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Review

Meningococcal disease surveillance in the Asia–Pacific region (2020): The global meningococcal initiative

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SUMMARY

The degree of surveillance data and control strategies for invasive meningococcal disease (IMD) varies across the Asia–Pacific region. IMD cases are often reported throughout the region, but the disease is not notifiable in some countries, including Myanmar, Bangladesh and Malaysia. Although there remains a paucity of data from many countries, specific nations have introduced additional surveillance measures.

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The incidence of IMD is low and similar across the represented countries (<0.2 cases per 100,000 persons per year), with the predominant serogroups of *Neisseria meningitidis* being B, W and Y, although serogroups A and X are present in some areas. Resistance to ciprofloxacin is also of concern, with the close monitoring of antibiotic-resistant clonal complexes (e.g., cc4821) being a priority. Meningococcal vaccination is only included in a few National Immunization Programs, but is recommended for high-risk groups, including travellers (such as pilgrims) and people with complement deficiencies or human immunodeficiency virus (HIV). Both polysaccharide and conjugate vaccines form part of recommendations. However, cost and misconceptions remain limiting factors in vaccine uptake, despite conjugate vaccines preventing the acquisition of carriage.

Introduction

The Gram-negative bacterium, *Neisseria meningitidis*, is a human commensal/pathogen that colonizes the nasopharyngeal mucosa. It can cause invasive meningococcal disease (IMD) by passing into the bloodstream via the mucosal membrane.[1] Although the precise mechanisms by which this occurs are not fully understood,[2] it is well established that the bacterium's virulence is associated with the expression of a polysaccharide capsule.[3] Of the 12 polysaccharide capsules, six (A, B, C, W, X, Y) are associated with most IMD cases,[3] which includes potentially life-threatening conditions, such as meningitis and/or septicemia. There are approximately 1.2 million IMD cases each year worldwide and case fatality rates (CFRs) have been documented to range from 4.1% to 20.0%.[4,5]

The Global Meningococcal Initiative (GMI) is a multidisciplinary group of scientists, clinicians and public health officials that was formed to raise awareness of IMD through education and research. Since the GMI's inception in 2009, a series of meetings have been held to discuss the latest data in surveillance and epidemiology, as well as control strategies and immunization schedules across different regions.[6,7]

As part of the GMI's activities, a group of experts has conducted a review of IMD epidemiology and control strategies in the Asia–Pacific region, as well as wider issues that may affect the incidence of IMD, such as occupational risks, religious beliefs and modes of transmission. The objectives of this review are to: (i) provide an update on IMD surveillance and prevention in the Asia–Pacific region; (ii) highlight the potential risk of IMD in high-risk groups, particularly for those participating in mass gatherings; and (iii) explore current barriers to vaccination, with a focus on Hajj pilgrims and religious beliefs.

In addition to the above objectives, several other topics that are not necessarily exclusive to the Asia–Pacific region are covered. These include: (i) unusual transmission pathways of meningococci; (ii) the impact of conjugate vaccines and meningococcal serogroup B (MenB) vaccination on disease and carriage; and (iii) the risk of invasive disease in specific occupations.

The surveillance, epidemiology and prevention of IMD in the Asia–Pacific region

Surveillance of IMD

Surveillance is of critical importance in controlling meningococcal disease, with the principal drivers of surveillance networks being outbreak detection; incidence monitoring; disease burden estimation; antibiotic resistance analyses; serogroup and strain distribution assessments; and control strategy evaluations.[8] Although many countries have the capability to confirm suspected IMD cases, the structural complexity of surveillance networks varies across regions (be it regionally, nationally or internationally).[7] Such networks may utilize passive, active or sentinel surveillance strategies, with cost, resource and national disease burden shaping the system health ministries adopt. A number of countries do not have an active, laboratory-based surveillance system in place.[4]

In a similar fashion to global trends, surveillance approaches differ across the Asia–Pacific region. IMD cases are often reported, but IMD is not recognized as a notifiable disease in some countries, including Myanmar, Bangladesh and Malaysia. In Myanmar, there is poor IMD awareness among physicians, with meningitis cases (without a characteristic rash) being under-recognized and under-reported. However, the under-estimation of IMD burden is not solely attributed to those countries with no established surveillance system. The incidence of bacterial meningitis in children is often underestimated in South Korea despite surveillance efforts. Although the reasons underlying such a trend are complex, there are several identifiable factors, including the prevalent use of antibiotics and limited diagnostic tools (generally, South Korean and Nepal hospitals only have access to culture method for case confirmation). Although not readily available in laboratories across the region, polymerase chain reaction (PCR) testing is a critical tool, which can help to diagnose suspected meningococcal cases, especially when culture specimens are negative for *N. meningitidis*.

Geographical limitations and regional capabilities also factor into the effectiveness of surveillance networks across the Asia–Pacific region. Cambodia has a robust surveillance network in place, with suspected cases being referred from district centers to provincial units, and subsequently to national hospitals. The country also has 20 microbiology laboratories, with a range of capabilities. However, these units serve up to 2000 private and public hospitals throughout the country, with 10 laboratories located in the capital, Phnom Penh. Conversely, Australia operates a state-based IMD surveillance system, with each state or territory funding its own microbiology reference laboratory. All cases are reported from the states nationally through the National Notifiable Diseases Surveillance System.

Incidence of IMD

IMD incidence is fairly similar across the Asia–Pacific region, ranging from 0.02 to 0.2 cases per 100,000 persons per year in the Philippines to Singapore, respectively.[9] However, there have been higher reported incidences in certain countries or within specific sub-populations. In New Zealand, for instance, the average incidence of IMD was 2.3 per 100,000 persons in 2019, with cases ranging from 0.0 to 4.5 per 100,000 persons, depending on the district health board.[10]

Although IMD incidence is low in South Korea[11] (~0.05 cases per 100,000 persons per year), the number of cases is higher

among army recruits (~2.2 cases per 100,000 persons per year).[12] Army personnel from differing socioeconomic backgrounds live in close proximity and undertake operations whereby maintaining good hygiene is challenging.[13] As a result of IMD outbreaks among this sub-population, the South Korean Government instituted a meningococcal vaccination program under the 2012 Military Healthcare Service Act.[13]

In Australia, higher IMD notification rates are observed within the Aboriginal and Torres Strait Islander populations in the Northern Territory (13 cases per 100,000 persons in 2017). This higher risk may be attributed to factors associated with socioeconomic disadvantage and living in over-crowded and remote communities. The IMD incidence among this demographic has been consistently higher than that observed in the non-Indigenous population across Australia, particularly in those aged 0–9 years.[14]

The burden of meningococcal disease is high among children and adolescents throughout the Asia–Pacific region. In the Philippines, ~75% of the total number of confirmed IMD cases were among those aged 0–14 years in 2012–2013.[15] High incidence rates among infants and children (0–4 years) have also been observed in Singapore and South Korea, with 1.6 (2018) and ~1.35 (2010) cases per 100,000 persons, respectively. IMD incidence is particularly acute among infants <1 year in Nepal, as was in evidence in the 1983 meningococcal meningitis outbreak in the Kathmandu Valley.

