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Review

The everchanging epidemiology of meningococcal disease worldwide and the potential for prevention through vaccination

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SUMMARY

Neisseria meningitidis is a major cause of bacterial meningitis and septicaemia worldwide and is associated with high case fatality rates and serious life-long complications among survivors. Twelve serogroups are recognised, of which six (A, B, C, W, X and Y) are responsible for nearly all cases of invasive meningococcal disease (IMD). The incidence of IMD and responsible serogroups vary widely both geographically and over time. For the first time, effective vaccines against all these serogroups are available or nearing licensure. Over the past two decades, IMD incidence has been declining across most parts of the world through a combination of successful meningococcal immunisation programmes and secular trends. The introduction of meningococcal C conjugate vaccines in the early 2000s was associated with rapid declines in meningococcal C disease, whilst implementation of a meningococcal A conjugate vaccine across the African meningitis belt led to near-elimination of meningococcal A disease. Consequently, other serogroups have become more important causes of IMD. In particular, the emergence of a hypervirulent meningococcal group W clone has led many countries to shift from monovalent meningococcal C to quadrivalent ACWY conjugate vaccines in their national immunisation programmes. Additionally, the recent licensure of two protein-based, broad-spectrum meningococcal B vaccines finally provides protection against the most common group responsible for childhood IMD across Europe and Australia. This review describes global IMD epidemiology across each continent and trends over time, the serogroups responsible for IMD, the impact of meningococcal immunisation programmes and future needs to eliminate this devastating disease.

Introduction

Invasive meningococcal disease (IMD) is known for its rapid onset and poor outcomes, with case fatality rates reaching up to 80% in untreated cases and ranging from 4-20.0% with appropriate treatment.[1] More than a third of survivors of IMD also experi-

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Table 1
Currently licensed and available polysaccharide-conjugate and broad-spectrum meningococcal vaccines

Vaccine	Coverage (*N. meningitidis* serogroup)	Manufacturer	Protein conjugate
Protein conjugate vaccines			
Meningitec®	C	Nuron Biotech Inc., Exton, PA, USA	CRM197
Menjugate®	C	GlaxoSmithKline Biologicals SA, Rixensart Belgium	CRM197
NeisVac-C®	C	Pfizer Inc., New York, NY, USA	Tetanus toxoid
MenAfriVac®	A	Serum Institute of India Ltd., Pune, India	Tetanus toxoid
Menactra®	A, C, W, Y	Sanofi Pasteur SA, Lyon, France	Diphtheria toxoid
Menveo®	A, C, W, Y	GlaxoSmithKline Biologicals SA, Rixensart Belgium	Diphtheria cross
Nimenrix®	A, C, W, Y	Pfizer Inc., New York, NY, USA	Tetanus toxoid
Combination conjugate vaccines			
Menitorix®	C + *Haemophilus influenzae* type b	GlaxoSmithKline Biologicals SA, Rixensart Belgium	Tetanus toxoid
Subcapsular meningococcal antigen vaccines			
Bexsero®	B	GlaxoSmithKline Biologicals SA, Rixensart Belgium	-
Trumenba®	B	Wyeth Pharmaceuticals Inc., Philadelphia, PA, USA*	-

*a subsidiary of Pfizer Inc.

ence significant complications, with 9% having major life-long disabling sequelae.[2,3] In many areas of the world, the gold-standard method of active surveillance and laboratory confirmation with strain characterisation is not possible. Thus, different combinations of active and passive surveillance with variable diagnostic methods are used in different countries, making ascertainment of true IMD burden and comparison across regions difficult. Understanding the local epidemiology, trends over time and impact of various immunisation vaccination programmes is important not only in understanding how such programmes impact disease patterns but also to identify knowledge gaps and potential for further reductions in disease burden through additional preventive strategies as new, more effective and higher-valent meningococcal vaccines become available.

The responsible pathogen for IMD, *Neisseria meningitidis* (the meningococcus), is a Gram-negative diplococcus, an obligate human pathogen that commonly colonises the upper respiratory tract.[4] The meningococcal polysaccharide capsule is a major virulence factor and the foundation of the categorisation and nomenclature of the bacteria referred to as the serogroup.[4] There are 12 meningococcal serogroups: A,B,C,E,H,I,K,L,X,W,Y and Z. Half of these (A,B,C,W,X and Y) are responsible for almost all IMD cases globally, with great variation in serogroup by geographic region. IMD affects individuals of all ages, but the highest incidence is in infants and young children as well as older adults, where case fatality rates (CFR) are high, often due to underlying comorbidities.[5] Many, but not all countries also have a small peak in IMD incidence during late adolescence and early adulthood.[6] IMD commonly manifests as meningitis or septicaemia, or a combination of the two; less common presentations include pneumonia, septic arthritis, pericarditis, supraglottitis or epiglottitis.[7]

Meningococcal vaccines

Vaccination is the key method of IMD prevention. Vaccines containing the polysaccharide capsule of single or multiple meningococcal serogroups have been available for more than 40 years.[8] While these remain ineffective in young children, they have been proven to be immunogenic and safe in older children and adults. They are, however, unable to induce immunological memory and, therefore, have a short duration of protection with poor responses to booster doses.[8] Polysaccharide vaccines are still used, mainly in lower- and middle-income countries (LMICs), due to their low cost.[9] Polysaccharide-protein conjugate vaccines, on the other hand, use a carrier protein to present the meningococcal capsular polysaccharide to the immune system, in a manner that induces a T-cell mediated response.[4] As a result, these vaccines are immunogenic from birth, induce immune memory, protect for a longer duration and provide a booster response with subsequent doses.[10] In addition to providing direct protection in vaccinated individuals, protein-conjugate vaccines also prevent acquisition of carriage, thus disrupting transmission to others and inducing indirect (herd) protection across the population.[11] The different monovalent and multivalent conjugate vaccines currently available are summarised in Table 1. Both polysaccharide and protein-conjugate vaccines are available against serogroups A, C, W and Y; since these vaccines are composed of the polysaccharide capsule, they do not provide cross-protection against other meningococcal serogroups. Polysaccharide-protein conjugate vaccines against MenB, however, have been difficult to develop because its polysaccharide contains components that are similar to human foetal neuronal cells and are, therefore, poorly immunogenic with the potential to induce autoimmune antibodies.[12]

In the past, MenB vaccines have been successfully developed against specific outbreak strains using their outer membrane vesicles (OMV) where the immunodominant antigen is the Porin A (PorA).[13] Such vaccines, however, provide little cross-protection against other MenB strains with diverse PorAs.[14] A novel, multicomponent protein-based vaccine (4CMenB; GSK Biologicals) was licensed in the UK in 2013 and in the US in 2015, with the aim of providing broad protection against MenB disease. 4CMenB consists of three subcapsular recombinant protein antigens which include NadA (Neisserial adhesion A), NHBA (Neisseria heparin binding antigen) and fHbp (factor H binding protein) as well as the outer membrane vesicle of the New Zealand outbreak containing PorA 1.4 (NZ OMV).[15] 4CMenB protects against most but not all MenB strains causing invasive disease, with strain coverage ranging from 66% to 91% in different parts of the world.[16] Although the vaccine was licensed on immunogenicity and safety studies only, there is now robust evidence of its effectiveness and impact against IMD in the real world.[17,18] 4CMenB is, however, unlikely to provide any indirect (herd) protection as it does not reduce meningococcal carriage in teenagers.[19] Another MenB vaccine, rLP2086 (Trumenba, Pfizer), was licensed in the US in 2014 and in the EU in 2017. This vaccine is composed of two fHbp variants (variants 1 and 3 or subfamilies A and B) in a lipidated form, which is present in nearly all invasive MenB strains, but is currently only licensed from 10 years of age.[20] Countries and regions that have implemented a MenB vaccine are summarised in Table 2. Although only licensed to protect against MenB disease, both vaccines have the potential to protect against any meningococcal serogroup that possesses a vaccine-related surface antigen.[21,22] For the first time, therefore, we have effective vaccines against all the major meningococcal serogroups causing IMD worldwide. The MenB and MenACWY vaccines are being implemented in many countries, targeting different age groups and populations, depending on local epidemiology and local neces-

Table 2
Countries and regions that have implemented the meningococcal B (MenB) vaccine into their national immunisation programmes; currently, all countries are utilising 4CMenB in their programmes

Country	Year introduced	Routine recommendations	Reference
Andorra	2016	NIP: Infants (2+1 at 2moa)	Government of Andorra. 2016. Vaccination schedule. http://www.salut.ad/images/stories/Salut/pdfs/temes_salut/Targeto_Vacunes.pdf
Ireland	2016	Infants ≥2 months of age 2+1 vaccination schedule (at 2, 4 and 12 months)	https://www.hse.ie/eng/health/immunisation/pubinfo/pcischedule/immschedule/
Italy	2017	All infants ≥2 months to 2 years of age 3+1 vaccination schedule	http://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf
San Marino	2017	All infants ≥2 months to 2 years of age 3+1 vaccination schedule	http://www.iss.sm/on-line/home/vaccini-e-vaccinazioni/vaccinazioni-raccomandate.html
Lithuania	2018	All infants aged ≥2 months 2+1 vaccination schedule (at 3, 5, and 12–15 months)	https://e-seimas.lrs.lt/portal/legalAct/lt/TAD/f4a925d0f50f11e79a1bc86190c2f01a?positionInSearchResults=0&searchModelUUID=1561434a-b283-4be2-87f5-4f556ad37c32
UK	2015	Infants ≥2 months of age 2+1 schedule (at 2, 4 and 12 months)	https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/741543/Complete_immunisation_schedule_sept2018.pdf
USA	2015	Healthy adolescents/young adults aged 16–23 years (preferred age: 16–18 years) Category B national recommendation†	https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6441a3.htm, https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf, https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf
South Australia	2019	Infants, 1-4 year-olds and 15–20 years-olds	https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/about+us/reviews+and+consultation/meningococcal+b+program+for+south+australia

sity . In this review, meningococcal experts across different continents review the ever-changing epidemiology of IMD in their region, highlighting the successes of past and current meningococcal immunisation programmes and providing insight into potential future preventive strategies.

