Meningococcal disease in the Asia-Pacific region: Findings and recommendations from the Global Meningococcal Initiative.

Ray Borrow, Jin-Soo Lee, Julio Vazquez, Godwin Enwere, Muhamed-Kheir Taha, Hajime Kamiya, Hwang Min Kim, Dae Sun Jo

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Review

Meningococcal disease in the Asia-Pacific region: Findings and recommendations from the Global Meningococcal Initiative

Ray Borrow [a,*], Jin-Soo Lee [b], Julio A. Vázquez [c], Godwin Enwere [d], Muhamed-Kheir Taha [e], Hajime Kamiya [f], Hwang Min Kim [g], Dae Sun Jo [h], on behalf of the Global Meningococcal Initiative

[a] Vaccine Evaluation Unit, Public Health England, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WZ, UK
[b] Inha University Hospital, Incheon, Republic of Korea
[c] Institute of Health Carlos III, Madrid, Spain
[d] PATH Europe, Ferney Voltaire, France
[e] Institut Pasteur, Paris, France
[f] National Institute of Infectious Diseases, Infectious Disease Surveillance Center, Tokyo, Japan
[g] Yonsei University, Wonju Severance Christian Hospital, Wonju, Republic of Korea
[h] Chonbuk National University Hospital, Jeonju, Republic of Korea

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ABSTRACT

The Global Meningococcal Initiative (GMI) is a global expert group that includes scientists, clinicians, and public health officials with a wide range of specialties. The purpose of the Initiative is to promote the global prevention of meningococcal disease (MD) through education, research, and cooperation. The first Asia-Pacific regional meeting was held in November 2014. The GMI reviewed the epidemiology of MD, surveillance, and prevention strategies, and outbreak control practices from participating countries in the Asia-Pacific region. Although, in general, MD is underreported in this region, serogroup A disease is most prominent in low-income countries such as India and the Philippines, while Taiwan, Japan, and Korea reported disease from serogroups C, W, and Y. China has a mixed epidemiology of serogroups A, B, C, and W.

Perspectives from countries outside of the region were also provided to provide insight into lessons learnt. Based on the available data and meeting discussions, a number of challenges and data gaps were identified and, as a consequence, several recommendations were formulated: strengthen surveillance; improve diagnosis, typing and case reporting; standardize case definitions; develop guidelines for outbreak management; and promote awareness of MD among healthcare professionals, public health officials, and the general public.

Contents

Abbreviations: CBHI, Central Bureau of Health Intelligence; CDC, [US] Centers for Disease Control and Prevention; CI, confidence interval; CSF, cerebrospinal fluid; DNA, deoxyribonucleic acid; GMI, Global Meningococcal Initiative; HCP, healthcare practitioner; HIRA, Health Insurance Review and Assessment Service; KCDC, , Korea Centers for Disease Control and Prevention; MCC, meningococcal C conjugate; MCV4, tetravalent meningococcal conjugate vaccine; MD, meningococcal disease; Men C/Men W, meningococcal group C/meningococcal group W; MPSV4, tetravalent meningococcal polysaccharide vaccine; NCR, National Capital Region; NESID, National Epidemiological Surveillance of Infectious Diseases; NIID, National Institute of Infectious Diseases; OMV, outer membrane vaccine; PCR, polymerase chain reaction; PIDSR, Philippine Integrated Disease Surveillance and Response; WHO, World Health Organization.

* Corresponding author.
E-mail addresses: Ray.Borrow@phe.gov.uk (R. Borrow), ljinsoo@medimail.co.kr (J.-S. Lee), jvazquez@isciii.es (J.A. Vázquez), genwere4@yahoo.co.uk (G. Enwere), muhamed-kheir.taha@pasteur.fr (M.-K. Taha), hakamiya@nih.go.jp (H. Kamiya), khm9120@yonsei.ac.kr (H.M. Kim), drjo@chonbuk.ac.kr (D.S. Jo).

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1. Introduction

Neisseria meningitidis is a leading cause of meningitis and septicemia and is estimated to cause more than 1.2 million cases of invasive meningococcal disease (MD) and 135,000 deaths each year across the globe [1,2]. MD is associated with substantial morbidity and high fatality rates (~10–20%, although higher rates of ~30% have been reported for serogroup W alone) [3,4]. However, in many countries in the Asia-Pacific region, the true burden of disease is unknown because the epidemiology of MD is not well described [5]. Indeed, in countries such as the Republic of Korea and Japan, which have frequently reported a low incidence of MD, the disease is not considered a high healthcare priority.