CFRs are high in some countries across the region. With a high burden of IMD in young infants and children, the Philippines reported a CFR in the same demographic of ≥50%. In Thailand, there was a similar CFR across all age groups at ~40% in 2012 for meningococcal meningitis cases. Although the overall IMD incidence is low in China (<0.1 cases per 100,000 persons per year), the CFR is >10% and, similarly, in Japan the CFR was estimated at ~16% during the period of April 2013 to June 2018.

Serogroup distribution

In the countries represented at the recent GMI meeting, the predominant reported serogroups were B, W and Y.

Serogroup B is prevalent in many Asia–Pacific countries/regions, both in IMD cases and carriage.[9,16] A large proportion of IMD cases ($n = 99/113$; 88%) in Taiwan from 2005 to 2018 were caused by serogroup B – a 34% increase over the previous 9-year period. With regards to the epidemiological data based on laboratory surveillance during 2015–2017 in China, MenB accounted for 35.8% ($n = 53/148$) IMD cases. Based on data collected from the National Epidemiological Surveillance on Infectious Disease (NESID) network in Japan, serogroup B accounted for 20% ($n = 13/65$) of reported IMD cases between January 2017 and June 2019. In Australia, over half of the reported IMD cases were caused by serogroup B during the first 6 months of 2019 ($n = 46/89$; 52%); although cases due to this serogroup have been declining nationally since 2017.[17] Carriage of serogroup B meningococci is also high in South Korea, with a carriage rate of 24.5% reported among 1460 first grade high school students (aged 16–17) in 2015.[18]

Serogroup W circulation is significant across the Asia–Pacific region. Based on PCR testing, the Philippines reported that 16.7% ($n = 8/48$) of blood and cerebrospinal fluid (CSF) specimens collected in 2018 were serogroup W. A higher percentage was reported in Australia during the first six months of 2019, with 25 out of 89 IMD cases (28%) being attributed to serogroup W (48% of these cases resulted in intensive care unit (ICU) admissions).[17] There was a similar proportion of serogroup W cases among laboratory-confirmed IMD in New Zealand during the same period (30%; $n = 30/99$).[19]

Antibiotic-resistant serogroup C (MenC) and MenB strains continue to emerge in parts of Asia. Prior to 2003, a small fraction of IMD cases were associated with MenC in China. However, there were a number of MenC outbreaks caused by clonal complex (cc) 4821 between 2003 and 2005 in Anhui province.[20] cc4821 has since spread to all provinces across the country, accounting for >95% of MenC cases. In addition, this particular clonal complex in MenB and MenC cases is non-susceptible to ciprofloxacin, leading to warnings that this antibiotic should be prescribed with caution as a prophylactic treatment.[21–23]

Prevention and control strategies

There are a range of prevention and control strategies employed across the Asia-Pacific region; however, most countries do not include meningococcal vaccination as part of their National Immunization Programs (NIPs). Although practices vary, chemoprophylaxis is commonly prescribed, with immunization only being recommended for those in high-risk groups.[24] These groups may include people with complement deficiencies, human immunodeficiency virus (HIV), or those attending a pilgrimage or a mass gathering in another country/region. Such recommendations are promoted in Vietnam, the Philippines, New Zealand, Thailand, Taiwan, Singapore and Indonesia. With sporadic cases and limited outbreaks in small communities, there is no direct impetus to incorporate meningococcal vaccination into the NIP in these countries. Vaccinations may still be accessible through private clinics, but cost is a limiting factor in vaccine uptake. For instance, a meningococcal vaccine is available in Myanmar, but can cost up to $70 USD per dose.

Other countries in the region have incorporated different meningococcal vaccines into their NIP in response to outbreaks or the emergence of virulent strains. Owing to the increased incidence of IMD related to serogroup B in South Australia, the state has now introduced the four-component MenB (4CMenB) vaccine into the immunization program.[25] The meningococcal serogroups A, C, W and Y (MenACWY) conjugate vaccine is also funded under the NIP in Australia.[26] China has a multistage meningococcal vaccination program with children between 6 and 18 months receiving two doses of a meningococcal serogroup A (MenA) polysaccharide vaccine (3 month interval), with subsequent doses of meningococcal serogroup A and C (MenAC) polysaccharide vaccine (free of charge) or MenAC conjugate vaccine (at parents' own cost) at 3 and 6 years.[27]

Chemoprophylaxis is in common usage despite the lack of national recommendations in some areas. The Chinese Center for Disease Control has no strict protocols for prophylactic treatments, which has led to each province prescribing different antibiotics based on local guidance. In Vietnam, all close contacts of a suspected IMD case will receive either ciprofloxacin or azithromycin.

Meningococcal immunization and treatment strategies

Polysaccharide and polysaccharide conjugate vaccines

As discussed previously, the polysaccharide capsule is the meningococcus' primary virulence factor.[3,28] The underlying chemistry of the repeating saccharide units defines the capsular group.[28]

Unconjugated polysaccharide vaccines cross-link B-cell receptors to drive cell differentiation to plasma cells. However, the body's immune system does not effectively recognize repeating saccharide units and so this differentiation only stimulates immunoglobulin G2 (IgG2) and M (IgM) production, but does not induce memory B-cells.[28,29] Therefore, polysaccharide vaccines do not stimulate immunological memory and repeated vaccinations may actually result in hyporesponsiveness.[29,30]

To overcome these limitations, the polysaccharide is linked to an immunogenic carrier protein, such as tetanus or diphtheria tox-

oid. The resulting polysaccharide conjugate vaccine is internalized and processed within a B cell. Peptide-specific T cells subsequently support cell maturation and the production of immunoglobulin G1 and G3, with the process also inducing a B-cell memory response.[28] As this adaptive immune response is not predicated on B-cell maturation, conjugate vaccines are immunogenic in infants (as well as older children and adults).[31,32]

As well as protecting against disease, polysaccharide conjugate vaccines may also prevent the acquisition of meningococcal carriage;[33] although there have been few clinical studies that have assessed this effect.[34–36] Most trials have been conducted in conjunction with mass vaccination campaigns.[37–39] Despite this, trials conducted in Africa have offered key insights into meningococcal carriage reduction following vaccination. A recent study was designed to assess the effect of MenAfriVac (PsA-TT) (meningococcal serogroup A [MenA] conjugate vaccine) on meningococcal carriage in Burkina Faso following a vaccination campaign.[39] Two years after the campaign, there remained a significant reduction in MenA carriage, with MenA carriage prevalence at 0.02%; a decrease from 0.39% (pre-vaccination).[39] Further surveillance data from 18 countries in sub-Saharan Africa indicates a 99% decline in MenA disease following the introduction of PsA-TT.

