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RESEARCH ARTICLE

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Invasive meningococcal disease in Malaysia, Philippines, Thailand, and Vietnam: An Asia-Pacific expert group perspective on current epidemiology and vaccination policies

Usa Thisyakorn[a], Josefina Carlos[b], Tawee Chotpitayasunondh[c], Tran M. Dien[d], Maria Liza A. M. Gonzales[e], Nguyen T. L. Huong[f], Zulkifli Ismail[g], Musa M. Nordin[h], Anna Lisa T. Ong-Lim[e], Terapong Tantawichien[i], Sangita D. Terumalay[j], Thiem D. Vu[k], Otavio Cintra[l], and Olakunle Oladehin[m]

[a]Tropical Medicine Cluster, Chulalongkorn University, Bangkok, Thailand; [b]University of the East Ramon Magsaysay Memorial Medical Center, Quezon City, Philippines; [c]Queen Sirikit National Institute of Child Health, Bangkok, Thailand; [d]Vietnam National Children's Hospital, Hanoï, Vietnam; [e]University of the Philippines - Philippine General Hospital, Manila, Philippines; [f]Hanoi University of Pharmacy, Hanoi, Vietnam; [g]KPJ Selangor Specialist Hospital, Selangor, Malaysia; [h]KPJ Damansara Specialist Hospital, Selangor, Malaysia; [i]Division of Infectious Diseases, Department of Medicine, Chulalongkorn University, Bangkok, Thailand; [j]Subang Jaya Medical Centre, Selangor, Malaysia; [k]National Institute of Hygiene and Epidemiology, Hanoi, Vietnam; [l]GSK, Rio de Janeiro, Brazil; [m]GSK, Kuala Lumpur, Malaysia

ABSTRACT

Invasive meningococcal disease (IMD) imposes a significant burden on the global community due to its high case fatality rate (4-20%) and the risk of long-term sequelae for one in five survivors. An expert group meeting was held to discuss the epidemiology of IMD and immunization policies in Malaysia, Philippines, Thailand, and Vietnam. Most of these countries do not include meningococcal immunization in their routine vaccination programs, except for high-risk groups such as immunocompromised people and pilgrims. It is difficult to estimate the epidemiology of IMD in the highly diverse Asia-Pacific region, but available evidence indicate serogroup B is increasingly dominant. Disease surveillance systems differ by country. IMD is not a notifiable disease in some of them. Without an adequate surveillance system in the region, the risk and the burden of IMD might well be underestimated. With the availability of new combined meningococcal vaccines and the World Health Organization roadmap to defeat bacterial meningitis by 2030, a better understanding of the epidemiology of IMD in the Asia-Pacific region is needed.

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Introduction

Invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* (meningococcus) imposes a considerable burden worldwide.[1–3] The World Health Organization (WHO) estimated 250,000 deaths due to meningitis in 2019, with one in five affected persons left with long-term severe sequelae.[4] The six meningococcal serogroups (MenA, MenB, MenC, MenW, MenX, and MenY) are responsible for almost all cases of IMD worldwide.[1,5]

Estimating the epidemiology and burden of IMD in the Asia-Pacific region can be very challenging. The recommendations and the organization of communicable disease monitoring systems varies by country and IMD is not classified as a notifiable disease in some countries.[6]

Material and methods

An expert group meeting was convened to discuss the IMD epidemiology and immunization policies in some Asia-Pacific countries. The objective of the meeting was to consolidate existing information and determine knowledge gaps regarding IMD burden and serogroup distribution in Malaysia, Thailand, Philippines, and Vietnam. In addition, current meningococcal immunization policies were reviewed to identify challenges and opportunities for improving immunization. The meeting was held online on 3 March 2021, with 23 participants, including 13 epidemiologists and infectious disease experts from these countries, and 10 experts from the GSK team. The proceedings of this meeting are reflected in this paper.