The Global Meningococcal Initiative (GMI) was established in 2009 to promote the global prevention of MD through education, research and cooperation. It comprises some 50 scientists and clinicians from around the world with expertise in meningococcal immunology, epidemiology, public health, and vaccinology. A regional meeting of the GMI was convened with the goal of gaining a better understanding of MD in the Asia-Pacific region. This article summarizes the discussions that took place at the meeting and outlines the regional recommendations for the control and prevention of MD based on the available data and regional expert opinion.

2. Meeting

2.1. Overview

The meeting, the first to be convened in the Asia-Pacific region, was held in Incheon, Republic of Korea, on 20–21 November 2014. The aim of the meeting was to provide an update on the epidemiology of MD in this region, with a particular emphasis on the recent outbreaks that have been reported in a number of Asia-Pacific countries and the control strategies that have been implemented.

Members from countries outside the region were also invited to share their experiences and the lessons learned from their vaccination and outbreak programs (e.g., reactive quadrivalent [serogroups A, C, W and Y] meningococcal conjugate vaccination in Chile, control of meningococcal group W [Men W] outbreaks in Latin America, Men B outbreaks in the United States, and Men A outbreaks in sub-Saharan Africa).

Representatives were not available from all Asia-Pacific countries and therefore this article focuses on those present at the GMI meeting.

2.2. Objectives

The specific objectives of the meeting were to: (1) understand the epidemiology of MD in the Asia-Pacific region over the past decade; (2) examine the surveillance and prevention strategies in Asia; (3) discuss key learning points from experience with meningococcal vaccine programs, and how these may be applied elsewhere; (4) develop recommendations to improve diagnosis and surveillance, and for the control and prevention of MD in Asia, including outbreak preparedness; and (5) devise methods for the dissemination of information.

3. Discussion

3.1. Overview of MD across the globe

The epidemiologic profile of MD varies across the globe; however, 6 of the 12 recognized serogroups (A, B, C, W, X, and Y) are known to cause the majority of the disease worldwide [6]. In Europe and North America, where serogroups B and C predominate, the disease is endemic, with a low overall incidence (~1 per 100,000), characterized by seasonal peaks and small clusters of cases [7]. By contrast, in the "meningitis belt" of sub-Saharan Africa, large periodic epidemics of MD occur frequently with an incidence that may reach 1000 per 100,000. Most African epidemics have been caused by meningococci belonging to serogroup A, but outbreaks of serogroup C, W, and X disease have also been recorded [7]. Although epidemiologic data from Asia are limited, it has been suggested that serogroup A and C predominate; but serogroup W is increasingly reported in several countries, such as China [8–10].

3.1.1. Latin America

In Latin America, incidence rates and serogroup distribution are highly variable, with the highest burden of disease reported in Brazil and the Southern Cone countries (Argentina, Chile, and Uruguay) [11]. Serogroups B and C are reported to be responsible for the majority of cases reported in the region, although there has been a recent increase of serogroup W disease in Argentina, Chile, and Southern Brazil [11]. In addition, it has been noted that the carriage data for Men W (cc11) from Chile were similar to the Men C (cc11) carriage data from the UK before the meningococcal serogroup C conjugate (MCC) vaccine introduction took place in

1999 [12]. These data show that adolescents were the main carriers of serogroup W in Chile during the outbreak.

Although progress has been made in improving and coordinating the surveillance of invasive disease in Latin America, there is a clear need to improve and establish more uniform quality surveillance across the region and standardize case definitions [11]. It is anticipated that there will be an increased use of the meningococcal quadrivalent conjugate vaccines in the near future, which will replace polysaccharide vaccines [11]. Three vaccines have been used in Latin America: an outer membrane vaccine (OMV) + C polysaccharide, a MCC vaccine, and quadrivalent conjugate (A + C + Y + W) vaccine. The OMV + C polysaccharide vaccine has been part of the routine immunization calendar in Cuba since 1991; it is administered in 2 doses in children at ages 3 and 5 months. Recent data suggest that the efficacy of the Cuban vaccine varies by age of recipient, and may be effective for prevention of serogroup B MD in older children and adults. The estimated efficacy of the vaccine in children younger than 24 months was −37% (95% confidence interval [CI]: <−100 to 73); 47% (95% CI: −72 to 84) in children 24–47 months and 74% (95% CI: 16–92) in children 48 months or older.

In 2010, in response to an outbreak, the MCC vaccine was introduced to the infant calendar in Brazil for all children aged <2 years. As a consequence, there was an immediate reduction in incidence rates of MD in children aged <2 years and those 2–4 years. However, in other age groups the vaccine did not have an early impact, which likely reflects the lack of a catch-up campaign targeting older age groups. Due to a notable increase in the number of cases and deaths due to serogroup W beginning in 2010, the Chilean health authorities implemented a vaccination campaign with the tetravalent conjugate vaccine. The vaccine is now part of the national infant schedule and involves vaccination of children aged >1 year with a single dose. Although the incidence and mortality rates of MD in Chile have decreased since the vaccination program was implemented in 2014, both remain high. Most recent cases are due to serogroup W and are seen in the urban capital area. The Latin American experience, specifically the carriage data of Men W from Chile, demonstrated that adolescents were the main carrier pools in the Chilean outbreak. However, no vaccine effectiveness data were collected and no evidence of herd protection was observed.