Meningococcal serogroup B vaccines

There remain a number of outstanding issues with respect to MenB vaccine development with early efforts to develop a capsular polysaccharide-based formulation failing to produce an immunogenic response.[40–42] The lack of immunogenicity is attributable to the MenB capsular polysaccharide being a mimic of human neural cell adhesion molecules.[43]

Outer membrane vesicles (OMVs) derived from meningococci have also been used to develop MenB vaccines. Such OMVs contain the surface-exposed protein, PorA, which can induce serum bactericidal antibodies; however, PorA is highly antigenically variable.[44,45] This results in OMV-based vaccines being strain-specific and unable to generate antibodies against heterologous strains.[46]

To mitigate this limitation, efforts have subsequently focused on developing MenB vaccines with multiple antigens to maximize strain coverage. Three of the main antigens in the multicomponent 4CMenB vaccine were identified using reverse vaccinology. The subsequent final formulation consisted of Factor H binding protein (fHbp), Neisseria Adhesin A (NadA) and Neisserial Heparin Binding Antigen (NHBA). These outer membrane proteins were then added to OMV [containing PorA P1.4] from the New Zealand vaccine strain (NZ 98/254) to further enhance strain coverage.[46,47] Since the coverage of protein-based vaccines is dependent on sufficient (i) antigenic similarity and (ii) surface expression of corresponding peptide within target strains, a system for estimating strain coverage, the Meningococcal Antigen Typing System (MATS), has been developed.[47,48] There is also a second licensed MenB vaccine (Trumenba®, MenB:fHbp [Pfizer]), which contains recombinant fHbp from each of the two subfamilies A and B found in *N. meningitidis*.[49]

Estimates since its introduction in England suggest 4CMenB (in a 2 + 1 schedule) has a vaccine effectiveness in infants (VE) of 59.1% against vaccine-preventable strains.[49] The same study in England has shown that the vaccine has led to a 75% reduction in the incidence of MenB in infants eligible for vaccination.[50] There is limited evidence to suggest the 4CMenB vaccine may disrupt carriage acquisition in adolescents.[51,52]

It should be recognized that the prevalence of MenB is high across various countries in the Asia–Pacific region (as indicated in Table 1), with limited MenB vaccination programs, excluding Australia. However, some countries, such as China, have now started to work on developing a suitable MenB vaccine.

Antibiotic resistance

Antimicrobial resistance was a recurring theme during this year's GMI roundtable meeting. Probabilistic treatment for suspected *N. meningitidis* cases relies on the effective use of antibiotics, with beta-lactam agents often being prescribed. It is well documented, however, that invasive *N. meningitidis* species are becoming more resistant to such treatments.[53] Resistance to this specific class of antibiotics is rarely due to beta-lactamase producing meningococci.[54] More frequently in *N. meningitides*, mutations in penicillin-binding proteins within bacterial species may also limit the effectiveness of penicillin and are the leading cause of reduced susceptibility among meningoccoci.[55] Although extremely rare among meningococci, beta-lactamase is an ongoing source of concern, with recent WGS analysis identifying the presence of a ROB-1-type beta-lactamase gene more typically found in *Haemophilus influenzae*. [53,55]

In Australia, an annual report monitoring the antimicrobial susceptibility of IMD isolates ($n = 210$), indicated that 1.4% ($n = 3/210$) were resistant to penicillin (minimum inhibitory concentration [MIC] ≥ 1 mg/L) with a decreased susceptibility (MIC 0.06–0.5 mg/L) to penicillin observed in 93.8% ($n = 197/210$). The three penicillin-resistant isolates were all from Queensland, with 2 being attributed to MenW and 1 to MenC.[56] Penicillin-resistant *N. meningitidis* isolates have also been detected in Thailand and Bangladesh; albeit to a lesser degree than those found in Australia (Thailand: isolates were resistant to penicillin with a MIC $\geq 0.125\ \mu$g/mL).[57]

Antimicrobial resistance across the Asia-Pacific region is not exclusive to beta-lactam antibiotics. A ciprofloxacin-resistant strain of MenC (cc4821) that emerged in China[20] has now been identified in both Canada and Japan.[58,59] Resistance to fluoroquinolones has been linked to mutations in the *gyrA* and *parC* genes in *N. meningitidis* isolates.[60] Owing to the spread of this clonal complex, there is the potential for the strain to reach sub-Saharan Africa. This, in turn, may pose issues in the Kingdom of Saudi Arabia where ciprofloxacin is used as a prophylactic treatment for people making the pilgrimage from the meningitis belt to Makkah (Mecca) during the Hajj.[61]

Sequence analysis and whole genome sequence surveillance across the Asia–Pacific region

Sequence analysis is applicable for many targets and offers highly transportable data. Whole genome sequence (WGS) analysis is being utilized in several countries within the Asia-Pacific region to analyze outbreaks, population structures, and the emergence of new strains.

Australia

Under current practice in Queensland, Australia, pathology laboratories will test specimens for *N. meningitidis* by either culture or PCR samples. Positive specimens or isolates are then sent to the Queensland Public Health Microbiology laboratory, as the state Neisseria reference laboratory, for further testing.[62] The laboratory has extensive experience in WGS and national accreditation for high-throughput sequencing, which can process a large number of DNA sequences in parallel (known as massively parallel sequencing). Similar testing workflows occur in the other states and territories of Australia, with varying levels of WGS in use. Surveillance in Australia for *N. meningitidis* is coordinated nationally through the National Neisseria Network (NNN), which includes molecular genotyping generated in silico from genomic data for several states

WGS for surveillance of *N. meningitidis* at the Queensland Public Health Microbiology laboratory has assisted in better understand-

Table 1
Overview of the epidemiology and prevention of IMD across the Asia–Pacific region.