Malaysia

Incidence data

IMD is not a mandatory notifiable disease. Moreover, there is little incidence data available[7–12] from the earliest publication in 1977[7] to the most recent review in 2015[13] and all are concerned with retrospective hospital patient records. Based on these retrospective studies, *Haemophilus influenzae* was found to be the most common cause of meningitis in Malaysia until the *H. influenzae* type b (Hib) conjugate vaccine was included in the National Immunization Program (NIP) in 2002.[14] Since 1980, *N. meningitidis* is responsible for 3.5–13.0% of meningitis cases in Malaysia.[13]

CONTACT Olakunle Oladehin olakunle.o.oladehin@gsk.com GSK, Level 6, Quill 9, 112, Jalan Semangat, 46300 Petaling Jaya Selangor Darul Ehsan 46300 Petaling Jaya, Wilayah Persekutuan, Kuala Lumpur, Malaysia.

Carriage and circulating serogroups

Rohani et al. (2007) found a carriage rate of 37.0% among 3195 healthy young army recruits.[15] In Al-Azeri et al. (2002), returning pilgrims had a 51.3% ($n = 41/76$) higher rate of *N. meningitidis* compared to pre-hajj.[16]

Among army recruits, the detected serogroups were either MenX, MenZ or MenY (81.0% cumulative for the three), MenW (4.7%) and MenA (3.3%).[15] MenW serogroups were detected in the majority of pilgrims returning from Hajj.[16] MenB and MenW were the predominant serogroups among 21% of 123 *N. meningitidis* genotyped isolates (114 carrier and nine clinical strains).[17] During 1987–2004, 11 microbiologically confirmed cases were reported in a large university hospital in Kuala Lumpur; mortality rate was 25%. One of the six serogrouped cases was MenB, while the other five were MenW.[11]

A pattern of increased *N. meningitidis* resistance to penicillin has been observed.[17,18] Among 123 *N. meningitidis* strains, 64.9% (74/114) of carrier strains and almost all (8/9, 89.0%) of clinical strains were susceptible to penicillin. Thus, 33.3% of all *N. meningitidis* strains had intermediate resistance to penicillin.[17]

Meningococcal vaccination

Routine meningococcal vaccination is recommended[6] for at-risk population, travelers to parts of the world with meningitis epidemics, and Hajj.[19,20] Only quadrivalent conjugate meningococcal ACWY (MenACWY) vaccines are available and routinely administered in the private sector on a case-by-case basis, in one or two injections. Hajj pilgrims should receive it within a period of five years to 10 days before pilgrimage.[19–22]

Thailand

Incidence data

Thailand has a well-established passive surveillance system for communicable diseases, under which healthcare professionals (HCPs) are required to report suspected cases within 24 hours.[23] However, confounding factors like low disease awareness among HCPs, low number of polymerase chain reaction (PCR) tests, cost of such PCR tests and antibiotic use prior to laboratory confirmation of the disease, appear to contribute to underestimation of the disease burden.

According to official annual surveillance reports, from 2010 to 2019 the IMD incidence was less than 0.10 per 100,000 population overall.[23] In 2012, the case fatality rate (CFR) reached 37.5%.[23] The incidence was highest in children aged 0–4 years, with only a few cases reported in adolescents and adults.[23] The southern and western borders had the highest incidence of IMD (1971–2019).[23]

Carriage and circulating serogroups

A retrospective analysis of bacterial cultures and cerebrospinal fluid (CSF) specimens collected in 13 public hospitals from 1994 to 1999 reported *N. meningitidis* in 0.002% and 0.02% of those samples, respectively.[24] Penicillin-resistant *N. meningitidis* isolates, with a minimum inhibitory concentration ≥0.125 g/mL, were also reported.[24]

Another study found an unadjusted incidence of 24.6 suspected meningitis cases of all causes per 100,000 people.[25] Hib, Gram positive cocci, Gram negative bacilli, and *N. meningitidis* caused 39.1, 26.1, 21.7, and 13.0% of confirmed bacterial meningitis, respectively.[25]

MenB was predominant (50–80%) among cases diagnosed in 1994–1999[6,24] and among 11 clinical isolates of *N. meningitidis* obtained from Shoklo Malaria Research Unit, Mae Sot in 2007; four of these isolates were resistant to chloramphenicol.[26]

Meningococcal vaccination

Only MenACWY conjugate vaccines are available in Thailand.[27] Meningococcal vaccination is recommended (a) in the event of an outbreak from a vaccine-preventable serogroup (serogroups A, C, Y, and W), (b) for people traveling to countries where the disease is endemic, such as Africa or the Middle East, and (c) for individuals routinely operating in laboratories where *N. meningitidis* may be present in the form of a solution.[28]