Europe

In Europe, the incidence of IMD has been declining since the early 2000s.[23] In 2017, there were 3,221 confirmed IMD cases reported to the European Center for Disease Control and Prevention (ECDC) by 30 EU/EEA countries, with an overall notification rate of 0.62 cases per 100 000 population. IMD incidence in Europe ranged from 0.45 (Northern and Southern Europe) to 1.33 (UK and Ireland) cases per 100,000 population (Fig. 1). There were 282 fatal cases reported, with a case fatality of 9.7% (Table 3). IMD incidence was highest in infants aged <1 year (8.2/100,000) followed by toddlers aged 1-4 years (2.5/100,000) and with a second peak in 15–24 year-olds (1.0/100,000).

MenB currently predominates in Europe, although MenW and MenY predominate in some areas (Fig. 2).[6] The introduction of MenC-containing vaccines in national immunisation programmes across Europe has resulted in a significant decline in the proportion of MenC-disease causing IMD in Europe, without affecting other serogroups.[24-26] Of the 2979 (92%) notifications with serogroup reported to ECDC, 51% were MenB (n=1527), followed by MenW (17%, n=511) and MenC (16%, n=485). However, MenY and MenW were main serogroups in the Northern EU region compared to MenB followed by MenC in the Central and Southern EU region; and MenB and MenW in UK and Ireland (Fig. 2).

In Europe, the highest IMD incidence was in the **Republic of Ireland** (1.48/100,000), while **the United Kingdom** had the highest number of confirmed cases reported (n=772) in 2017 (Table 1). Overall, IMD incidence in the UK and Ireland was more than twice the mean in Europe (1.33 vs 0.62/100,000). **In the UK,** IMD is a notifiable disease in all four nations (England, Scotland, Wales and Northern Ireland), each with their own surveillance for IMD. In England, Public Health England conducts IMD surveillance nationally and maintains consistently high case ascertainment through its national reference laboratory.[27] Scotland,[28] Wales.[29] and Northern Ireland.[30] all have surveillance systems in place and provide regular updates on IMD epidemiology online.

In 1999, the UK was the first country to introduce a MenC conjugate vaccine to control a national outbreak of invasive MenC disease due to a hypervirulent strain belonging to clonal complex 11 (MenC:cc11).[31] Many other countries followed suit, resulting in large and sustained declines in MenC disease across Europe.[24-26] Since 2009/10, the UK has been experiencing a national outbreak of MenW:cc11, which initially originated from South America.[32] By 2014/15, MenW was responsible for 24% of all IMD cases across England, associated with severe disease and fatalities across all age groups.[33] This led to the emergency implementation of a MenACWY conjugate vaccine programme for 13-18 year-olds in August 2015 to provide direct protection to teenagers and, over time, indirect (herd) protection across the population. After the first year, there were 69% fewer MenW cases than predicted by trend analysis in MenACWY-eligible adolescents and no cases in the vaccinated cohorts.[34] Other European countries have reported increases in MenW cases since 2014/15, many of them also recommending MenACWY vaccination in different age groups.[35] Up-to-date recommendations for meningococcal vaccination across different European countries can be found on the ECDC website: https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=48&SelectedCountryIdByDisease=-1.

In the UK, as in most of Europe, MenB disease has been declining since the early 2000s due to secular trends,[36] reaching its lowest incidence in 2013/14 (1.1/100,000; 636 cases).[27] In September 2015, the UK became the first country to introduce 4CMenB into its nationally-funded, infant immunisation programme.[17] Within 10 months of the programme, there was a 50% (95% CI, 29%-64%) reduction in MenB cases compared to the pre-vaccine period in the 4CMenB-eligible infants, irrespective of the infants' vaccination

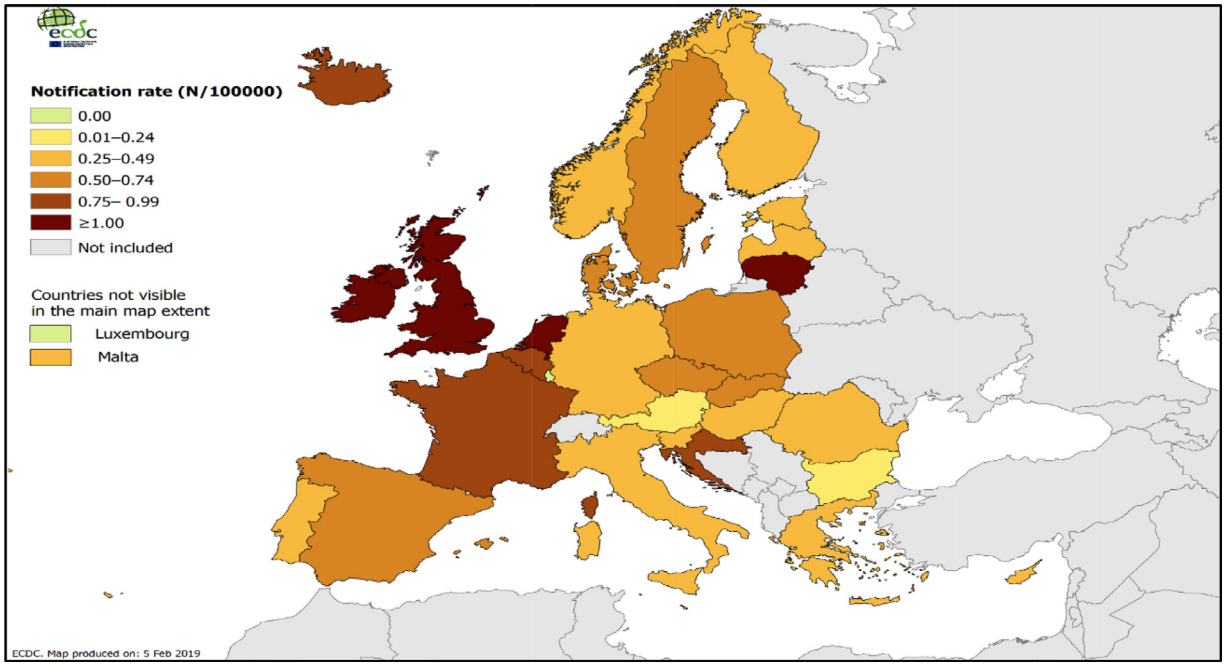

Fig. 1. Incidence if invasive meningococcal disease (IMD) in Europe during 2017. Reproduced from the ECDC 2017 Annual Report (https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2017-invasive-meningococcal-disease.pdf)