Region/ country	Surveillance system (Y/N)	Epidemiology (key points)	Control strategies (vaccines only)
Philippines	Y	• 0.02–0.1 cases/100,000 persons/year, with ~100 cases/year and no seasonal variation • CFR is highest among infants and young children ~≥50% • Between Jan–Jun 2019, there were 130 IMD cases and 68 deaths, according to the Department of Health • Serogroup B was the most prevalent in blood and CSF PCR surveillance testing (68% of cases) (2017–2018)	• Vaccines are available, but only privately, and not included in the NIP • The MenACYW-135 vaccine is only recommended for children >9 months old at high risk of IMD (e.g., HIV positive; persistent complement deficiencies; travelers moving to an epidemic region)
China	Y	• Overall incidence of IMD is low (<0.1 cases/100,000 persons/year) • CFR is considered high at >10% • Since 2005, serogroup B (cc4821) cases have been increasing, as well as W (cc11). Serogroup Y cases (cc23; cc175) have also increased • A ciprofloxacin-resistant clonal complex within serogroup C (cc4821) has also emerged and spread across at least 18 countries	• Both MenA and MenAC polysaccharide/conjugate vaccines are incorporated into the NIP for children • Children (6–18 months): Two doses of MenA. Subsequent MenAC dose at 3–6 years • The MenACYW polysaccharide vaccine is available, but will need to be paid for by the parents
Japan	Y	• 0.028 cases/100,000 persons/year (2014)[139] • Average CFR ~15% (April 2013–June 2018)[140] • Serogroups Y, C and B are the predominant bacterial variants, with serogroup Y accounting for ~45% of reported IMD cases[142] • There are low rates of carriage across Japan (0.4–0.8% of the population)	• The MenACWY conjugate vaccine is licensed, but not included in the NIP
Australia	Y	• 1.1 cases/100,000 persons (2018)[141] • 281 IMD cases in 2018, with 16 deaths reported[141] • CFR was 6% in 2018, compared with 10% in 2,017,[142] • Serogroups B, W and Y are the predominant serogroups across Australia[142] • MenB remains prevalent among adolescents (15–19 years) and infants[142]	• MenACWY conjugate vaccine is funded for 1 year olds and14–19 year olds under the NIP • There is a state government funded 4CMenB vaccination schedule in South Australia • The 4CMenB vaccine will soon be included in the NIP for Aboriginal and Torres Strait Islander children up to 2 years of age
New Zealand	Y	• Notification rate was 2.3/100,000 persons in 2,019,[143] • MenB, W and Y are the predominant serogroups[143] • Most cases are among those <1 year[143] • CFRs were 7.9%, 12.8% and 8.3% for serogroups B, W and C, respectively, between 2014 and 2,019,[143]	• No meningococcal vaccines included in the NIP • MenC and MenACWY conjugate vaccines are recommended for certain high-risk groups (e.g., HIV positive, complement deficiencies)
Nepal	N (cases of acute encephalitic syndrome are recorded)	• 9 clinically suspected meningitis cases linked to meningococci (2.3% of CSF samples) between 2017 and 2018[144] • All *N. meningitidis* isolates belonged to serogroup A[144] • Between 1982 and 1984, there was a 3-fold increase in meningococcal meningitis cases in Kathmandu. This declined after the introduction of a mass vaccination campaign[145]	• Vaccination is not included in NIP • Vaccination with bivalent ($A+C$) or quadrivalent (A, C, Y and W) meningococcal vaccine is recommended for people at risk
Myanmar	N	• There have been five IMD outbreaks since 1990 • IMD occurs sporadically throughout Myanmar, with 34 deaths in a total of 391 cases since 2000 • Both serogroups A and B were detected in recent outbreaks	• Vaccination not included in NIP • MenACWY conjugate vaccine is commercially available, but expensive (~$70 per dose)
South Korea	Y	• 0.05 IMD cases/100,000 persons in 2014.[146] Estimated annual incidence is 2.2 cases/100,000 persons in the Korean Army[13] • Highest incidence among young infants (0–4 years) • Serogroup B and C are the most common meningococcal carriage isolates among Korean adolescents; although serogroup distributions are consistently changing[18] • IMD remains an under-recognized disease in South Korea based on the limitations of culture surveillance methods	• There is a mandatory vaccination program in place for Korean Army recruits, which includes a meningococcal vaccine

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Table 1
Overview of the epidemiology and prevention of IMD across the Asia–Pacific region.

Region/ country	Surveillance system (Y/N)	Epidemiology (key points)	Control strategies (vaccines only)
Malaysia	N	• There is limited data in Malaysia on MD epidemiology • In Sarawak, a Malaysian state, there was a peak in the number of meningococcemia cases ($n = 7$). In 2018, there were four meningococcemia cases	• Meningococcal vaccination is not routinely recommended and there is no formal record on vaccination in private clinics • Since 1988, Malaysian Hajj pilgrims have received a bivalent MenAC vaccine
Bhutan	N	• There is limited surveillance data on IMD in Bhutan • Outbreaks of meningococcemia occurred in 1985, 2012 and 2016, with two positive blood culture cases in 2018 and 2019	Meningococcal vaccines are not included in the NIP
Thailand	Y	• Incidence was 0.04 cases/100,000 persons in 2019. Incidences are generally higher in young infants (0–4 years)[147] • Serogroup B was the most common serogroup among cases (1994–1999: 56.3%)[147] • CFR peaked at 37.5% in 2012 for meningococcal meningitis (2006–2015 data)[147]	• Meningococcal vaccination not recommended within NIP, but is recommended for those attending a mass gathering or those with a complement deficiency
Taiwan	Y	• IMD incidence: 0.008–0.192 cases/100,000 persons (1993–2019)[148] • Between 2004–2018, serogroup B was the most common *N. meningitidis* serogroup (88% of cases; 99/113) • Both the cc32 and cc4821 clonal complexes were most common among isolates,[149] with B:cc32 being linked to a IMD outbreak in a high school and B:cc4821 at a military camp	• No routine vaccination • Only recommended in contracted hospitals or clinics for high-risk groups (pilgrims; those in high-risk areas)
Cambodia	N	• No official data on meningococcal infection in Cambodia • There have been two cases in Calmette Hospital (culture-confirmed) • 8 culture-confirmed cases in 2012 at one non-governmental organization (NGO) hospital	• Meningococcal vaccination not included in the NIP • However, a MenACWY conjugate vaccine is used at the IPC's vaccination center
Vietnam	Y	• Following an outbreak of IMD (serogroup C) from 1977 to 1979, there have been sporadic serogroup C cases in Ho Chi Minh City (2006 and 2012) • Since 2012, serogroup B has been detected in IMD cases • A carriage study among military personnel in 2015 indicated carriage rates of between 30% and 40% (serogroups B and C)	• A meningococcal vaccine is not included in the Expanded Programme on Immunisation • Only small communities in cities may be recommended for vaccination
Singapore	Y	• Incidence is ~0.2 cases/per 100,000 persons/year, with 1.6 cases/100,000 persons in young infants (0–4 years)[150] • Since 2004, serogroup B has been the predominant serogroup among IMD cases[150]	• There is no formal control strategy in place due to the country's low incidence of IMD • MenACYW is recommended in the national guidelines for travelers, pilgrims, immunocompromised patients, overseas students and close contacts • MenB vaccination is to be included in the 2020 guidelines
Bangladesh	Y (small-scale and only among the pediatric population)	• Limited and sporadic data on IMD incidence in Bangladesh (~1 case/100,000 persons [based on one meta-analysis]) • There was a potential outbreak in 2003–2004 (serogroup A) • 349 cases of sepsis and meningitis over the past 25 years, which have been attributed to *N. meningitidis* • Majority of cases occur in children <1 year • Serogroup B is the most prevalent serogroup in IMD, with a median age of 5 months. Between 1994 and 2009, serogroup A was the most prevalent (median age: 36 months) • Many clonal complexes of serogroup B are in circulation in Bangladesh, with several sequence types being specific to the country	• Two MenB vaccines are available in Bangladesh, but coverage is low (~25% of the population)

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Table 1
Overview of the epidemiology and prevention of IMD across the Asia–Pacific region.