Philippines

Incidence data

Meningococcal disease is endemic to Philippines, with about 100 cases reported yearly and no seasonal variation.[29] It is among the priority notifiable diseases under the Philippine Integrated Disease Surveillance and Response (PIDSR) protocol.[30] The latest available PIDSR reported 130 meningococcal cases of any severity level, from suspected symptomatic to laboratory confirmed, from January 1 to 29 June 2019.[31] The highest incidence was among the youngest age groups: 49.2% (64/130) aged <5 years, and 25.4% (33/130) aged <1 year.[31] There were 68 deaths accounting for an overall CFR of 50.0%.[31] Aye et al. (2020) reported an annual incidence of 0.02 cases per 100,000 population.[6]

Carriage and circulating serogroups

MenB caused two of the seven epidemics during 1998–2011, while MenA caused the largest epidemic during 2004–2006 with 418 cases.[32,33] In a large prospective, cross-sectional study on carriage among school and university students (age 5–24 years), MenB was the predominant serogroup (65.7%, 23/35) isolated across age groups, followed by MenC (8.6%, 3/35), and MenY (5.7%, 2/35).[34] Aye et al. (2020), also reported a predominance of MenB serogroup (68.0% of cases) in 2017–2018 PCR surveillance data and the presence of MenW (16.7%) in 2018 PCR surveillance data.[6]

Meningococcal vaccination

Meningococcal vaccination is not included in the Philippine Expanded Immunization Program.[35] However, polysaccharide

and conjugate MenACWY are available in Philippines and vaccination is suggested for immunocompromised individuals, patients with retroviral infections, travelers, pilgrims, and residents of hyperendemic or endemic areas, and during outbreaks.[29,33,36]

Vietnam

Incidence data

First evidence of IMD in Vietnam involved an outbreak with 1015 cases in Ho Chi Minh City in 1977.[37–39] Since 2012, an IMD surveillance system has been implemented in the country.[37] In 2018, the incidence rate was 0.02 per 100,000 population.[40] High incidence rates have been recorded in surveillance studies, ranging from 1.9 per 100,000 among army recruits[41] to 36.2 per 100,000, among newborns aged less than one month in Hanoi.[42] In Hanoi, reported incidence rates for children under the age of five years varied from 2.6 to 7.4 per 100,000.[42,43] Reported CFRs are also high, ranging from 8.7%[41] to 34.7%.[39]

Carriage and circulating serogroups

Sporadic cases of MenC were reported in southern Vietnam in 2006 and 2012, and MenC caused an outbreak during 1977–1979.[6,38] MenC was predominant in CSF samples and MenB in bacterial isolates from the Kim et al. (2012) study, but the number of samples examined was small.[42] Hib was detected in 16.6% of the specimens, *N. meningitidis* in 14.2%, and *S. pneumoniae* in 4.7%.[42] MenB was the predominant serogroup (94%), among 109 isolates from Southern Vietnam collected between the 1980s and 2019. MenC was only found in 6% of isolates.[44] Similarly, MenB predominated among the carrier serogroups at 56% ($n = 34$), followed by MenC at 21% ($n = 13$), and the remaining isolates were not typeable.[44] A prospective, population-based surveillance study conducted in all Vietnamese military hospitals from January 2014 to June 2021 identified 69 IMD cases, of which 91% were MenB.[41]

Meningococcal vaccination

Meningococcal vaccine is not provided under the NIP and is recommended only for high-risk groups. MenACWY polysaccharide vaccine and a bivalent B Outer Membrane Vesicles and C meningococcal polysaccharide vaccines are the only meningococcal vaccines available in Vietnam.[45,46] These are mainly provided through the private health sector.