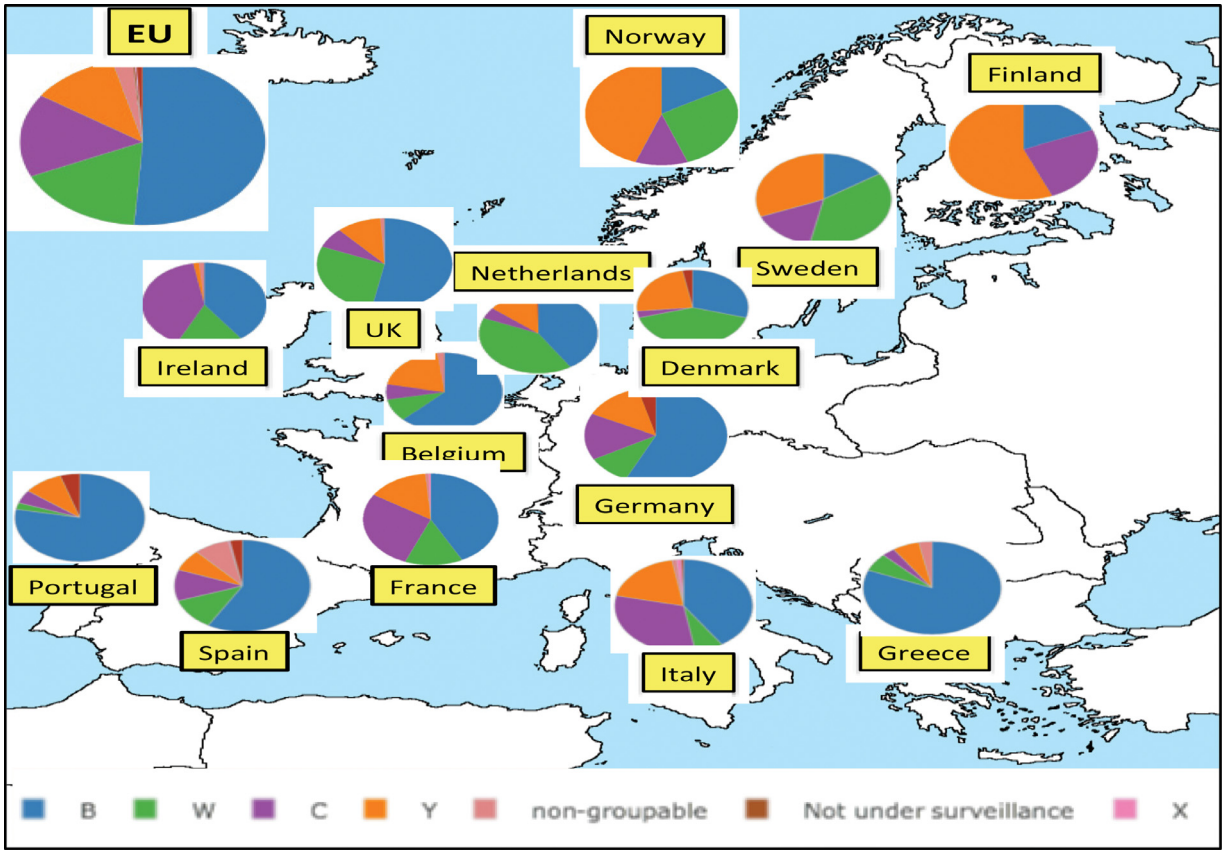

Fig. 2. Serogroup distribution of invasive meningococcal disease (IMD) cases in Europe during 2017. Reproduced from the ECDC 2017 Annual Report (https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2017-invasive-meningococcal-disease.pdf)

Table 3
Number of cases and incidence of invasive meningococcal disease (IMD) overall and by major serogroups as well as overall IMD deaths and case fatality rates (CFR) in Europe

Region	IMD Cases	IMD incidence	IMD deaths	CFR (%)	MenB cases	MenB incidence	MenC cases	MenC incidence	MenY cases	MenY incidence	MenW cases	MenW incidence
EU (total)	**3221**	**0.62**	**282**	**9.7**	**1527**	**0.3**	**485**	**0.09**	**345**	**0.07**	**511**	**0.1**
Northern EU	**31**	**0.45**	**5**	**10.2**	**5**	**0.09**	**4**	**0.05**	**10**	**0.15**	**9**	**0.13**
Norway	18	0.34	0	0	3	0.06	2	0.04	8	0.15	5	0.1
Sweden	49	0.49	10	20.4	7	0.07	7	0.07	14	0.14	17	0.17
Finland	16	0.29	-	-	3	0.05	4	0.07	9	0.16	0	0
Denmark	39	0.68	-	-	10	0.17	1	0.02	8	0.14	14	0.24
Central Europe	**280**	**0.79**	**33**	**9.2**	**126**	**0.38**	**50**	**0.09**	**39**	**0.12**	**47**	**0.17**
France	545	0.81	62	11.6	226	0.34	149	0.22	78	0.12	74	0.11
Belgium	96	0.85	-	-	60	0.53	6	0.05	19	0.17	9	0.08
Netherlands	198	1.16	16	8.3	81	0.47	9	0.05	27	0.16	80	0.47
Germany	281	0.34	22	7.9	139	0.17	38	0.05	33	0.04	24	0.03
Southern Europe	**139**	**0.45**	**12**	**8.7**	**68**	**0.24**	**22**	**0.05**	**15**	**0.04**	**11**	**0.11**
Portugal	49	0.48	3	6.1	32	0.31	2	0.02	4	0.04	1	0.01
Spain	268	0.58	24	9.1	139	0.3	26	0.06	18	0.04	27	0.06
Italy	197	0.33	20	12.5	74	0.12	57	0.09	34	0.06	12	0.02
Greece	42	0.39	3	7.1	26	0.24	1	0.01	2	0.02	2	0.02
UK + Ireland	**421**	**1.33**	**25**	**9.1**	**219**	**0.61**	**42**	**0.34**	**42**	**0.07**	**115**	**0.29**
UK	772	1.17	43	5.6	410	0.62	55	0.08	82	0.12	217	0.33
Ireland	71	1.48	7	12.5	28	0.59	28	0.59	1	0.02	12	0.25

status or predicted MenB strain coverage. A reduced 2-dose infant priming schedule at 8 and 16 weeks of age was estimated to be 82.9% (95% CI, 24.1-95.2%) effective against all MenB cases, equivalent to a vaccine effectiveness of 94.2% against the highest predicted MenB strain coverage of 88%.[17]

After the first three million doses administered to 1.3 million children aged 2-18 months in the UK, no major safety concerns were identified.[18] In particular, there was no evidence of increased seizures within seven days of immunisation, Kawasaki disease or sudden infant death. Additionally, almost all infants receiving their first dose of 4CMenB at 8 weeks of age returned for their second dose at 16 weeks of age, indicating that 4CMenB introduction had not reduced compliance with doses of other routine vaccinations.[18] After three years of the programme, 4CMenB has been shown to reduce 62% (446 cases expected, 169 cases confirmed) of MenB cases in vaccine-eligible infants in England and protects children at least until their third birthday.[37] IMD trends in other UK regions generally reflect those observed in England, but are reported separately by the individual regions.

In the **Republic of Ireland**, IMD incidence increased from 1996/97 and peaking at 11.6/100,000 in 1999/2000,[38] before declining to 1.9/100,000 in 2018.[39] Similar to the UK, the introduction of the MenC conjugate vaccine in 2000 led to large declines in MenC disease across the population.[38] From 2014, however, MenC disease increased from six cases (0.1/100,000) to 30 cases (0.1/100,000) in 2017 before declining to 20 cases (0.4/100,000 population) in 2018, likely because of the introduction of the adolescent MenC conjugate vaccine booster in 2014.[39] The Republic of Ireland also had an increase in MenW cases from one (<0.1/100,000) case in 2014 to 12 (0.3/100,000) in 2018, as well as MenY cases from three (0.1/100,000) to eight (0.2/100,000 population) cases over the same period. This led to the implementation of the MenACWY conjugate vaccine for adolescents and new university entrants from September 2019.[39] MenB disease has been declining in the Republic of Ireland from 292 cases (8.1/100,000) in 1999 to 46 cases (1.0/100,000) in 2018.[39] Like the UK, large declines were particularly observed among children aged <5 years, with MenB disease incidence more than halving from 2014 to 5.7/100,000 (19 cases) in 2018. However, the Republic of Ireland is one of the few countries that also implemented a national immunisation programme offering 4CMenB to all infants born since 01 October 2016.[40]

Central Europe had the second highest IMD incidence in the EU in 2017, with a stable rate since 2006 (Table 2). IMD epidemiology in the Netherlands has closely followed that of the UK, starting with the MenC outbreak in the 1990s that led to the implementation of a MenC conjugate vaccine programme for Dutch children aged 14 months in 2002, alongside a catch-up campaign for 1–18 year-olds.[41] More recently, the Netherlands has been experiencing a national outbreak of MenW:cc11 disease, with cases increasing from an average of 4 (0.02 cases per 100,000) during 2010-14 to 80 cases in 2017 (0.5/100,000) in 2017, representing 40% of all IMD cases.[42] Incidence was highest in children <5 years (0.92/100,000; n=8), especially <2 year-olds (2.0/100,000; n=7), followed by 15–24 year-olds (0.81/100,000; n=17) and adults from 45 years of age. This increase led to the replacement of the toddler MenC conjugate vaccine dose at 14 months with the MenACWY conjugate vaccine from May 2018 and offering the latter vaccine to 13-14 year-olds from October 2018.