Region/ country	Surveillance system (Y/N)	Epidemiology (key points)	Control strategies (vaccines only)
Indonesia	N	• 1995–1996: *N. meningitidis* cause of meningitis in 16.7% of bacterially-confirmed cases in children <5 years[151] • 1998–2002: *N. meningitidis* detected in 17.6% of culture-positive meningitis cases in children <2 years[152] • Outbreak of 14 cases of meningococcal meningitis with 6 deaths in 2000 (lab-confirmed *N. meningitidis* serogroup B in one case)	• MenACWY conjugate vaccine no longer available due to religious concerns • MenB vaccines are also not available • No children <2 years receive a meningococcal vaccination • All Hajj and Umrah pilgrims, as well as migrant workers and students going abroad, should be vaccinated
India	Y	• 10 cases of *N. meningitidis* from invasive bacterial disease isolates at the Christian Medical College in Vellore, between 2014 and 2019	• No information available on vaccination strategy

CFR, case fatality rate; CSF, cerebrospinal fluid; IMD, invasive meningococcal disease; NIP, National Immunization Program; MenAC, meningoccoal serogroups A and C; MenACWY, meningococcal serogroups A, C, W and Y; MenB, meningococcal serogroup B; MenC, meningococcal serogroup C.

ing of IMD, including an unusual serogroup found to have caused a number of IMD cases in Queensland (serogroup E) (E:P1.21–7,16:F5–36:ST-1157 [cc1157]).[63] Genomics also assisted in characterizing isolates from a cluster of *N. meningitidis* (predominantly serogroup C) cases in Queensland, where the single serogroup Y case within this cluster was confirmed as not being the product of a capsular switch via MLST.[64]

IMD isolates or sequences from 2017 to 2018 were provided by all NNN laboratories across Australia to the Microbiological Diagnostic Unit (Doherty Institute, University of Melbourne). A coordinated genomics analysis was performed, producing national reports important for understanding the changing epidemiology of IMD in Australia, particularly the emergence of MenW.

China

Prior to the introduction of the MenA polysaccharide vaccine in the 1980′s, MenA was the most predominant serogroup causing IMD in China between the 1950s and 1980s, with sequence types including ST-3, ST-5 and ST-7.[26] Recent genotypic analyses have elucidated a capsular switch in an ST-7 lineage from MenA to serogroup X (MenX).[65,66] Between the donor and recipient strains, eight potential recombination sites were identified, indicating the capsular switch occurred through a recombination involving 8540 base pairs spanning from the *ctrC* to the *galE* genes.[65] It has also been shown this switch can occur at high frequency (6.3×10^{-6} per bacterium per μg of DNA).[66]

A MenC cc4821 hyperinvasive strain has increasingly been isolated since 2003[67] and cc4821 has also been identified among MenB isolates. Capsular switching between the two serogroups is well documented.[68] A recent study on the lineage of serogroup B (cc4821) indicates the hyperinvasive MenC strain is the likely origin, with a characterization of the outer membrane protein genes showing the two serogroups have similar genotypic profiles.[67]

A recent collaboration between China and the UK has probed the genetic relationship of cc4821 isolates across 11 countries using the PubMLST database. The underlying population structure shows that cc4821 isolates from countries outside of China are more closely clustered, with the Chinese isolates being more genetically diverse.

A phylogenetic analysis of serogroup W ST-11 complex [MenW:cc11] isolates from China indicated that two Chinese subclusters are closely related to, but distinct from, the MenW:cc11 Hajj-strain and South American strain sublineages currently causing IMD elsewhere around the world (as indicated in Fig. 1).[69]

The global spread of cc11

An update on the global spread of cc11 was provided during the GMI meeting highlighting (i) the presence of the MenW:cc11 Hajj strain sublineage in Russia and Bangladesh, (ii) the MenW:cc11 South American strain sublineage in Russia, Japan and New Zealand, (iii) the MenW:cc11 Chinese strain sublineage in China and Japan, and (iv) a further distinct MenW:cc11 strain in Bangladesh.

The expansion of a penicillin resistant sublineage of the original UK strain of the MenW:cc11 South American strain sublineage that was first identified in Australia was demonstrated to include countries in Europe, North America, and the Asia-Pacific region including Japan and New Zealand. Additionally, a ciprofloxacin-resistant strain of MenW:cc11 has been identified in China.

Mapping out a course to defeat meningitis and raise awareness

Defeating meningitis by 2030: a global roadmap

There are an estimated 300,000 deaths per year due to bacterial meningitis across all age groups.[70] Disease is also resulting in a number of sequelae, including neurological complications.[71]

In 2017, a global meeting, which involved governments, public health experts and health organizations, convened to outline a vision to ‘defeat meningitis by 2030′.[72] The overarching goals are to: (i) Eliminate bacterial meningitis epidemics; (ii) Reduce cases and deaths from vaccine-preventable bacterial meningitis; (iii) Reduce the risk of disability and improve quality of life.

A global roadmap has been outlined to achieve this vision.[73] Three types of phased activities form the roadmap: (i) Set up a technical taskforce designed to develop the roadmap; (ii) Conduct a baseline situation analysis to identify critical gaps and research advances; (iii) Conduct an iterative consultation process to establish consensus through technical and public consultations. As part of the baseline analysis, several gaps have been identified, which include a sub-optimal use of vaccines globally; a lack of vaccine access; and an inability to control *N. meningitidis* epidemics partly as a result of insufficient laboratory capacity.

The next steps as part of the global roadmap are to develop a business case, identify research priorities and enter into regional engagement.

Advocacy and vaccine hesitancy considerations for the Asia–Pacific region

In 2017, the Philippines withdrew a dengue vaccine due to questions over its safety.[74] Concerns surrounding the vaccine then

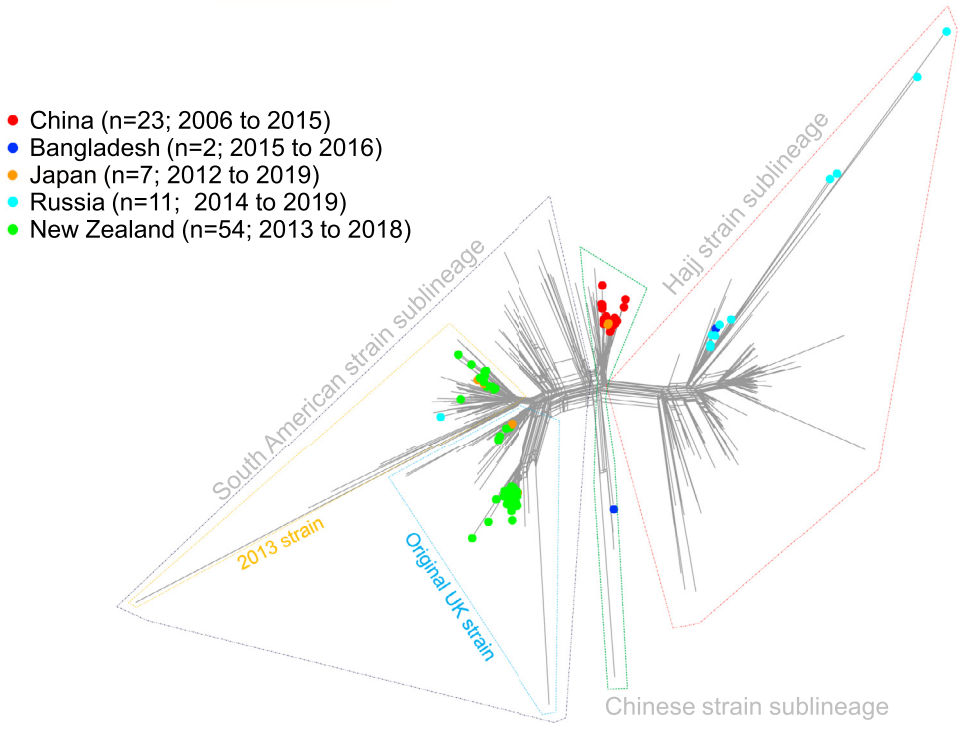

Fig. 1. Distribution of Asian/Asia-Pacific and Hajj-/South American strain-sublineage genomes.

spread more widely and without basis to vaccine safety in general, fueled by a combination of genuine concern and misinformation. This ultimately led to lower measles vaccine uptake, which was not the original vaccine under question.