Experts commentary

The limited data accumulated so far suggest low incidence of IMD in Southeast Asia, but the burden remains unclear.[47] Sporadic cases in the region are now more easily identified due to advances in diagnostic tools, genotyping, and disease awareness (e.g. outbreaks increased appreciation of preventive measures). The available data from the Asia-Pacific region in general,[6] and from the four countries in this paper, suggest a shifting epidemiology, with MenB serogroup currently predominating. IMD is not considered a notifiable disease in several countries, and reliable epidemiological data is scarce in the region, necessitating surveillance system improvements.[6] The limited *N. meningitidis* carriage data available are inconclusive due to the variability in the populations involved, the study design, the sample handling and the method of analysis.[47] Because most of the disease transmission occurs between carriers,[29,47,48] inter-epidemic carriage data are vital to determine the most effective local prevention strategies.[6,47] Future research should involve collaborative regional multicenter studies applying similar designs.[47] Larger representative populations and age groups across countries would fill evidence gaps and allow regional comparisons of carriage and seroprevalence.[47] Pilgrims deserve special consideration in study designs evaluating pre- and post-mass gathering carriage, including vaccination status and potential impact on carriage.

Given the high morbidity and mortality rates of IMD, the experts agreed that vaccination is the most effective approach for prevention in the Asia-Pacific countries considered. Current recommendations are geared toward high-risk groups, travelers and outbreak control. Locally generated disease burden data, based on IMD surveillance evidence, are needed to document the potential need to broaden the existing meningococcal vaccine recommendations.[49] MenB and MenACWY conjugate vaccines could be considered eventually in NIPs for immunization of the identified high-risk groups. Their administration to non-high risk groups is currently only possible through the private health sector. Simultaneously, vaccination awareness campaigns should be conducted, considering the problems and impediments to a successful immunization plan. HCPs rarely, if ever, contribute to building up knowledge of local meningococcal disease morbidity, mortality, and medical implications.[1,50] Even in countries with available laboratory facilities like Thailand, HCPs rarely order PCR tests. As a necessity, HCPs should receive adequate training in the collection, processing, and diagnosis of clinical samples. Moreover, guidelines should be developed and proactively communicated to HCPs to ensure that clinical samples are appropriately sent for laboratory detection. Simultaneously, awareness should be increased among HCPs regarding meningococcal disease burden.

A graphical abstract of the context, novelty, and impact of the expert meeting that can be shared with patients, healthcare professionals, and decision-makers is available in Figure 1.

Conclusion

The expert group meeting revealed a paucity of credible monitoring data on IMD epidemiology in Southeast Asia and recognized the severity of the disease and the importance of prevention through vaccination. The absence of robust epidemiological data highlights the importance of implementing reliable surveillance systems.

National immunization programs currently only involve at-risk populations, while the general population can access vaccination only through the private sector. With new