In 2017, **France** reported the second highest number of confirmed IMD cases in Europe (n=545) but IMD incidence was lower than in the Netherlands. IMD incidence in France has been relatively stable over the past decade (Fig. 3). The MenC conjugate vaccine was introduced in 2010 but the decline in IMD incidence from 1.23/100,000 in 2006 to 0.78/100,000 in 2016 was mainly related to the secular decline in MenB IMD.[43] MenC disease incidence de-

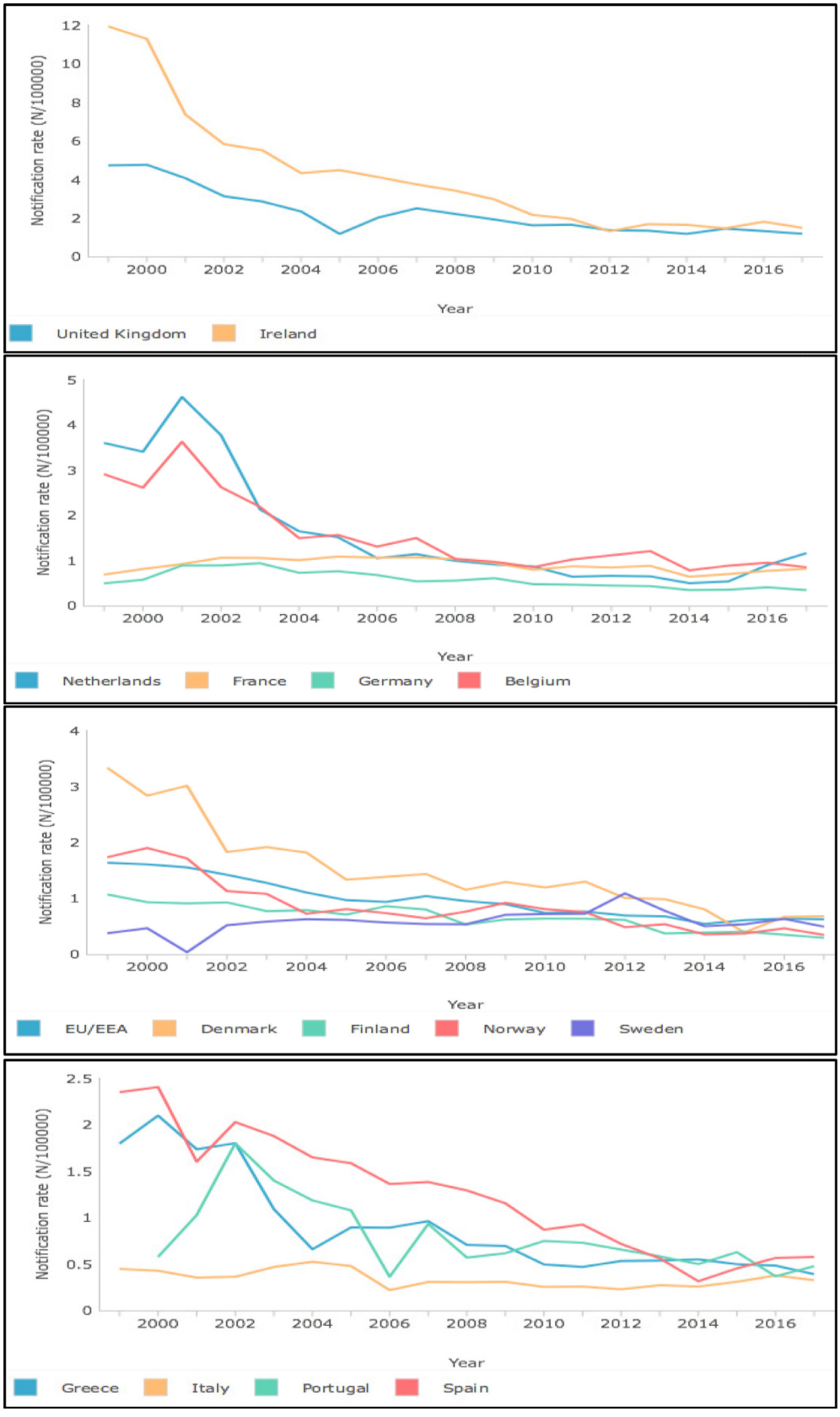

Fig. 3. Notification rates for invasive meningococcal disease (IMD) per 100,000 by country in (A) the UK and Ireland, (B) Southern Europe, (C) Central Europe and (D) Southern Europe. Reproduced from the ECDC 2017 Annual Report (https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2017-invasive-meningococcal-disease.pdf)

creased from 0.29/100,000 in 2006 to 0.13/100,000 in 2010 but increased thereafter in age groups not targeted by the vaccination programme; this trend may at least in part be explained by poor vaccine uptake (<25%) among 15-19 year-olds in 2015. Since 2016, an increase in MenW:cc11 IMD was also reported in France, affecting mainly adults, and associated with a high CFR of 28%.[44]

Germany had the lowest IMD incidence among central EU countries in 2017, with declining rates from 0.95/100,000 in 2001 to 0.35/100,000 in 2017. During 2013-16, IMD incidence was highest in infants (4.6/100,000) followed by toddlers (1.8/100,000) and adolescents (0.73/100,000).[4] MenB was the most prevalent serogroup (0.27/100,000), accounting for 58% of IMD cases during 2013-16; CFR due to MenB (9.4%) was almost as high as for the second most common serogroup MenC (13.6%; incidence, 0.07/100,000 persons).[45]

In **Northern Europe**, Denmark had the highest IMD incidence in 2017, followed closely by Sweden since 2012 (Fig. 2). Notification rates in both Northern and Southern Europe (0.45/100,000) have been lower than in the other European regions. In **Southern Europe**, Spain had the highest incidence in 2017 (0.58/100,000). IMD incidence reached its lowest in 15 years during 2013/14, following MenC conjugate vaccine introduction in 2000 and secular declines in MenB disease.[6] Since then, however, IMD incidence increased because of both MenW and MenY disease.[6] During 2016/2017, 321 IMD cases were notified and 270 (84.1%) were confirmed; including 139 (51.5%) MenB (0.30/100,000), 31 MenC (0.07/100,000), 22 MenW (8.2%), 17 MenY (6.3%) and 10 other serogroups.[6] Non-typable strains were isolated in 14 and the serogroup was not identified in 37 confirmed cases.[6] There were 51 clinically-diagnosed cases (0.11/100,000), representing 15.9% of the total notified cases, lower than in previous seasons (~22%).[6] MenB cases have been declining for 15 years; the moderate uptake of MenB vaccine in the private market (reaching 40-50% per birth cohort) may also be contributing to this decline.[4,6] Between 1999/2000 and 2016/2017, the average annual decline was -9.4% (95% CI, -11.3 to -7.6) for MenB and -16.4% (95% CI, -18.9 to -13.9) for MenC, both statistically significant.[6]

In **Eastern Europe**, IMD surveillance is limited in many countries or restricted to acute bacterial meningitis.[46] The overall trend, however, has been a declining IMD incidence over recent decades with current rates below 1/100,000 population annually, even in countries with more robust national surveillance in place and a CFR ranging between 3% and 30%. MenB accounts for 60-90% of confirmed IMD cases followed by MenC (30%) and less commonly MenA which has been reported in Romania, Republic of Belarus, Russia, Azerbaijan and Turkey.[46] Occasional cases due to MenW, MenY and MenX are also emerging in some countries. Both conjugate and polysaccharide vaccines are available in Eastern Europe and but not recommended in national immunisation programmes in the majority of countries, except for high-risk groups. In many countries, meningococcal vaccination is recommended but not mandatory or reimbursed.[46]

Across Europe, IMD incidence is currently very low and widespread immunisation may, therefore, not be justified. The recent emergence of MenW:cc11, however, has led many countries to implement – or at least recommend – either replacing the MenC conjugate vaccine or initiating a new programme with the MenACWY conjugate vaccine. Offering the vaccine to young children protects them directly against the four meningococcal serogroups whilst offering the vaccine to adolescents has the additional benefit of providing indirect (herd) protection over time if sufficient vaccine uptake can be achieved in this age group. Although the incidence of MenB disease is currently at its lowest in decades, even in infants, countries that implement the newly licensed MenB vaccines will achieve further declines in those who are vaccinated.

North America

United States

In the United States (US), IMD epidemiology has changed dramatically over the past few decades, with the current incidence at historically low levels. For many years after World War II, annual IMD incidence fluctuated between 0.5-1.5/100,000. Since the middle of the 1990s, however, IMD incidence has declined >90% to 0.13/100,000 in 2017, with only 310 cases and 50 deaths.[47] Like many other countries, infants have the highest incidence, with a smaller peak during adolescence and young adulthood and an increase among the elderly.[48] Serogroup distribution for 599 isolates during 2006-2015 was: MenB, 38%; MenC, 24%; MenW, 7%; and MenY, 30%.[47]

IMD cases in the US are primarily sporadic, but small outbreaks are relatively common. Before routine MenACWY vaccination, MenC caused most outbreaks.[49] but, currently, MenB outbreaks are more common, mainly among college and university students.[50] During 2008-2017, there were 11 MenB outbreaks, resulting in 53 cases and 3 deaths,[51,52] as well as MenC outbreaks among men who have sex with men.[53] IMD outbreaks can be extremely disruptive because they often require large, labour-intensive and expensive immunisation campaigns.[53-55]

In 2005, the MenACWY conjugate vaccine was recommended for adolescents, preferably at 11-12 years of age but, because of rapidly waning effectiveness of the MenACWY vaccine conjugated to diphtheria toxoid (MenACWY-DT; Menactra),[56] a booster dose is now recommended at 16 years of age. The vaccine is also recommended for high-risk groups. The MenACWY programme was associated with a decline in MenC and MenY disease among adolescents and young adults.[48] The decline, however, began in the mid-1990s and the slope of the decline has not been greatly altered by the vaccines.[51,57] In addition to the MenACWY conjugate vaccine, both MenB vaccines can be used for 10-25 year-olds.[51,57,58] and is recommended for high-risk individuals as well as 16-23 year-olds who are not at increased risk based on “individual clinical decision making”.[58] This type of recommendation is problematic because of major knowledge gaps among physicians about both MenB disease and vaccines.[59] MenB cases also began to decrease well before the recent availability of MenB vaccines. The low IMD incidence has made it difficult for policymakers to justify routine vaccine use in some age groups because of the remarkably low disease burden.