This case highlights the complex nature of the rising impact of vaccine hesitancy that has led WHO to identify it as one of the top 10 threats to global public health. The concept involves an interconnected set of issues including concerns about adverse events and safety; misinformation spread either intentionally or unintentionally; vaccine access; as well as cultural, religious, and sociodemographic perceptions and attitudes.[75] Assuming vaccine hesitancy is only synonymous with intentional misinformation spreading alone is therefore inaccurate, even though this factor is important.

All genuine barriers to uptake of vaccines, including hesitancy, need addressing if vaccines are to reach all those that need them and advocacy has a critical role to play across all aspects. The Confederation of Meningitis Organisations (CoMO) has developed the 'change equation' to identify the key elements that support successful vaccine advocacy that influences national policy.[76] The model identifies three factors; compelling patient stories; health professionals and spokespeople who communicate well; and the effective use of compelling evidence and data as key to success. Such advocacy models can be applied at international, regional and national levels, and can be adapted to the intended audience.

Unusual transmission of meningococci

Transmission through saliva

It is well established that *N. meningitidis* is transmitted from person to person via air-borne droplets or through contact with respiratory secretions,[77] with various risk factors being associated with carriage and disease (e.g., attending pubs or clubs, intimate kissing and cigarette smoking).[78] However, other studies have indicated that sharing drinks or food items with others, leading to the potential transfer of saliva, may increase the risk of epidemic meningococcal disease.[79] Despite this, prophylaxis guidelines for those who have shared drinks with a confirmed IMD case vary globally.

Meningococcal transmission through saliva has previously been reported. In these cases, two patients were diagnosed with primary meningococcal conjunctivitis following incidents in which a person had spat directly into their eye.[80,81] In the more recent case, the patient cultured a MenC isolate.[82] Both patients were given chemoprophylaxis, which is in line with the current recommendations for primary meningococcal conjunctivitis treatment.[82] However, as meningococcal carriage in pure saliva has previously been documented to be extremely low (0.4%),[81] transmission in these cases may have been via oropharyngeal secretions contained within the spit.

Despite ongoing debate about the source of infection in these cases, previous studies have found *N. meningitidis* within saliva. A study on the salivary flora of 50 school children (7–12 years) in Scotland showed that *N. meningitidis* was present in 2 salivary samples, with a mean surface viable count of colony-forming units between 1×10^5 and 5×10^5 counts per mL.[83] For comparison, pneumococci was found in saliva at the order of 9×10^4 counts per mL.

Detecting bacterial species is dependent upon the sampling method utilized, as well as the site swabbed. A recent study used swab sampling to collect saliva, tonsil and nasopharynx samples from 258 students in England. There was a high prevalence of meningococci ($n = 83$;32.2%) among the nasopharynx samples compared with low detection in the saliva swabs ($n = 1$;0.4%), suggesting that low levels of salivary contact are unlikely to transmit meningococci.[84] In the B Part of It study, saliva drool samples and oropharyngeal swabs were taken from 239 university students in Australia. Based on these data, there was a slightly higher proportion of carriage detected in the oropharyngeal swabs ($n = 16$;6.2%) compared with the saliva samples ($n = 13$;5.4%).[85] Tzeng et al. reported survival of *N. meningitidis* A, B and C strains is for up to

3 days dried on glass, plastic or metal and concluded that encapsulation did not confer greater survival. This suggests that salivary transfer through bottle sharing and eating should be considered.

Ano-genitourinary transmission

The meningococcus and the gonococcus, the two pathogenic *Neisseria*,[86] are part of the same genus, but have clinically distinct characteristics. Meningococci mainly infect the oro/nasopharynx, with gonococci mainly infecting the ano-genitourinary tract. There have, however, been numerous reports of diverse meningococci sampled from ano-genitourinary sites.[87,88] In the past decade or so, invasive outbreaks among men who have sex with men (MSM) in Europe and North America have been caused by a particular cc11 lineage 11.2 strain expressing PorA P1.5–1,10–8. In high-resolution genomic analyses, the isolates responsible for different outbreaks were interspersed with IMD cases from the wider community. Co-clustering of MSM IMD outbreak isolates with urethritis and proctitis isolates at a local level, however, suggest a possible sexual transmission component to the MSM outbreaks. In addition, the corresponding isolates exhibited distinct adaptations to the ano-urogenital niche, including the ability to grow anaerobically and in the case of the urethritis/proctitis isolates, the loss of a functional *fhbp* gene.[89,90]

Around 2015, in the USA, the emergence of a closely related sub-strain (US_NmUC) has caused a large multi-state outbreak of urethritis, predominantly among heterosexual males who have recently participated in oral sex.[91,92] The strain responsible also exhibits gonococcus-like adaptations to the ano-urogential site, including the loss of the polysaccharide capsule and the ability to grow anaerobically having acquired a gonococcal nitrite reductase allele.[93]

The broad lineage 11.2 PorA P1.5–1,10–8 strain remains of particular concern owing to the ongoing occurrence of invasive disease outbreaks among MSM, its potential to cause invasive disease in immunocompromised individuals, its potential for the acquisition of antibiotic resistance from gonococci, and a general propensity to escape capsular and subcapsular vaccines. The recent arrival of the US_NmUC strain in the UK in 2019 was reported.

Mass gatherings and the potential transmission of meningococcal disease

Mass gatherings are an integral part of society, with festivals, sporting events and religious meetings taking place globally every year. The congregation of large groups of people into a confined area carries both logistical implications and public health risks, particularly with the potential transmission of invasive diseases, including IMD.

The Kumbh Mela

The Kumbh Mela is a major Hindu festival that is celebrated every 12 years at sites along the Ganges, the Shipra and the Godavari rivers in India, with vast tent cities built along the riverbanks. Although a large-scale gathering, the Kumbh Mela is regarded as a domestic festival that attracts up to 80 million travelling pilgrims.[94] There have not been any recorded outbreaks of IMD at the festival, but there have been several meningococcal serogroup A outbreaks in northern India.[95] Crowded conditions at the Kumbh Mela may be conducive to IMD transmission. In addition, some pilgrims may not be immunized, based on previous evidence that 56% of children in India (1–2 years) are not immunized or are only partially immunized.[96]

The Russ celebration

The Russ celebration (Norwegian: “Russefeiring”) is an annual event where graduating high school students celebrate the end of their school year in the spring semester. The event involves partying and the consumption of alcohol. In Norway, IMD incidence is generally considered low, with serogroups Y, B, W and C (reflecting order of prevalence) in circulation. However, in 2010 there was a peak in IMD incidence (specifically, serogroups B, C, Y and W) among Norwegian adolescents (16–19 years), with an incidence of 6 cases/100,000 persons.