3.1.2. United States

In 2013, 2 universities in the United States responded to outbreaks of Men B disease with mass vaccination campaigns using an unlicensed Men B vaccine. Both outbreaks resulted from the same rare strain of B. Vaccination coverage was high (97% students received a first dose and 91% received a second dose). To date, the vaccine effectiveness has not been established. Safety data were not collected, but it appeared that there was a significant amount of local site reactogenicity.

In New Jersey, although it was not licensed in the United States at the time, Bexsero® (a serogroup B vaccine) was employed to control an outbreak at Princeton University that was caused by a serogroup B ST-409 strain. Vaccine coverage with Bexsero was high: 97% of undergraduate students received a first dose and 91% received a second dose. Despite this high coverage, nasopharyngeal carriage was not eradicated, since a student at another university who came in contact with a vaccinated Princeton student contracted MD. This was to be expected since this recombinant vaccine does not eliminate carriage, but prevents new acquisitions of any meningococci, regardless of serogroup [13]. Safety data were not collected at the time of the outbreak. In 2014, a new serogroup B vaccine was licensed, Trumenba™; it is a bivalent vaccine and is licensed as a 3-dose series at 0, 2, and 6 months for those aged 10–25 years.

3.1.3. Europe

The development and introduction of MCC vaccines in several European countries, Australia and Canada has been associated with a substantial decline in serogroup C disease [7]. A large part of the success of MCC vaccines has been attributed to the ability of the vaccines to reduce carriage and transmission of vaccine-type bacteria in the population, thus indirectly reducing disease even among the unvaccinated [7].

3.1.4. Africa

Outbreaks are typically cyclical in Africa, and are primarily caused by serogroup A. Following international standards, a Men A conjugate vaccine, MenAfriVac® (Serum Institute of India Ltd), has been successfully developed and licensed. In an effort to eliminate meningococcal serogroup A, mass vaccination campaigns with the vaccine began in 2010 and targeted the 26 countries in the "meningitis belt" region of sub-Saharan Africa. By 2014, 153 million people aged 1–29 years had been vaccinated. High coverage rates of >90% were achieved in these countries where the vaccine was introduced. Notably, pregnant women were included in the program, and follow-up studies of women and their babies did not identify any safety concerns [14]. Currently, it is recommended that this finding be added to the package insert of the MenAfriVac® vaccine so that it can be given freely to pregnant women. Research from recent and ongoing studies suggests that immunization should start in late infancy (3–24 months, possibly with polysaccharide A 5-μg dosage). Since the program was implemented, there has been a decrease in the number of meningitis cases attributable to serogroup A. A herd effect protecting infants and those aged >30 years has been observed. Due to the mass vaccination program, serogroup A carriage has decreased, which could, in the long run, affect population immunity due to a lack of natural boosting. In addition, since the introduction of MenAfriVac®, the number of meningitis cases – both overall, and in particular due to serogroup A – has decreased. There has also been a marked change in the bacteriological cause of meningitis following vaccine introduction: a larger proportion of meningitis cases are now due to other serogroups (e.g. W, X, and Y), highlighting the fact that surveillance to detect other serogroups needs to be strengthened. This also brings to attention the unmet need for vaccines to protect against these other serogroups in this region of Africa.

3.2. Overview of MD in the Asia-Pacific region

3.2.1. China

No representative of China attended the GMI meeting, therefore this country was not described in-depth previously. However, as a brief summary, and for completeness, this section has been included.

In China, serogroup A polysaccharide vaccine was first used in the routine immunization program; however, the bivalent (A, C) polysaccharide vaccine was later introduced following a number of serogroup C outbreaks.

Between 1996 and 2002, there were only 292 reported cases of MD in Taiwan, of which 158 were culture confirmed [15]. The majority of these cases were due to serogroup B, but a large proportion was due to serogroup W. In China, shifts in the disease-causing serogroups have been observed. For example, in a study carried out in Shanghai, serogroup A was shown to be the predominant serogroup noted for many decades, but in 2005–2013, serogroups B and C predominated (accounting for 62% of cases) [16]. Furthermore, prior to 2006, in China, all MD cases were caused by serogroups A, B, and C; however other serogroups (e.g. W) have now been reported [9].

The serogroups associated with outbreaks in China have also altered over time: while serogroup A was initially the main causative, serogroup C became of increasing concern following the implementation of Men A vaccination. However, there have also been an increasing number of invasive cases caused by serogroups B and W [9,10,17].