Canada

Historically, IMD incidence in Canada was highest during winter with cyclical peaks of epidemic disease occurring every 5-10 years and sporadic outbreaks arising more frequently. From 1924 (the earliest year data were collected) to 1984, the average annual incidence was 1.6/100,000 with a high of 3.8/100,000 in the 1940s driven by MenA to a low of 0.59/100,000 in the 1960s.[60] From 1985-2000, annual IMD incidence remained <2.0/100,000. By the 1970s, MenA disease had disappeared, to be replaced with endemic MenC and MenB disease. In the mid-1980s, the MenC:2a serotype emerged in Canada,[61,62] peaking in 1992 and again in 2000-2001, with high attack rates and fatalities in adolescents and young adults.[63] In response, reactive vaccination strategies were implemented in several provinces using polysaccharide vaccine in the 1990s followed by the MenC conjugate vaccine when available in 2001.[64] As in other developed countries, IMD incidence in Canada exhibited a bimodal peak with the highest incidence in infants, followed by 1-4 year-olds and a second smaller peak in 15-24 year-olds.[65] Consequently, the first universal infant immunisation programs started in 2001 with the MenC conjugate vaccine in high en-

Table 4
Canadian Provincial and Territorial Meningococcal C and Quadrivalent Immunization Programme

Province/Territory	Infants MenC	Year Started	Children/Adolescents	Year Started
British Columbia[1]	2, 12 months	2003	14-16 years	2003 MenC, 2016 ACWY
Alberta[2]	4, 12 months	2002	14-16 years	2002 MenC, 2011 ACWY
Saskatchewan	12 months	2004	14-16 years	2004 MenC, 2011 ACWY
Manitoba	12 months	2005	10-11 years	2005 MenC, 2019 ACWY
Ontario	12 months	2005	12-14 years	2005 MenC, 2009 ACWY
Quebec[3]	18 months	2001	14-16 years	2013 MenC
New Brunswick	12 months	2004	14-16 years	2004 MenC, 2007 ACWY
PEI	12 months	2005	14-16 years	2005 MenC, 2006 ACWY
Nova Scotia	12 months	2005	12-14 years	2005 MenC, 2015 ACWY
Newfoundland	12 months	2005	10-11 years	2005 MenC, 2009 ACWY
NWT[4]	2, 12 months	2004	17-18 years	2004 MenC, 2007 ACWY
Nunavut	12 months	2007	14-16 years	2007 MenC, 2017 ACWY
Yukon[5]	2, 12 months	2005	10-11 years	2005 MenC, 2018 ACWY

MenC = monovalent conjugate serogroup C vaccine
ACYW = Quadrivalent serogroups $ACYW_{135}$ conjugate vaccine
The following vaccines are authorized for use in Canada and all have been used in provincial and territorial programs: Meningitec (Pfizer), Menjugate (Novartis), NeisVac-C (Baxter), Menactra (Sanofi Pasteur), Menveo (Novartis).
[1] BC switched from a 1-dose program at 12 months to a 2-dose program at 2 and 12 months in 2005. Catch up program with MenC was offered for adolescents 14-18 years of age from 2004-2007.
[2] Alberta switched from a 3-dose infant program at 2, 4 and 6 months to 2, 4 and 12 months in 2007 and to a 2-dose infant program at 4 and 12 months in January 2015.
[3] Quebec mass immunization of 2 month to 20 year olds in 2001 with MenC. Infant program switched from 12 months to 18 months Jan. 1, 2019.
[4] NWT switched from a 2-dose program at 2 and 4 months to a 2-dose program at 2 and 12 months in 2007. ACYW is provided to post-secondary students attending school outside of NWT.
[5] Yukon switched from a 2-dose program at 2 and 6 months to a 2-dose program at 2 and 12 months in 2007.

demicity provinces and was in place nationally by 2005. The MenACWY programme for adolescents began in 2006 and is now used in all but one province (Quebec) (Table 4). Currently, MenC is extremely rare across the country (incidence 0.05/100,000), with only sporadic cases in older, unvaccinated adults.[66-69] The effect of the MenACWY programmes have been more difficult to measure.[67,70] because of very slow implementation across Canada and low disease incidence at baseline (<0.10/100,000 MenY, <0.05/100,000 MenW).[71]

In Canada, IMD cases due to the South American MenW:cc11 strain emerged in 2014.[72] and, by 2016, was circulating in five provinces (British Columbia, Alberta, Manitoba, Ontario and Quebec), accounting for 19% of all culture-confirmed IMD.[73,74] The strain was also responsible for a 2017 outbreak among adolescents in British Columbia that resulted in a mass vaccination programme in the outbreak jurisdiction.

Quebec presents different IMD epidemiology from the rest of Canada. In 2000-2001, Quebec was the only province to implement mass MenC vaccination for individuals aged 2 months to 20 years, which led to a decline in MenC cases. Thereafter, MenB was responsible for >80% of cases, with 55% of cases caused by the ST-269 clonal complex, which emerged in 2003 among adolescents and spread across all age-groups.[69] In response, Quebec implemented a targeted mass immunisation programme in the jurisdictions with the highest incidence with 4CMenB in 2014.[75] and the incidence declined from 11.4/100,000 in 2006-2014 to 0.4/100,000 in 2014-2018 ($p<0.0001$).[76] Elsewhere in Canada, MenB vaccine (4CMenB) has only been used reactively to combat sporadic outbreaks,[77] although this serogroup continues to account for most cases in Canada but with low incidence (~0.25/100,000 nationally).[78] Since the initiation of meningococcal vaccination programmes, Canada has experienced historically low IMD incidence overall (<1.0/100,000), virtual elimination of MenC disease and very low MenW and MenY incidence, particularly in provinces with long-standing MenACWY programmes.[70,71]

Central and South America

The overall incidence of IMD in Central and South America varies widely by geographic region, serogroup prevalence and time, with a decreasing trend in disease incidence observed in recent years. The highest age-specific incidence was consistently observed in infants less aged <1 year and, in contrast to Europe, North America and Australia, there is no apparent second peak of incidence in adolescents in the region.[79] Most IMD cases are sporadic, with outbreaks occurring at irregular intervals. Although IMD reporting is mandatory in the region, surveillance and reporting systems, as well as the quality of published data for IMD are not uniform across the countries, with limited robust data available and exceedingly low rates of meningococcal disease reported by some countries. Additionally, limited access to hospital care, lack of adequate laboratory-based microbiologic infrastructure incorporating molecular methods in routine testing and restrictive case definitions of IMD in some countries may contribute to underestimate the true burden of disease in the region. Brazil, Chile and Argentina are the countries with the highest IMD burden in Central and South America, probably reflecting more robust surveillance and a well-established laboratory infrastructure for IMD.[79] Serogroups B, C and W are responsible for most IMD cases reported in the region, with rare reports of MenY, while serogroup A has not been circulating for many years.[80] Much like the epidemiology of IMD, routine meningococcal vaccination programmes also vary by country in this region (Table 5).

In **Brazil**, the health authorities incorporated the MenC conjugate vaccine in the National Immunization Program in late 2010. This was motivated by a significant rise in the number and proportion of cases due to MenC, associated with the ST-103 complex, with several outbreaks affecting different regions across the country and a CFR of 20%, The program resulted in an immediate reduction in MenC cases among <2 year-olds, the age group targeted for vaccination.[81,82]

Table 5
Latin American countries with routine meningococcal vaccination programmes.

Country	Infants and children / Vaccine	Year started	Adolescents / Vaccine	Year started
Cuba	MenB OMV 3 and 5 months	1991	-	
Brazil	MenC conjugate 3, 5 and 12-15 months	2010	MenC conjugate 11-14 years	2017
Chile	MenACWY conjugate - 9 months – 5 years - 12 months	 2012 2014	-	
Argentina	MenACWY conjugate 3, 5, 15 months	2017	MenACWY conjugate 11 years	2017

Since 2017 adolescents aged 11-14 years were also included in the MenC immunisation programme and, from 2020, the MenACWY conjugate vaccine will replace the MenC vaccine for adolescents. In 2018, according to the Notifiable Diseases Information System (SINAN), 1,131 cases of IMD were reported, with an incidence of 0.54 cases/100,000 population, the lowest incidence reported in the last 30 years. MenC remains the leading cause of IMD, responsible for 53% of the identified cases in 2018, followed by MenB (27%), MenW (16%) and MenY (3%).[83]

In **Chile**, after a long period of MenB predominance and stable incidence rates, IMD incidence doubled in 2012 (0.8/100,000) comparing to 2011, associated with the emergence of a hypervirulent genetic lineage MenW: P1.5, 2:ST-11, responsible for >80% of the identified cases. In addition, unusual clinical presentations including gastrointestinal symptoms, increased morbidity, and CFR as high as 28% have been reported for the South American MenWcc11 sublineage.[84] In 2012, Chile implemented a reactive immunization campaign with MenACWY conjugate vaccines, initially targeting children aged 9 months to 5 years and, after 2014, as a one-dose schedule at 12 months of age. As expected, the MenACWY programme resulted in significant reductions in cases among vaccine-eligible children (1-5 year-olds) but cases in other age groups continued to increase. Consequently, MenW disease incidence in 2016 (0.34/100,000) was similar to 2012 (0.37/100,000).