Attendance at the Russ celebration is one risk factor associated with meningococcal carriage among Norwegian adolescents (odds ratio [OR]: 2.85; 95% CI: 1.62, 5.02). Other risk factors include sharing bottles (OR: 1.39; 95% CI: 0.69, 2.79), kissing (OR: 2.73; 95% CI: 1.58, 4.70), partying (OR: 3.50; 95% CI: 1.45, 8.48), and the consumption of smokeless tobacco (OR: 1.56; 95% CI: 1.07, 2.27) – a factor that is perhaps unique in Scandinavia.[97]

In Norway, there are now meningococcal vaccination recommendations in place for teenagers (16–19 years) involved in high-risk activities, including the Russ celebration. However, there remains debate as to whether this vaccination should be included in the NIP.

Funerals

Certain funerals, such as those of political or religious leaders, may result in mass gatherings that can pose a potential risk for IMD transmission; although, there is a low number of reported cases in the literature.

A number of suspected cases and deaths were reported following the funeral of a religious leader in Sinoe County (Liberia), held on April 21–22, 2017. The subsequent day, a girl (11 years of age) experienced vomiting, diarrhea and mental confusion. Over the next two weeks, there were another 31 reported cases, with 13 deaths. All cases were linked to the funeral, with the US Center for Disease Control (CDC) using PCR to confirm 13 cases as meningococcal serogroup C.[98] In six out of 10 specimens subsequently analyzed via metagenomics, there was the presence of a strain with 91–98% similarity to ST-10,217, which previously caused meningococcal disease outbreaks in Niger and Nigeria.[99]

The World Scout Jamboree (Japan, 2015)

In 2015, there were six confirmed IMD cases following the 23rd World Scout Jamboree (WSJ) held in the Yamaguchi prefecture, Japan.[100] During the event, there were 33,628 scouts (14–17 years) in attendance from 155 countries. Three Scottish scouts and one parent, along with two Swedish scouts contracted IMD; all cases were reported to public health agencies following the event. All six cases were attributed to the same serogroup W strain (ST-11).[100] Genomic analysis indicated that this strain was identical to a strain that had recently emerged in the UK; as a consequence, it is likely this ST-11 strain was introduced from abroad to the WSJ.[101]

There was also a potential transmission of MenW during an international flight following the WSJ. In October 2015, an IMD case and a carrier were reported in Osaka City (a married couple that were on the same return flight as the Scottish scouts).[102] ST-11 was detected in synovial fluid of the wife, who reported a fever, as well as arthritis in her right knee (later diagnosed as thrombocytopenia).

This particular outbreak demonstrates how such events can occur even in countries with a historically low incidence of IMD. It is important that organizations have a working understanding of IMD incidence in other countries who may be participating in a mass gathering.

Table 2
Rates of carriage among pilgrims before and after the Hajj, as well as close household contacts (post-Hajj), taken from several studies.[104]

Population	Year	Overall (%) Pilgrims	Pre-Hajj (%) Pilgrims	Post-Hajj (%) Pilgrims	Household contacts	Antibiotic use (%)
USA	1987	–	–	11.6	–	15
Singapore	2001	8	0.5	17	8.2	41
8 countries	2001	9.2	8	10.4	–	–
USA	2001	1.9	0.9	2.6	–	15–44.8
Thailand	2001	–	–	0	–	–
Singapore	2001	–	–	16.4	11.1	Some
Singapore	2002	1.7	2.6	1.3	–	53
UK	2002	7.5	8.3	6.3	12.9	21
29 countries	2003	3.2				12.8
Iran	2003	4.9	5.2	4.6	–	>58.2
14 countries	2009	7.3	6	11	–	–
Turkey	2010	18.7	13	27	25.6	–
Iran	2012	0.7	0	1.4	–	58.5
France	2012–13	0	0	0	–	
Australia	2014	–	0	0.5	–	17.2
14 countries	2014	–	3	1.4		

The Hajj

The Muslim pilgrimage to Makkah, the Hajj, is one of the largest and most ethnically diverse annual mass gatherings in the world. During the pilgrimage, people are in heavily over-crowded conditions and live in close proximity to one another (>2 million pilgrims). A large proportion of those attending are elderly or have underlying health conditions, with respiratory tract infections being very common (up to 80% suffer from a cough during the Hajj).[103]

There are multiple factors to consider for IMD outbreaks during the Hajj, which include: carriage and transmission, disease, and prevention. The carriage rate among pre-Hajj pilgrims is low compared with post-Hajj carriage.[104] However, the percentage of carriers is generally high among household contacts following the Hajj (8.2–25.6%), as indicated in Table 2. [104] These individuals may not be vaccinated and are considered at risk. Since the 2000 international Hajj-related meningococcal disease outbreak, serogroup W has been one of the most prevalent strains among pilgrims following the Hajj, with serogroup B cases also increasing.[104]

There have been several outbreaks of IMD in Saudi Arabia over the past three decades, with the three most prominent occurring in 1987 (1841 cases), 2000 (338 cases) and 2001 (316 cases).[105] The main circulating serogroup in the latter two instances was W, which subsequently led to a global outbreak and the international spread of the disease.[105–107] However, there have been no recorded cases of IMD in Makkah since 2006.[105]

Based on the size of the Hajj and the potential for IMD outbreaks, there are a range of preventative measures to limit disease transmission. These include vaccination, targeted/mass chemoprophylaxis, health awareness campaigns, and an active surveillance system.[61] Vaccination is a visa requirement for all visitors entering the Kingdom of Saudi Arabia for the Hajj. Those visitors who fail to provide a vaccination certificate at a point of entry or who were vaccinated less than 10 days prior to arrival in Saudi Arabia are given chemoprophylaxis to eliminate carriage and are allowed to participate in the Hajj.[108] This specific vaccination is also required for domestic pilgrims, Medina and Makkah residents and any person in potential close contact with pilgrims (e.g., healthcare workers).[108] Antibiotic prophylaxis is also a possibility for those pilgrims travelling from a country with frequent meningococcal meningitis epidemics.

Across various countries, the reported uptake rate for conjugate or polysaccharide vaccines is very high among pilgrims.[61] However, a number of potential barriers remain for vaccine uptake.