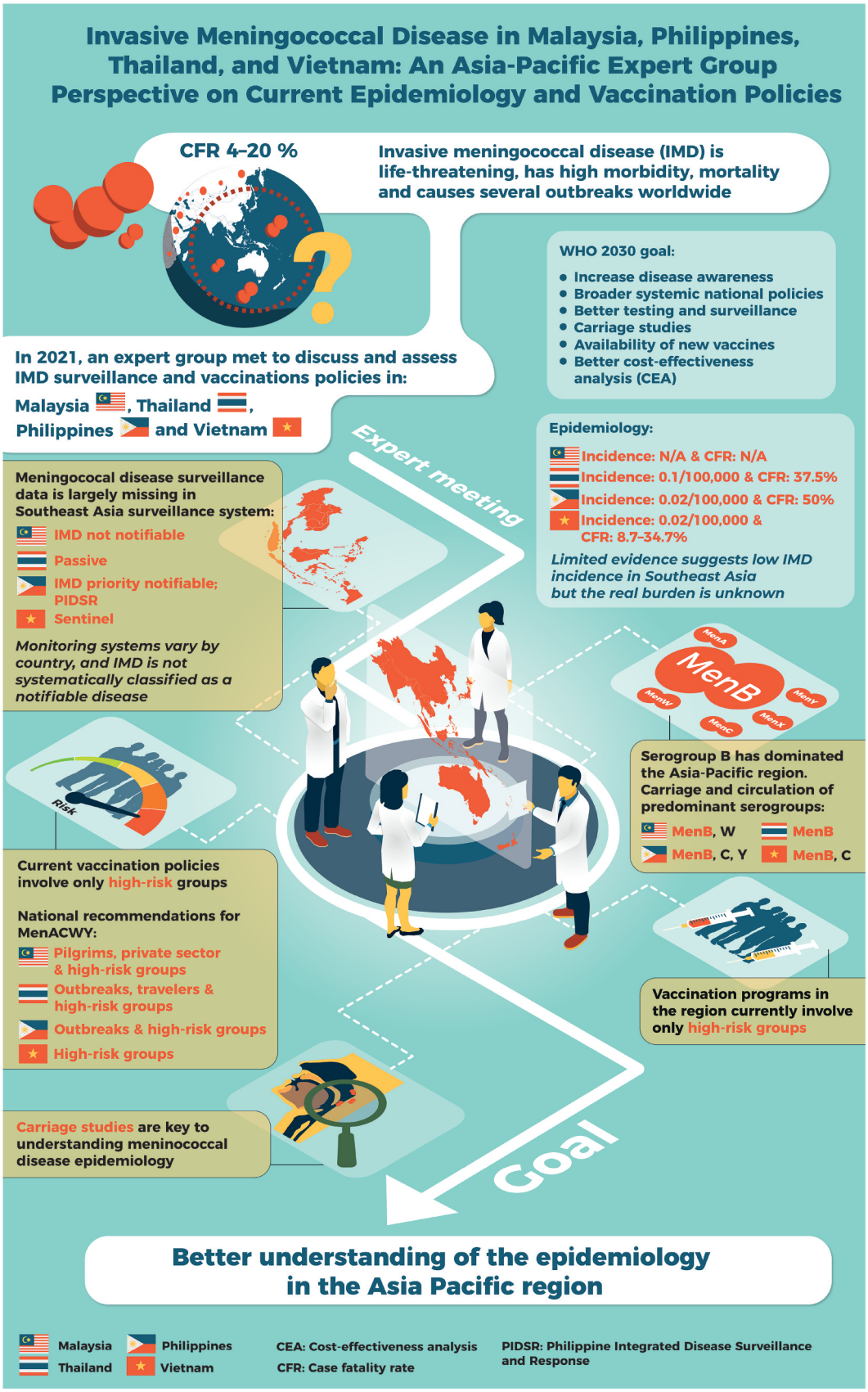

Figure 1. Graphical abstract.

combined meningococcal conjugate vaccines available and the WHO roadmap to defeat bacterial meningitis by 2030,[50] a better understanding of the epidemiology of IMD in the Asia-Pacific region is warranted. Vaccination has proven successful to contain and control other types of bacterial meningitis, such as Hib. Many countries are currently implementing pneumococcal conjugate vaccine programs and IMD appears as one of the next bacterial meningitis challenges to overcome.

Abbreviations

CFR	case fatality rate
CI	confidence intervals
CSF	cerebrospinal fluid
HCP	healthcare professionals
Hib	*H. influenzae* type b
IMD	Invasive meningococcal disease
MenACWY	quadrivalent meningococcal ACWY
MenAC	bivalent A and C meningococcal conjugate vaccine
MenBC	bivalent B and C meningococcal conjugate vaccine
MIC	minimum inhibitory concentration
NIP	national immunization program(s)
PCR	polymerase chain reaction
PIDSR	Philippine Integrated Disease Surveillance and Response
WHO	World Health Organization

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Author contributions

OC and OO were in charge of supervision and project administration and performed data curation and investigation. All authors participated in the discussion and the development of this manuscript and gave final approval before submission.

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analyzed during the current work.

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ORCID

Usa Thisyakorn http://orcid.org/0000-0002-9119-2348
Josefina Carlos http://orcid.org/0000-0002-2680-4918
Tawee Chotpitayasunondh http://orcid.org/0000-0002-1102-349X
Tran M. Dien http://orcid.org/0000-0003-4012-764X
Maria Liza A. M. Gonzales http://orcid.org/0000-0001-6540-7678
Nguyen T. L. Huong http://orcid.org/0000-0002-8051-5017
Zulkifli Ismail http://orcid.org/0000-0002-1370-5910
Anna Lisa T. Ong-Lim http://orcid.org/0000-0002-3261-0167
Terapong Tantawichien http://orcid.org/0000-0003-1970-5118
Sangita D. Terumalay http://orcid.org/0000-0001-6218-0981
Thiem D. Vu http://orcid.org/0000-0001-6168-4555
Otavio Cintra http://orcid.org/0000-0002-3485-8780
Olakunle Oladehin http://orcid.org/0000-0002-6151-1467

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