3.2.2. India

N. meningitidis is the third most common cause of bacterial meningitis in India in children aged <5 years, and is responsible for an estimated 1.9% of all cases regardless of age [5]. The majority of reported cases are due to serogroup A, with rare reports of serogroups B and C. Since 2002, the number of reported meningitis cases due to MD in India has decreased markedly, while case fatality rates have also dropped (from 9.8% to 5.2%).

There has, however, been an increase in the number of MD outbreaks reported throughout India, with more outbreaks reported in the temperate northern regions than the tropical southern regions [5]; the majority of cases occur in late winter and early spring. Three significant outbreaks have been reported since 2005: in New Delhi (2005–2009) and, for the first time, in Meghalaya (2008–2009) and Tripura (2009) in north-eastern India [5]. These unexpected outbreaks affected treatment because, as clinicians did not suspect MD, patients were initially treated incorrectly. Also of note, during recent outbreaks a shift in the affected age group was observed and for the first time there was an increase in the proportion of cases in young adults. This observation may suggest the emergence of a new potentially epidemic clone, against which the population is immunologically naïve [18].

The New Delhi outbreak from 2005 to 2009 was due to serogroup A, with the majority (40%) of cases occurring in people aged 15–30 years. The outbreak was concentrated in urban areas and involved both types of clinical presentations, with cases of meningitis (60%) and meningococcemia (40%) observed. Mass vaccination was not recommended since there was a low attack rate, the disease was not focalized, and the quadrivalent vaccine (A, C, W, and Y), which was used only in vaccination of healthcare practitioners (HCPs), is not known to be effective in children aged <2 years. Isolation wards were established and cases of meningitis were managed using third-generation cephalosporins and penicillins. Chemoprophylaxis, using ciprofloxacin, of close contacts and high-risk groups was implemented. The outbreak was managed through mandatory daily reporting of all probable and lab-confirmed cases, augmentation of hospital surveillance for early reporting of cases, strengthening of laboratories and case management facilities, and by "around-the-clock" control rooms, which were set up to provide information to HCPs and the general public.

The Meghalaya outbreak, which occurred in 2008–2009, also involved both clinical presentations (meningitis, 60–70%; meningococcemia, 30–40%). The majority of cases were seen in people aged 15–49 years, with more than 250 lab-confirmed cases of Men A. Unfortunately, the health infrastructure in Meghalaya was not prepared for the outbreak as cases had never before been seen in the state. Outbreak management involved establishing a 7-day control room in Shillong in order to provide information to the public and to HCPs, strengthening of case management facilities in hospitals and lab services at the state level, and meningococcal vaccination of all HCPs. Chemoprophylaxis of close contacts of affected people was implemented and mass chemoprophylaxis in selected areas was undertaken. Similar to the management of cases in the Delhi outbreak, third-generation cephalosporins were used to treat patients; additional penicillin or chloramphenicol was used in some hospitals. A mass vaccination program of the entire populations of the 2 most affected districts was carried out in May–June of 2009 using the bivalent (A + C) meningococcal polysaccharide vaccine, which led to a significant reduction in cases; no cases have been reported since 2010.

Similar to the outbreaks in Delhi and Meghalaya, the Tripura outbreak in 2009 also involved cases of mixed presentation (meningitis, 60–70%; meningococcemia, 30–40%). The majority of cases occurred in patients aged 20–30 years and, like the other outbreaks in India, serogroup A was the dominant causative strain. Third-generation cephalosporins were again used (with injectable chloramphenicol used in some hospitals), and most patients responded rapidly to antimicrobials. Meningococcal vaccination was implemented for all HCPs. Chemoprophylaxis of close contacts of affected patients began in early February 2009 and mass chemoprophylaxis was implemented in the most affected area, the Dhalai district, in late February 2009. Mass chemoprophylaxis led to no reduction in cases. In June–July, a mass vaccination of the entire population of people aged 2–50 years in the Dhalai district, using the bivalent (A + C) meningococcal polysaccharide vaccine, led to a significant reduction in cases; no cases have been reported since 2010. The bivalent polysaccharide vaccine is known to provide protection lasting 3–5 years.

Reports from India highlight the need for studies to determine how long antibodies persist post immunization; data from these studies are critical for countries where outbreaks are cyclical. This information is also important for formulating vaccination strategies for HCPs who may be repeatedly exposed to MD.

The preparation for an outbreak in India varies between large cities and remote communities. Whereas in the former, organisms can be quickly identified and appropriate measures mobilized, this is not the case in the latter. With help from the US Centers for Disease Control and Prevention (CDC), many HCPs are being trained in how to perform surveillance and deal with outbreaks. Units consisting of a microbiologist, an epidemiologist, and a clinician are described as rapid response teams. However, the major issue in outbreak preparedness is laboratory diagnostics; these are lacking at the state level and need to be strengthened.

