks related to the World Scout Jamboree in Japan in 2015 and a case of MD at the World Youth Day Catholic Gathering in Poland in 2016, as well as recent outbreaks among

men who have sex with men. However, further work is needed to characterize the aspects of mass gatherings that may pose significant risks for transmission of MD.

- A recommendation for the vaccination of individuals who are HIV positive. This proposal is based on studies showing an increased risk of MD in those with HIV and the incorporation of such recommendations into a number of national vaccination guidelines.

Summary and conclusion

Conjugate vaccines are, in most respects, superior to plain polysaccharide vaccines, which do not provide long-term direct protection in infants, toddlers, or younger children. Indirect (herd) protection has been instrumental for MenC disease control in the United Kingdom, and adolescent vaccination programs have been introduced with the aim of providing direct protection to those vaccinated and indirect protection to other age groups. Further consideration is required regarding revaccination recommendations for conjugate vaccines and recommendations for mass-gathering events. It is difficult to define clear criteria for this recommendation, but aspects to consider include the age of attendees (adolescents and young adults being more likely to carry meningococcus) and the type of mass gathering (e.g. camping or living in communal quarters). Further work is needed to characterize those types of mass gatherings that may pose significant risk for transmission of MD. Pentavalent meningococcal vaccines are under development, including an ACWYX conjugate and an ACWY conjugate combined with Bexsero®. The new-generation MenB vaccines have the potential to replace outer membrane vesicle vaccines in epidemics. The IBVPD offers a range of technical and standard methodology support, quality assurance and quality control, partnering, data management, and funding opportunities, and in the future will focus on disease burden and vaccine impact, as well as surveillance for other vaccine-preventable pathogens and antimicrobial resistance. Presentations on invasive MD in Algeria, Morocco, Tunisia, and Turkey illustrated the differences of surveillance, epidemiology, case definitions, and control (i.e. vaccination and chemoprophylaxis) in North Africa and the Middle East. It has been shown that although the

MenAfriVac® campaign has been a success, there have been recent outbreaks of non-MenA serogroups. Carriage studies are needed to support and guide the introduction of meningococcal vaccines, and it was shown how study design was the most critical point in these studies. New GMI recommendations on vaccination of patients with HIV and of those attending certain types of mass-gathering events were proposed. The role of vaccine advocacy was also highlighted in the effective prevention of MD.

Author contribution

All authors have contributed original content, reviewed and revised the manuscript, and approved the final version.

Conflict of interest

The authors are the members of the Global Meningococcal Initiative (GMI) which is sponsored by Sanofi Pasteur. The GMI is not influenced in any way by Sanofi Pasteur. GMI members hold the full right to determine meeting agenda items and lead the discussions and outputs. Sanofi Pasteur representatives have attended the meetings, but as observers only, and they do not influence the findings of the group. RB and JF perform contract research on behalf of Public Health England for GlaxoSmithKline, Pfizer, and Sanofi Pasteur. DAC has performed in the past contract research on behalf of the Norwegian Institute of Public Health for Novartis, Pfizer, and Sanofi Pasteur. HC reports receiving an honorarium from Sanofi Pasteur in 2015 and 2016, and consultancy fees from AstraZeneca and IMS Health, all paid to her employer. JVM has received honoraria from GlaxoSmithKline, Pfizer, and Sanofi Pasteur. MC, ECD, LG, AVG, AK, AR, VS, M-KT, HT-M, and KZ report no conflicts of interest.

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Tables

Table 1 Comparison of plain polysaccharide and conjugate vaccines.

Immunogenicity	Polysaccharide vaccines	Conjugate vaccines
Adults	High	High
Young children	Poor	High
Avidity	Low	High
Persistence	Low/Medium	High
Functional activity	Low	High
Response to a booster	Poor	High
Induction of hyporesponsiveness	Yes	No
Induction of immunological memory	No	Yes
Prevention of acquisition of carriage	No	Yes

Figures

Figure 1 Direct and herd protection against MenC in the United Kingdom.

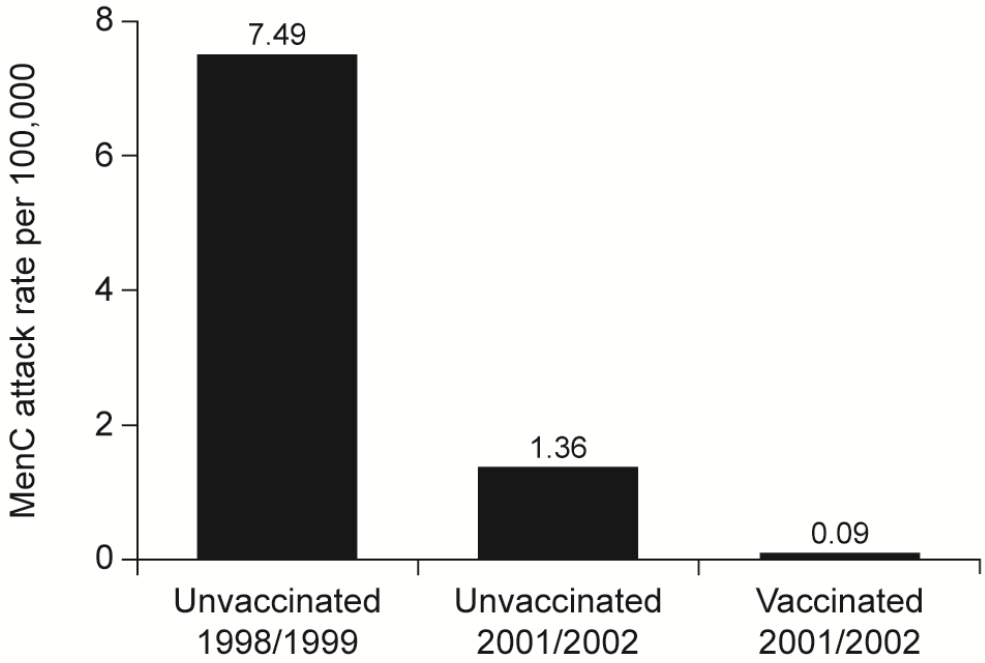

Figure 2 Possible approaches for vaccine advocacy.