In **Argentina,** approximately 120-300 cases were reported during 2012-2016, with incidence declining from 0.75/100,000 in 2012 to 0.28/100,000 in 2016. IMD incidence was highest in infants and overall CFR was 10%. In 2016, MenB was the predominant serogroup, responsible for 54.3% of identified cases, followed by MenW (33.3%), MenC and MenY (6.2% each). In 2017, the MenACWY conjugate vaccine was introduced in the national immunisation programme for infants at 3, 5 and 15 months, with a dose for adolescents at 11 years of age.[85]

In **Colombia**, the median IMD incidence during 2013-2016 was 0.16/100,000, with the highest incidence in infants and overall CFR of 13-21%. MenC became the predominant serogroup causing IMD since 2015, with several outbreaks reported in the country.[86]

In **Mexico**, IMD is considered to be rare, with incidence as low as 0.01/100,000 reported during 2014-2017 [9]. However, recent active-surveillance-based studies across different regions found significantly higher IMD rates, associated predominantly with MenC disease.[87] Central America, Caribbean and Andean countries also report very low incidence rates of disease. Since 1991, Cuba has been routinely using a locally produced MenB OMV vaccine as well as a MenC polysaccharide vaccine in its childhood immunization schedule, which are given at 3 and 5 months of age. Consequently, IMD incidence has remained very low and nearly all cases reported in recent years are due to MenB.[88]

Overall, in Central and South America, the predominance of MenC and, more recently, MenW has led to widespread implementation of the MenACWY immunisation programme, mainly in countries with adequate surveillance in place. Experience from Chile confirms the high effectiveness of the MenACWY vaccine in children but highlights the importance of vaccinating teenagers – the age group with the highest meningococcal carriage – to achieve disease control across the population by preventing carriage and interrupting onward transmission. The success of the Cuban immunisation programme, including the childhood meningococcal B OMV and the adolescent MenACWY programmes, is commendable. There is a desperate need to improve IMD surveillance across the regions as well as standardising diagnostics and case definitions so that vaccine recommendations can reflect local epidemiology.

Africa and the Middle East

Meningitis Belt

Historically, the meningitis belt in Northern Africa has had the highest IMD incidence in the world. This region spans across 26 countries, from Senegal in the West to Ethiopia in the East, with a population of nearly 300 million.[89] Periodic epidemics occur and the timing of the epidemic season varies from year to year and country to country. The epidemics typically occur during the dry season which can be earlier in the East and later in the West. Large-scale epidemics occur every 5 to 12 years when IMD attack rates can reach 100-800/100,000, with individual countries reporting rates up to 1,000/100,000 population (i.e. 1% of the population). The case fatality rate ranges from 6.6 to 10.0% and permanent sequelae including hearing loss and motor impairment affecting over 30% and 12% of survivors, respectively.[89]

Historically, the outbreaks have been due to MenA, which was responsible for nearly all IMD cases in sub-Saharan Africa.[90] A recent study showed that even during epidemics, the responsible MenA strains may be heterogeneous with several closely-related but genetically distinct co-circulating clones, highlighting the dynamic nature of the meningococcal genome.[91] A MenA conjugate vaccine, MenAfriVac, (Serum Institute of India Pvt, Pune, India) was developed as part of the Meningitis Vaccine Project (MVP), which was created as a partnership between WHO, Bill & Melinda Gates Foundation and the Program for Appropriate Technology in Health (PATH) in 2001.[92] The MenAfriVac programme was implemented in 2010 and by 2016, more than 235 million persons aged 1–29 years in 16 countries had received a single dose of MenAfriVac.[89] This led to a 57% decline in suspected meningitis cases with corresponding 59% reduction in epidemics and 99% decline in confirmed MenA cases during 2010–2015, such that, during 2016–2017, MenA was responsible for only 0.8% of 2,897 confirmed IMD cases in the region.[89] Consequently, IMD epidemiology has shifted and most disease is now caused by MenC, MenW and MenX.

In 2013, a novel MenC strain emerged in Nigeria and by 2017 had spread to Niger and across Northern Nigeria, causing more than 30 000 cases and almost 2500 deaths in 2017. This new hy-

perinvasive MenC ST-10217 clone (unassigned clonal complex) was genetically distant from previous MenC strains and only found in the African meningitis belt.[93] In 2017, a meningococcal outbreak associated with high attack and case fatality rates at a funeral in Liberia was identified to be due to MenC which was similar to ST-10217.[53] MenW can occasionally cause epidemics in the meningitis belt. Notably, MenW caused large-scale outbreaks affecting thousands in Ghana and Togo during 2016.[94] MenW is responsible for around a third of meningococcal meningitis confirmed in the meningitis belt.[89] MenX is a rare cause of IMD but has occasionally caused outbreaks and small epidemics in the meningitis belt. An increase in MenX has been reported recently, with the proportion of cases increasing from 2.7% of 4150 confirmed cases during 2013–2016 to 22.0% of 1410 cases in 2017, mainly from Niger, Burkina Faso and Togo.[94] There are currently no licensed vaccines against MenX, although clinical trials are-ongoing.[95]

Outside the Meningitis Belt

Outside the meningitis belt, data are scarce apart from South Africa, where established IMD surveillance is in place and vaccine use is negligible.[96] IMD incidence was 0.97/100,000 in 2003, peaked to 1.4/100,00 in 2006 and declined to 0.23/100,000 in 2016, most likely due to secular trends.[96] Of 3,917 cases with confirmed serogroups, MenW was responsible for 49.5%, MenB 23.3%, MenY 12.3%, MenC 9.4% and MenA 4.7%. Of those tested, 37% were HIV-positive and HIV-infected persons had a 2.5-fold higher risk of IMD and patients; additionally, HIV co-infection was twice as common in patients with MenW and MenY disease. The in-hospital CFR was 17%.

In Malawi, *N. meningitidis* was responsible for <5% of bacterial meningitis in children.[97] A prospective study in rural Mozambique estimated an IMD incidence of 11.6/100,000 in children under 15 years during 1998-2008, with MenW:cc11 being responsible for 81% of tested isolates.[98] A more recent hospital-based study from Mozambique reported MenA to be responsible for 50% of meningococcal meningitis cases during 2014, followed by MenW/Y (19%), MenC (8.5%), MenX (7.5%) and MenB (0.9%).[99]

Above the meningitis belt, there has been a shift from MenA to MenB disease in Northern Africa. Although no formal surveillance is in place in Tunisia, data from one hospital show that 85% of cases occur in children aged <5 years and MenB is responsible for 80% of cases.[100] In Morocco, IMD incidence is estimated to be 2.0-3.6/100,000 and 95% of cases during 2011-15 were due to MenB, followed by MenC (2%), MenY (2%) and MenW (2%).[100] IMD incidence in Algeria was estimated to be 0.09/100,000 overall and 0.48/100,000 in children aged <5 years. Both MenB and MenW also cause IMD, but MenY appears to be rare.[100] In Egypt, *N. meningitidis* was identified in 16% of confirmed cases, with MenB responsible for 51% of 135 cases, followed by MenA (35%) and MenW (4%).[101]

In summary, MenA has been nearly eliminated in the African meningitis belt following a massive global effort that led to the vaccination of millions of children and young adults across many countries. The emergence of other serogroups in the region, however, highlights the importance for on-going surveillance and emphasises the need for affordable multi-serogroup conjugate vaccines for the region. Outside the meningitis belt, the most robust data come from South Africa and the declining incidence is reassuring but on-going surveillance is vital to support local and national vaccine recommendations. Elsewhere, data are scarce. Establishing routine surveillance to monitor both incidence and trends over time for the major infectious diseases, especially vaccine-preventable diseases including IMD, need to be prioritised.