The decision to undertake mass vaccination following an outbreak is based upon the attack rate within an area. During inter-epidemic and epidemic periods, immunoprophylaxis of high-risk populations (e.g. HCPs) is implemented and chemoprophylaxis with antimicrobials is used for close contacts. In addition, during epidemic situations, social distancing (closure of schools, colleges, cinemas, etc.) is used to slow the spread of the disease. However, the impact and success of social distancing remains uncertain. This is to be expected given the different capabilities of the different communities in India: for those living in crowded conditions, school closure may not have the same impact as on those living with fewer contacts.

The lack of a strong surveillance system in India appears to have hampered accurate epidemiologic quantification of the MD burden

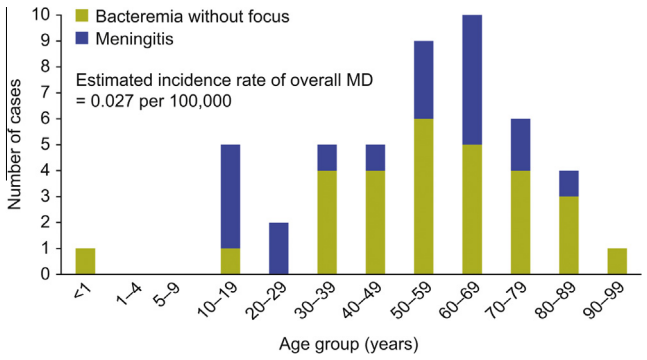

Fig. 1. Reported number of invasive MD cases, Japan, April 2013 to August 2014. *Source:* National Epidemiological Surveillance of Infectious Diseases (NESID).

Table 1
The epidemiology of MD in the Asia-Pacific region.

	Japan	India	Republic of Korea	The Philippines
Quality of data	Detection of MD is reliant on clinicians' ability to suspect meningococci. Surveillance system in place and laboratory resources good	Mostly only available during outbreaks	Little reliable epidemiologic data	Only the septicemic form, meningococcemia, is reported
Data source	NESID	3 recent major outbreaks (Delhi/NCR [2005], Meghalaya [2008–2009] and Tripura [2009])	KCDC, HIRA and individual published reports	PIDSR
Incidence	0.027/100,000 during April 2013 to Aug 2014	Not reliably known	0.012–0.05/100,000/year in the general population (KCDC and HIRA data) 6.8/100,000/year in children aged <5 years (CSF PCR study data)	0.02–0.1/100,000/year
Age groups affected	Since April 2013, MD has become more prevalent in elderly individuals due to a change in surveillance	An increase in the proportion of cases in young adults has recently been reported	Varies across the 3 reporting systems	The number of cases was greatest in infants and young children (case fatality high; females more than males)
Predominant serogroups	Serogroup Y, followed by C and B (but these data are based on only 59 cases)	Serogroup A with rare reports of B and C	No predominant serogroups at this time	Serogroup A, although B has been documented
Case definition	MD with either culture- or PCR-positive cases, using blood or CSF sample, are confirmed cases and need to be reported as soon as diagnosed	Suspect: Sudden onset of fever >38.5 °C rectal or 38.0° axillary with stiff neck or bulging fontanel in patients aged <1 year Probable: Suspect case as defined above, with Gram stain showing diplococci or ongoing epidemic or purpural rash Confirmed: suspect or probable case as above, with either positive CSF/blood culture or positive CSF antigen detection for meningococcus or positive PCR test	Differ depending on location and situation, i.e. outbreak definition different from non-outbreak situations	Suspect: Acute fever with hemorrhagic rash and/or meningeal signs Probable: A suspect case with turbid CSF *or* Gram-negative diplococci from CSF, blood, skin, *or* close contact with a confirmed case during the previous 10 days Confirmed: A suspect case with *N. meningitidis* isolated from a sterile site (CSF, blood, skin) *or* presence of *N. meningitidis* DNA from a sterile site (CSF, blood, skin)

CSF, cerebrospinal fluid; DNA, deoxyribonucleic acid; HIRA, Health Insurance Review and Assessment Service; KCDC, Korea Centers for Disease Control and Prevention; MD, meningococcal disease; NCR, National Capital Region; NESID, National Epidemiological Surveillance of Infectious Disease; PCR, polymerase chain reaction; PIDSR, Philippine Integrated Disease Surveillance and Response.