Barriers to vaccination

The Hajj

As discussed, the Hajj is a large religious mass gathering in Makkah, with a sizable at-risk population (at least 25% of pilgrims are >65 years old, many with underlying health conditions).[109] A significant proportion of the pilgrims also have a low level of education or health literacy.[110,111] As mentioned previously, meningococcal vaccine uptake remains generally high among Hajj pilgrims, particularly in recent years;[60] however, there have been very low rates reported for pneumococcal vaccination (1.2–11.3%).[112] There is also a discrepancy between certified and self-reported vaccination, as the latter tends to be appreciably higher than rates confirmed through certification.[113]

Multiple barriers to vaccination uptake exist among the Hajj population. One of the most common reasons is a lack of knowledge about vaccines,[114] with some pilgrims being unaware that there is a vaccine available.[115] Equally, availability is an ongoing issue as vaccine shortages are a possibility.[13] Cost is also cited as a reason for not receiving a vaccine,[114] but pilgrims will receive a vaccination if the cost is low or free. In France, 100% of pilgrims accepted a proposed diphtheria, tetanus and pertussis vaccination when it was offered for free upon attending their travel clinic for mandatory vaccinations.[116]

In general, a small proportion of pilgrims do not want to be vaccinated owing to misconceptions regarding immunization, such as vaccines weakening the immune system and not being safe.[117] There has also been evidence of certain Muslim communities refusing vaccination on religious grounds;[118] although, the Islamic faith generally recognizes vaccination as a means to protect life.[119]

Religious grounds

Most religions do not offer formal advice on vaccination, with vaccine refusal often centering on personal religious beliefs or safety concerns among small denominations. However, the major religious faiths, including Catholicism, Islam and Hinduism, generally hold no objections to vaccination as a concept.[120]

Despite the lack of resistance to vaccination, there has been 60 outbreaks of vaccine-preventable disease reported in religious settings.[120] Such outbreaks often occur within small religious communities or sects across Canada and the USA. These outbreaks include, but are not limited to, measles, with 400 cases in British Columbia

(linked to the Netherlands Reformed Congregation); >2499 cases in the Dutch 'Bible Belt'; and >500 cases connected to Orthodox Jewish communities in New York.[121–123] As the latter community does not prohibit vaccination as part of their religious doctrine, the reasons behind this outbreak remain somewhat unclear.

In the case of the Dutch 'Bible Belt', a few hundred thousand orthodox protestants, part of the Dutch Reformed Church, object to vaccination. This initially stemmed from a fear of adverse events, but has developed into a link with religious doctrine.

Vaccine components are another concern for certain religious groups. For instance, whether a vaccine is Halal is a legitimate issue for some in the Muslim faith, with Islamic law prohibiting medicines from 'haram' sources (i.e., containing ingredients with porcine elements or relevant derivatives).[124] It is considered the most important factor for vaccine acceptance in Muslim-majority countries,[125] which is borne out through examples of certain vaccines being declared 'haram' by Islamic leaders. This was the case in 2018, when the Indonesian Ulama Council in Jakarta made such a declaration against a measles and rubella vaccine. This impacted the success of a mass immunization campaign, launched by the Ministry of Health, to vaccinate 67 million children aged 9 months to 15 years.[126] The first phase of the campaign in 2017 was a success, with Java reaching the 95% coverage target. However, since the ruling, coverage on other islands has been lower, reaching only 68% so far.[126]

To improve vaccination uptake, it remains critically important for governments, health officials, and religious leaders to educate and inform the public on the benefits of vaccination. The recent Dakar Declaration on Vaccination states that vaccination is not in contravention of Islamic law.[127] However, the impetus should be placed on tailor-made and targeted education in different countries, which involves local religious leaders.

Groups at risk of invasive disease

Occupational risks

Various forms of employment may carry a certain risk of being exposed to invasive bacteria; particularly among those handling specimens in a laboratory setting. A safety cabinet should always be used when preparing and handling specimens of meningococci.[128,129] In the UK, Public Health England staff working with meningococci are offered MenACWY conjugate vaccine, with boosters every 5 years, as well as two doses of 4CMenB. However, immunization is seen as the 'last line of defense'. Any staff who are potentially exposed to live meningococci are prescribed ciprofloxacin prophylaxis, even if the worker is fully vaccinated. Such protocols may vary in other countries.

Other occupations, which are not associated with laboratory work, also carry a risk of meningococcal exposure and carriage or progression to IMD. Although there is limited direct evidence, coal miners may be at risk of exposure to *N. meningitidis*. A recent study found a positive correlation between meningococcal meningitis rates and male occupation rates for coal mining in England and Wales during the national epidemic of 1931–1932.[130]

The risk of meningococcal disease may also be evident in other heavy industries. In 2010, there was an outbreak of meningococcal disease (serogroup C) among workers at an oil refinery in Paulinia, Brazil. Six IMD cases occurred among workers, with another 12 cases reported in the adjacent community of Cosmopolis in Sao Paulo state.[131] All isolates had the phenotype C:23:P1.14–6, with a close genetic relationship.[131] Ultimately, 15,848 workers at the refinery were vaccinated following the outbreak, with another 18,571 people offered a MenC conjugate or MenAC polysaccharide vaccine in the local community.[131]

Welders may also be at increased risk of meningococcal disease; although, this is based on limited evidence of an increased risk of pneumococcal disease in this population.[132,133]

Complement deficiencies

A proportion of patients with IMD may have a complement deficiency, ranging from 13% to 39%, according to numerous reports.[134,135]

The complement system is a crucial component of the humoral innate immune system. It comprises acute-phase proteins (19 plasma and at least 9 membrane proteins), with concentrations fluctuating over time. The system serves as a link to the cellular innate immune system and to the adaptive immune response.[136]

The system is activated through three pathways: the classical pathway (C1, C2, C4); the lectin pathway; and an alternative (initial C3 convertase and downstream). These pathways converge towards a terminal pathway (C5 to C9).[137] The end product of the terminal pathway is the formation of a stable pore within bacterial cell membrane, leading to lysis. This system is tightly regulated to avoid damage to the self. Deficiencies in the terminal pathway are associated specifically with invasive *Neisseria* infections.[137] The incidence of these deficiencies varies worldwide but C9 deficiency is frequent among Japanese population (up to 1/1000).[138] The bacteria are also adept at evading complement-mediated killing through molecular mimicry, as well as phase and antigenic variation.[138]

Conclusions

The risk and burden of IMD across the Asia–Pacific region is relatively low, with a degree of surveillance in place. As described, however, monitoring practices vary and a minority of countries do not consider IMD a notifiable disease, which leads to underreporting. Irrespective of these discrepancies in practice, specific countries across Asia and the Pacific region have now implemented serotyping or genotypic/genomic analysis for case confirmation and strain tracking.

Based on available data, the incidence of IMD remains low across the region, with outbreaks predominantly occurring among certain sub-populations. However, the expansion of specific clonal complexes, particularly cc4821 and cc11, remains a source of concern as isolates have exhibited some level of non-susceptibility to antibiotics. The issue of antimicrobial resistance was consistently revisited during the GMI meeting.

In terms of IMD treatment and prevention, meningococcal vaccination is not included in the majority of NIPs across the region. However, specific vaccines do form part of national recommendations for high-risk individuals, be they travelers or those with complement deficiencies or HIV. Even so, there are a number of potential barriers to vaccine uptake, including cost, availability, a lack of knowledge or basic medical knowledge, as well as misconceptions surrounding vaccination. Religious beliefs may also conflict with vaccination; albeit to a small degree as most major religions do not oppose the strategy.

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