Asia

China

Before 1980s, meningococcal disease had been serious public health problem in China. The highest incidence was 403/100,000 with a CFR of 5.3% in 1967.[102] Most of the cases were caused by MenA, with a small proportion of cases due to MenB, which were generally sporadic and had not caused significant public health concern. In the early 1980s, therefore, polysaccharide vaccines against MenA were incorporated into the routine immunisation programme which led to significant declines in MenA disease. From 1990s, the incidence decreased to and remained at lower than 1/100,000. The most prevalent serogroup had been MenA until 2003 when MenC belonging to a novel clonal complex (ST-4821) emerged and caused several outbreaks and many sporadic cases.[103] To combat this serogroup replacement from group A to C, several polysaccharide vaccines against MenC or MenAC were introduced into the Expanded Programme for Immunization (EPI) in China in 2008. IMD is one of 39 statutorily notifiable diseases in China, all cases, including suspected cases, must be reported to the Chinese Center for Disease Control and Prevention via the National Notifiable Disease Reporting System (NNDRS). According to the data from the NNDRS, meningococcal disease incidence was 0.047/100,000 during 2006-2014.[104] and 0.0079/100,000 during 2015-2017,[105] although these are likely to be underestimated, since a recent meta-analysis of 11 albeit heterogeneous regional observational studies and representing only a small proportion of the Chinese population estimated an average incidence rate of 1.84/100,000 (95%CI, 0.91–3.37) and CFR of 33% (95%CI, 0.12-0.86) during 2000-2010.[106] Of the notified cases, however, CFR during 2006-14 and 2015-17 were 9.6% and 14.2%, respectively. Between these periods, the serogroups responsible for IMD have changed substantially and become more complicated. The percentage of MenA cases continued to decline and that of MenC cases decreased after initially increasing. MenB cases have increased significantly and account for more than half of the serogroup-defined cases. Invasive cases caused by MenW had not been observed until 2006 and then caused sporadic cases and outbreaks in several provinces,[107,108] accounting for an increasing proportion of IMD nationally (4.2% during 2006-2014 to 6.1% during 2015-2017).[104,105] MenX and MenY invasive cases were observed but not associated with any geographical spread or increase in cases. The highest CFR was due to MenW (32.4%), followed by MenB (15.6%).[104,105]

In the decades since 1956 when the first strain was isolated in China, the molecular characteristics of meningococci has also changed dramatically. The earliest MenA isolated in the 1950s belonged to ST-5 (ST-5 clonal complex, cc5).[109] Since 1960s, ST-3 (cc1) emerged and gradually became the main clonal lineage. After 1980, ST-7 (cc5) gradually took over ST-3 and has been the predominating clonal lineage. Comparatively, MenC cases are mainly due to a single clonal lineage, cc4821, since it was identified in 2003.[110] Currently, cc4821 has been identified in 30 provinces and account for >95% of the invasive MenC cases nationally.

Before 2004, MenB had no dominant lineage and generally caused sporadic infections. The hyper-invasive clonal complexes prevalent in many other countries, such as cc32 and cc41/44,[111] were rarely isolated in China. Since 2005, MenB disease and carriage have both increased. Among the MenB isolates, cc4821 was the most common clonal lineage. Analysis based on whole genome sequencing showed that there could be multiple recombination events between cc4821 MenB and MenC.[112] In 2006, both cc4821 and cc11 MenW were isolated from invasive cases.[113] In the following years, cc11 exceeded cc4821 in terms of both transmission and the number of isolates, with cc11 accounting for most invasive MenW cases. At present, MenW:cc11 is circulating in at

least 12 provinces dispersed throughout China. Whole genome sequence-based analysing revealed that the Chinese MenW:cc11 isolates formed a novel cc11 sublineage which was distinct from the Hajj-strain sublineage and the South American-strain sublineage. Isolates from North Africa and the UK were closest to the origin of the Chinese subclusters.[114,115] Among the reported two MenX cases,[116,117] one was caused by ST-7 which was confirmed to originate from ST-7 MenA by horizontal exchange of capsule biosynthesis genes.[118] Although the first MenY case was reported in 2016, no further information was available. In 2019, a MenY meningitis case in a teenager was caused by cc23, which has been the major clone in North America and some countries in Europe was identified.[119]

Other regions

IMD data from other regions are scarce and often outdated.[120] Where reported, IMD incidence is estimated to be well below 1.0/100,000.[24] In Japan, IMD surveillance was initially restricted to meningitis cases until April 2013, when meningococcal bacteraemia also became notifiable.[121] Of the 59 IMD cases reported until the end of 2014, the median age was 56 years with MenY (42%) predominating, followed by MenC (12%), MenB (7%) and MenW (3%). Annual incidence was estimated to be 0.028/100,000 with a CFR of was 19%. Whilst all the evidence indicates that IMD is rare in Asia,[122] the reported incidence rates are likely to be significantly underestimated because of many reasons, including restricted case definitions for surveillance, inconsistent diagnostic testing practice, antibiotic overuse in the community and the passive nature of the surveillance, which are common problems across Asia.[120,123] Recent data from the Indian subcontinent are also unavailable, restricted mainly to local outbreaks and epidemics, which occur with regular frequency.[124] In India, however, there have been increasing reports of IMD outbreaks since 2005, mainly affecting adolescents and young adults, and due to MenA.[124,125] Whilst current surveillance data are not readily available, *N. meningitidis* has been reported as a cause of bacterial meningitis in Pakistan.[126] and Bangladesh.[127,128]

In summary, much of the data on IMD comes from China where regional surveillance studies frequently identify substantially higher IMD incidence compared to national notifications. Elsewhere, current data indicate that IMD incidence is very low, although unlikely to be as low as reported estimates because of the reasons already highlighted. On-going syndromic and laboratory-based regional and national surveillance will be important for identifying any increase in IMD in the future.

Australasia

Australia

In Australia, IMD is nationally notifiable and includes laboratory-confirmed cases and probable cases requiring clinical evidence only.[129,130]; quarterly updates are provided online.[131] IMD notifications declined after MenC conjugate vaccine implementation in 2003 but gradually increased from 2013 to 2017 (1.5/100,000).[132] During 2002-15, MenB was responsible for most IMD cases; since then MenW became the predominant serogroup.[133] In 2017, a MenW outbreak (141 cases in 2017 compared to 34 in 2015) mostly involving young Aboriginal and Torres Strait Islander children within their communities in Central Australia affecting parts of the Northern Territory (NT), South Australia (SA), Western Australia (WA) and Queensland (QLD) prompted the introduction of state-funded MenACWY programmes across Australia except SA,[134] where MenB disease continues to predominate. MenACWY vaccine replaced MenC vaccination at 12 months of age from July 2018 and is offered to 14-16 year-olds through a school-based program since April 2019. MenY cases have also increased since 2011, with 75 cases accounting for 19% of notifications in 2017 compared with 40, 22 and 12 in the previous three years.[133] In 2018, there were 281 IMD cases in 2018 with reductions in both MenW (100 cases) and MenY (45 cases) disease.[133]

Most MenB cases over the past few decades have been caused by the New Zealand epidemic strain CC41/45: PorA 1.7,2.4.[135-138] In 2016, 92% of MenW isolates had the P1.5,2 PorA antigen and, of these, 72% were MenW:cc11 belonging to the South American-UK strain.[130,139] Like Europe, infants had the highest IMD incidence, followed by toddlers and adolescents aged 15–19 years.[132] IMD incidence was higher in Aboriginal and Torres Strait Islander children aged 0-4 years (21.3 vs. 4.3/100,000)) and 5-9 years (5.4 vs. 0.8/100,000) compared to non-Indigenous children.[133] MenB predominated in <5 and 15–19 year-olds,[137,138,140] whereas MenW predominated among ≥45 year-olds.[141] In 2018, IMD notifications dropped from 380 to 281 cases with MenB representing 42% and MenW 36% of all cases.[133]

Significant differences in meningococcal serogroup and genetic diversity exist between Australian states. The increase in MenW cases varied between states, with the largest increases in Victoria (VIC) and WA.[130,141] In SA, MenB caused 79% of all IMD in 2018.[133,142] and most cases were due to the New Zealand strain, which is covered by 4CMenB. SA became the first state to offer a funded 4CMenB programme to all infants, young children, adolescents and young adults in addition to the national MenACWY program.[142] In other Australian states, there is more diversity in MenB strains causing disease. The Pharmaceutical Benefits Advisory Committee recently recommended inclusion of 4CMenB vaccine in the National Immunisation Program for Aboriginal and Torres Strait Islander infants with a catch-up program up to 2 years of age and for any child or adult with medical conditions associated with increased risk of meningococcal disease.[143]

Overall CFR was 5%.[141,144,145] and higher for MenW (10.7%) and MenC (9.1%) disease compared with other serogroups.[141] MenW:CC11 was associated with more severe disease and higher CFR.[33] In 2017, all 16 deaths due to MenW:cc11.[133] CFR has not decreased significantly despite MenC vaccine implementation and improvements in diagnosis and clinical management.