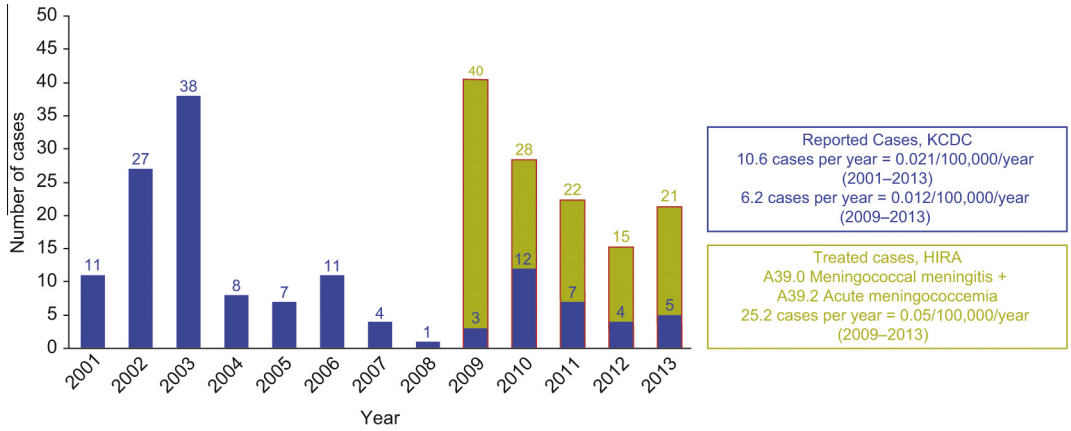

Fig. 2. Different incidence rates of MD, depending on reporting system. *Sources:* KCDC data from Disease Web Statistics System, KCDC (http://is.cdc.go.kr/dstat/index.jsp). HIRA data from Statistics Service, HIRA (http://www.hira.or.kr/main.do).

and has had a negative impact on efforts to control and manage the disease. As a consequence, it is likely that MD is markedly underreported in India. Furthermore, much of the epidemiologic data that are available have been collected during outbreaks [6] and, as such, the experts (epidemiologists, microbiologists, and clinicians) tend to collaborate only during these epidemics. Case definitions employed in India are based on the World Health Organization (WHO) guidelines. Moreover, polymerase chain reaction (PCR) methods for accurate detection of the bacterium are only performed on special request or if a study is being undertaken. During inter-epidemic periods, data are collected from the Central Bureau of Health Intelligence (CBHI), Integrated Disease Surveillance Project, and individual published reports. However, the data may be incomplete or inaccurate since many patients receive antibiotics from their HCP if MD is suspected, and this tends to occur before hospital admission. Another variable that results in underreporting is that some patients die from complications without being seen by an HCP or at a hospital early in the course of MD.

3.2.3. Japan

Japan is exceptional in that it has an estimated low incidence of MD (Fig. 1). For the last few decades, the only outbreak in Japan was caused by serogroup B and occurred in a high-school dormitory (May 2011). From 1999 to 2013, the number of cases of MD was highest in adolescent males (59% of total cases). Since 2013, the proportion in males has increased to 69% of total cases and the age cohort effect shifted (Table 1). In order of frequency, the major serogroups isolated were Y, C, and B (Table 1).

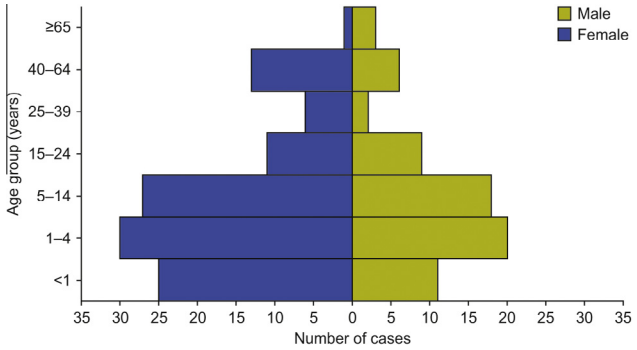

Fig. 3. MD cases by age group and sex in the Philippines, 2013 (N = 182). *Sources:* Philippine Integrated Disease Surveillance and Response (PIDSR) Annual Report 2013, the National Epidemiology Center of the Department of Health (http://www.doh.gov.ph/nec-orgchart). Available from: https://xa.yimg.com/kq/groups/85999055/777284928/name/pidsr2013.pdf.

Surveillance in Japan is undertaken by the National Epidemiological Surveillance of Infectious Diseases (NESID). Since 1999, only meningitis cases have been reported and data are collected on the detection/isolation of meningococci from patients with meningitis. From April 2013, in addition to meningococcal meningitis, meningococcal bacteremia without focus has been added to the list of notifiable diseases as an invasive MD. In Japan, detection of MD is dependent upon the clinicians' ability to suspect meningococci. Following confirmation of *N. meningitidis*, the disease is reported to the local health department. For more detailed testing, the sample may be sent to the National Institute of Infectious Diseases (NIID) or local public health laboratory (NESID).

MD outbreaks are relatively rare in Japan. However, in August 2015, several European children were diagnosed with serogroup W MD following their return from a World Scout Jamboree in Japan. No Japanese inhabitants were affected and the strain involved had been reported since 2009 in the UK [19].

Immunization is not obligatory in Japan, but individuals may be vaccinated upon request based on the national recommendations. From 2015, the tetravalent meningococcal (ACYW) conjugate vaccine (MCV4) has been available, although it is a voluntary vaccine and only available for private purchase. While serogroup B has been detected, it is unclear when the vaccine against MD serogroup B will be licensed in Japan.

To improve preparedness in Japan, 3 aspects must be improved: raise awareness of MD among HCPs, determine the true burden of disease in the country, and educate HCPs on how to use the vaccine in outbreak settings.

3.2.4. Republic of Korea

There is a paucity of reliable epidemiologic data from the Republic of Korea; although the reporting of meningococcal meningitis cases is mandatory, MD surveillance is passive and reporting varies across medical facilities. There are 3 main sources of surveillance data: the central laboratory (Korea Centers for Disease Control and Prevention [KCDC]), the Health Insurance Review and Assessment Service (HIRA), and individual report papers. Data reported by these sources vary widely (Fig. 2), as do impacted age cohorts and incidence rates (Table 1). In addition, bacterial culture is the most commonly used diagnostic method, and it may be compromised by prior antibiotic use, which is prevalent countrywide.

There are no guidelines for the management of MD outbreaks in the Republic of Korea. Importantly, it is thought that there is a risk

Table 2
GMI recommendations for the Asia-Pacific region.

GMI Recommendations
• Strengthen surveillance systems
• Standardize case definitions, including all clinical forms and not only meningitis
• Centralize reporting
• Develop guidelines on how to diagnose MD in different settings (based on resources available)
• Improve matching between epidemiologic and laboratory data (i.e. capture-recapture studies)
• Develop guidelines on how to detect and manage outbreaks
• Increase awareness of MD among HCPs and health authorities – regional and global networking
• Identify which cohorts asymptomatically carry meningococci – crucial for controlling transmission of MD and ensuring herd protection

GMI, Global Meningococcal Initiative; HCP, healthcare practitioner; MD, meningococcal disease.

of outbreaks in the Republic of Korea due to a lack of herd protection.

The last outbreak in the Republic of Korea was in 2011 in the Korean Army; although outbreaks are rare, close contacts always receive chemoprophylaxis. The emphasis is on attempting to determine who is at high risk of infection. To improve preparedness in the Republic of Korea, surveillance systems need to be improved and outbreak guidelines specific for MD should be developed. It was suggested that the establishment of reporting systems with a reference center would allow HCPs who are recognized as having expertise for MD to send alerts that could increase the interest and awareness of the health authorities.

3.2.5. The Philippines

According to data reported to the Philippine Integrated Disease Surveillance and Response (PIDSR) group, which was created in 2005 in response to the International Health Regulations of the WHO from 2008 through 2013 the number of meningococcemia cases in the Philippines increased from 73 in 2008 to 182 in 2013. PIDSR is an enhanced surveillance system, which monitors notifiable diseases and other health-related events of public health importance using an integrated approach.

Surveillance for bacterial meningitis has been adopted by the National Epidemiology Center as a surrogate for Invasive Bacterial-Vaccine Preventable Disease; however, only the septicemic form, meningococcemia, is reported to the surveillance and response systems in the Philippines. As a consequence of this, data are skewed to reflect a high case fatality rate and are extremely unlikely to report the true burden of meningitis.

Surveillance of MD is based on clinical case definitions that can be used in all types of healthcare settings. For confirmation of MD, PCR is mostly used in the central laboratory but is also available in local hospitals.

An average of 100 cases is reported every year without seasonal variation (Table 1). The number of cases is greatest in infants and young children, and the case fatality rate is highest among infants ($\geqslant$50%). The incidence tended to be higher among males than females (Table 1; Fig. 3). Serogroup A predominates, although serogroup B has been documented in the past.

During the 2004/2005 outbreak in the Cordillera Administrative Region, 2 vaccines were used: the bivalent polysaccharide A and C vaccine, which was used extensively; and the tetravalent polysaccharide vaccine. The target group for mass vaccination was initially children aged 2–8 years. Vaccination target groups were later expanded and included grade school children and local healthcare workers.

Meningococcal vaccines are not part of the Philippine Expanded Program on Immunization, but available data support their use in certain conditions or selected populations. Two meningococcal vaccines are available, the MCV4 and the tetravalent meningococcal polysaccharide vaccine (MPSV4).