New Zealand

In New Zealand, MenB has predominated, although outbreaks of MenA and MenC have occurred over the past few decades with an increase in MenW cases recently.[146,147] In response to a MenB epidemic (B:4:P1.7b,4, ST-41/44 clonal complex) during 1999-2007, a MenB strain-specific OMV vaccine (MeNZB™) was developed and implemented nationally during 2004-2008.[148] This led to a reduction in notification rates from a peak of 17.4/100,000 to 1.2/100,000 in 2009. Vaccine uptake was 81% and vaccine effectiveness was estimated to be 73-77%.[149,150] In 2011, a community outbreak of MenC disease occurred in northland, which was associated with a 33% CFR.[151] Since 2014, IMD incidence has been increasing nationally and, although MenB predominates, an increase in MenW:cc11 cases has also contributed to this increase.[146,152] MenW cases increased from 5 in 2016 to 33 in 2018, with a CFR of 18%.[153]

IMD in New Zealand mainly affects <5 year-olds, with Māori and Pacific people disproportionately affected. The highest IMD rates occur in Pacific people aged <20 years, but the highest percentages of cases occur in Māori and European New Zealanders.[148] IMD incidence is also highest in the northern part of the North Island of New Zealand.[154] There are no meningococcal vaccines in the national immunisation programme, although a targeted vaccination programme for MenW disease was implemented in Decem-

ber 2018 for Northland children aged 9 months to 4 years and 13 -19 years.[155] In addition, MenC and MenACWY conjugate vaccines are recommended and funded for certain high-risk groups.[156]

In summary, IMD epidemiology in Australasia reflects other high-income countries, especially in Europe. The recent MenW:cc11 outbreak has led to widespread implementation of the MenACWY conjugate vaccine, and South Australia is leading the field of MenB disease prevention with the recent introduction of 4CMenB for infant, toddlers and adolescents. The impact of the programme will provide useful information for policy makers worldwide on extending the use of this novel, protein-based vaccine to wider age groups. In New Zealand, the use of the outbreak strain OMV vaccine during 2004-2008 provided reassurance for many countries considering 4CMenB (which contains the New Zealand OMV) implementation, because of the high vaccine uptake, effectiveness and impact achieved.

Discussion

This review summarises the immense burden of IMD globally and highlights the changing and dynamic epidemiology of IMD that is intricately intertwined with local, regional and national meningococcal immunisation programmes targeting different age-groups and serogroups in different parts of the world at different times. Unlike other publications, this review did not aim to identify or document every study reported globally but, instead, to highlight the significant studies across the different continents that provide an insight into the current burden of disease, meningococcal immunisation programmes and the potential for further prevention.

MenB is the predominant serogroup across Europe, North America and the Australasia, while MenC and MenW account for substantial proportions of cases across Africa, Latin America and parts of Asia. In addition to natural fluctuations, disease trends are also influenced by public health interventions, including prevention and control through vaccination, which will inevitably cause significant shifts in IMD epidemiology and serogroup distribution. IMD is also heavily influenced by behavioral and environmental factors, including ease of travel (globalisation), with larger and larger groups coming together in mass gatherings,[157,158] classically the Hajj pilgrimage.[159] but also other events such as the recent international scouts jamboree.[160]

The epidemiology of IMD across the African meningitis belt, in particular, highlights the ability of the pathogen to cause large epidemics, affecting millions of children and young adults. The lack of adequate healthcare in most of the affected countries leads to high case fatality rates and, importantly, high rates of long-term neurodevelopmental sequelae among survivors. The sudden onset of disease, initially with non-specific symptoms and signs, followed by rapid progression of illness to death, highlights the importance of prevention through vaccination as demonstrated by the phenomenal success of the MenAfriVac programme. The emergence of other serogroups causing IMD across the African meningitis belt, however, reinforces the need for multivalent vaccines against all major meningococcal serogroups. The development and licensure of low-cost, highly immunogenic pentavalent vaccines targeting serogroups A, C, W, X and Y is, therefore, eagerly awaited.[95] Conjugate vaccines not only provide direct protection for vaccinated individuals but, by preventing carriage acquisition, they can protect the whole population (indirect or herd protection) if sufficiently high vaccine uptake is achieved. Fortunately, MenB, for which a conjugate vaccine is unlikely to be developed, is as yet a rare cause of sporadic IMD, outbreaks or epidemics in the meningitis belt.

Data on the burden of IMD in other LMICs are scarce for many reasons, including the ease and availability of broad-spectrum antibiotics in the community without appropriate diagnostic testing as well as inadequate disease surveillance.[120,161] Sentinel surveillance in many countries, however, does allow monitoring of disease trends, including any shifts or emergence of new meningococcal serogroups,[162] thus allowing for implementation of control measures, such as meningococcal vaccination for appropriate age and risk groups.

Many of the countries where MenB predominates have established national immunisation programmes for one or more of the other meningococcal serogroups causing IMD. Until recently, the MenC conjugate vaccine was routinely used in many parts of Europe, Canada and Latin America, while other countries such as the US, for example, have always recommended the MenACWY conjugate vaccine based on their local IMD epidemiology. The recent emergence and spread of the highly-virulent MenW:cc11 strain from Latin America to Europe and beyond, in particular, has led to rapid implementation of the MenACWY conjugate vaccine for teenagers and young adults, and, in some countries, toddlers and young children.[163]

The recent licensure of two new protein-based MenB vaccines with broad coverage has provided a major boost for the fight against meningococcal disease in high-income countries where this serogroup is the main cause of IMD. In September 2015, the UK became the first country to implement 4CMenB into its national infant immunization programme and, three years on, large reductions have been observed in vaccine-eligible cohorts.[37] After the first 3 million doses, too, no major safety concerns have been identified.[18] A few other countries and regions have now implemented the vaccine into their national infant immunisation programmes, while South Australia also offers 4CMenB to toddlers and adolescents. MenB-fHbp, on the other hand, is currently not included in any national immunization programme but has been successfully used to control university-associated MenB outbreaks.[164] With increasing use of these vaccines, uncertainties about their safety, reactogenicity, effectiveness and duration of protection will be overcome with real world evidence.[165] Current barriers to routine MenB immunisation include the very low disease incidence and the relatively high cost of the vaccines. Unfortunately, the lack of impact on MenB carriage in teenagers makes 4CMenB less attractive for adolescent immunisation because MenB disease incidence is very low in this age group.[19]

Nonetheless, protein-based MenB vaccines hold great promise for preventing all meningococcal disease since these protein antigens may be present across all meningococci, irrespective of serogroup.[21,22] These vaccines also have the potential to be combined with already available meningococcal conjugate vaccines (MenACWY) to provide broad protection against five major serogroups that responsible for nearly all IMD globally.[95] Additionally, next generation vaccines are likely to contain more meningococcal antigens to provide broader coverage, not only against meningococcal disease but, since some of these antigens are also present on other Neisseria species, including *Neisseria gonorrhea*, they could also help protect against gonorrhoea.[166] Given the rapid increase in the incidence of gonorrhoea and increasing concerns about multidrug resistance, such a vaccine would become very attractive for adolescents and young adults who could potentially be protected against both IMD and gonorrhoea by the same vaccine.[167]

A universal meningococcal vaccine, particularly one that combines the capsular polysaccharide and surface protein antigens, is important because meningococci are promiscuous bacteria that are capable not only of switching their polysaccharide capsules, but also of switching off capsular expression, which poses the risk of potential vaccine evasion, as seen in recent outbreaks of meningococcal urethritis.[168] The meningococcus also has a propensity to rapidly acquire and discard different virulence factors and genes, as evidenced by acquisition of antibiotic resistance alleles from gono-

cocci.[169] The ability of meningococci to acquire critical genes that allow them to survive in anaerobic environments such as the urogenital and anorectal tract, and to propagate through sexual transmission demonstrates their ability to adapt to hostile environments and external pressures.[170]

Conclusions

Meningococcal disease is stochastic and capable of causing large outbreaks associated with severe disease and high case fatality, as evidenced by recent epidemics in the African meningitis belt. The MenAfriVac programme has been greatly successful in controlling MenA disease but has highlighted the need for low-cost, multivalent meningococcal conjugate vaccines to control the major serogroups capable of causing future outbreaks and epidemics, especially MenX, for which a vaccine is currently not available. In high-income countries, many with already established MenC and MenACWY immunisation programmes, MenB is the predominant serogroup responsible for most IMD cases. Two new MenB vaccines with broad coverage are now available but few countries have opted to use them, mainly because of the low disease incidence. Next generation MenB vaccines with better strain coverage, combined with ACWY conjugates and/or greater protection against gonorrhoea may make them more attractive for implementation into national immunisation programmes.

Declaration of Interests

LHH has served as a consultant for GSK, Merck, Pfizer, and Sanofi Pasteur. MAS has received grants to support research projects and consultancy fee from GSK, Pfizer and Sanofi Pasteur. RB performs contract research on behalf of Public Health England for GSK, Pfizer and Sanofi Pasteur. HSM is an investigator on vaccine trials sponsored by industry; her institution receives funding from GSK, Pfizer and Sanofi-Pasteur for investigator-led research: she receives no personal payments from industry. FM-t has received financial and non-financial support outside the submitted work from Pfizer, GSK, MSD and Sanofi Pasteur; he also has received personal fees from Pfizer, Novavax, MSD, GSK and Sanofi Pasteur as consultant/advisor; his institution has also received financial support as trial fees from Ablynx, Jansen, Regeneron, Medimmune, Pfizer, MSD, Sanofi Pasteur, Novavax and Novartis, as well as non-financial support from GSK, Pfizer and MSD and research grants from Pfizer, GSK, MSD and Astra Zeneca. AvG has received reimbursements from Pfizer and Sanofi Pasteur; and students under her supervision have received grants from Sanofi Pasteur. SNL performs contract work for pharmaceutical companies on behalf of St. George's University of London, but does not receive any personal remuneration. All other authors: no conflicts declared

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