3.3. Achievements and remaining challenges in the Asia-Pacific region

In the Asia-Pacific region, there are limited data and many improvements are needed. In addition, the incidence of MD varies substantially between countries, and this may not be a true reflection of the disease prevalence in this region. For example, Japan and the Republic of Korea have frequently reported a low incidence of MD, while India by comparison has a higher incidence of disease. Costs have been suggested as an explanation for the lack of data gathering; however, logistic issues may also play a role. For instance, in India it was noted that sample flow was erratic and therefore it was difficult for the laboratories to maintain the required reagents. Moreover, diagnostic guidelines need to be implemented and reference laboratories established that can maintain the awareness and quality of PCR as a diagnostic tool. Laboratory-based surveillance for MD should be strengthened or initiated in Asia-Pacific countries to determine the true disease burden.

Immunization with the polysaccharide and conjugate vaccines in this region has highlighted the importance of carriage studies in understanding disease transmission. The polysaccharide vaccine is very poor at disrupting carriage, while the conjugate vaccine disrupts acquisition of carriage. The GMI outlined the importance of quality control of carrier studies to ensure reliability of the data.

3.4. Recommendations for the control and prevention of meningococcal disease in the Asia-Pacific region

Based on the discussions during the meeting, the GMI made a number of key recommendations that will lead to better understanding of MD and reduce its public health impact in the Asia-Pacific region (Table 2).

It was generally accepted that the incidence rates in the Asia-Pacific region do not reflect the true burden of MD and, as such, there is a need to improve case reporting and standardize case definitions. The GMI recommended the development of new guidelines to aid the diagnosis of MD. It was felt that surveillance systems need to be strengthened across the region, especially in countries were there have been several recent outbreaks, e.g., India. The development of outbreak management guidelines, including a definition of the term "close contact," was seen as essential. The GMI felt that targeting vulnerable group(s) for vaccination during outbreaks would be critical for disease control. In addition, the GMI emphasized the need to undertake inter-epidemic carriage studies in order to determine which cohorts (i.e., age groups) asymptomatically carry meningococci, as these studies would be crucial in controlling the transmission of MD and ensuring herd protection.

Finally, it is vital to increase awareness of MD among HCPs and public health authorities. Improving interactions with decision-makers and recommendation committees was deemed of great importance for improving awareness of the disease and in ensuring

that MD prevention and management initiatives have the resources they need. It was noted that the GMI members could reach out to funding bodies/apply for grants for training courses on areas of importance, such as PCR training.

4. Summary and conclusions

Based on the surveillance, diagnosis, and confirmation data presented at this meeting, the incidence of MD in the Asia-Pacific region appears to be low; however, these data may not be a true reflection of disease prevalence across the region. The reasons for this appear to be multifactorial and include underreporting, weak surveillance systems, lack of guidelines, inconsistent case definitions, and varying awareness of MD. Indeed, in the Republic of Korea, data discrepancies between the different surveillance systems employed emphasize this point and suggest potential underreporting of MD in the country by some systems.

In order to better understand the epidemiology of MD in the Asia-Pacific region, the GMI has developed a number of recommendations, including strengthening surveillance, developing diagnosis and management guidelines, and increasing disease awareness.

Conflict of interest statement

The authors are all members of the Global Meningococcal Initiative (GMI). The GMI is funded by an educational grant from Sanofi Pasteur; however, the group is not led in any way by the company. GMI members determine meeting agenda items and lead the discussions and outputs. Sanofi Pasteur representatives may attend the meetings, but in the role of observers only, and they do not influence the findings of the group; nor do they write, review, or take part in the GMI's decision to submit articles for publication.

RB performs contract research on behalf of Public Health England for GSK, Novartis, Pfizer, Sanofi Pasteur, and Sanofi Pasteur MSD. **J-SL** performs contract research for GlaxoSmithKline, Green Cross, Pfizer, Sanofi Pasteur, and SK Chemicals and has received speaker's and/or consultant fees from Pfizer and Sanofi Pasteur. **JAV** has received grants to support research projects and speaker's and/or consultant fees from Baxter BioSciences, GSK, Novartis, Pfizer, and Sanofi Pasteur. **M-KT** performs contract research and expertise on behalf of Institut Pasteur for GSK, Novartis, Pfizer, and Sanofi Pasteur. **GE** and **HK** have no conflicts to declare. **HMK** performs contract research for GlaxoSmithKline, Green Cross, Sanofi Pasteur, and SK Chemicals and has received speaker's and/or consultant fees from Sanofi Pasteur. **DSJ** performs contract research for GlaxoSmithKline, Green Cross, Sanofi Pasteur, and SK Chemicals and has received speaker's and/or consultant fees from GlaxoSmithKline, Sanofi Pasteur, and SK Chemicals.

Author contributions

RB wrote the initial draft of the manuscript. All authors have revised and reviewed the manuscript and approved the final version.

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