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Prevention and control of meningococcal disease: Updates from the Global Meningococcal Initiative in Eastern Europe

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SUMMARY

The Global Meningococcal Initiative (GMI) aims to prevent invasive meningococcal disease (IMD) worldwide through education, research and cooperation. In March 2019, a GMI meeting was held with a multidisciplinary group of experts and representatives from countries within Eastern Europe. Across the countries represented, IMD surveillance is largely in place, with incidence declining in recent decades and now generally at <1 case per 100,000 persons per year. Predominating serogroups are B and C, followed by A, and cases attributable to serogroups W, X and Y are emerging. Available vaccines differ between countries, are generally not included in immunization programs and provided to high-risk groups only. Available vaccines include both conjugate and polysaccharide vaccines; however, current data and GMI recommendations advocate the use of conjugate vaccines, where possible, due to the ability to interrupt the acquisition of carriage. Ongoing carriage studies are expected to inform vaccine effectiveness and immunization schedules. Additionally, IMD prevention and control should be guided by monitoring outbreak progression and the emergence and international spread of strains and antibiotic resistance through use of genomic analyses and implementation of World Health Organization initiatives. Protection of high-risk

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groups (such as those with complement deficiencies, laboratory workers, migrants and refugees) is recommended.

Introduction

Invasive meningococcal disease (IMD) is caused by the bacterium *Neisseria meningitidis* (Nm), which may invade the bloodstream resulting in life-threatening illnesses, the most common of which are meningitis and septicemia.[1] Nm is classified into 12 serogroups based on the capsular polysaccharide and six main serogroups (A, B, C, W, X, Y) are responsible for the majority of the IMD burden worldwide.[2,3] Globally, IMD affects approximately 1.2 million individuals each year and is associated with high fatality rates (up to 40%), as well as long-term sequelae (such as neurological complications) in approximately 20% of infected individuals.[4,5] As such, effective surveillance and prevention strategies are essential for the control of IMD.[6]

The Global Meningococcal Initiative (GMI) was formed in 2009 with the objective to prevent IMD worldwide through education, research and cooperation.[7] Over the last decade, the GMI has held a number of regional and global meetings with multidisciplinary groups of experts across fields including vaccinology, immunology and public health. Global recommendations for the management of IMD have been previously developed and published.[2,8]

The GMI held a roundtable meeting in Prague, Czech Republic in March 2019, with attendees representing a number of countries within the Eastern European region. The objectives of the meeting were to: (i) discuss IMD surveillance, epidemiology, prevention and control strategies in Eastern Europe, including current issues and barriers to implementation; (ii) share learnings and experiences from IMD immunization programs worldwide; (iii) discuss the importance of conjugate vaccines in the prevention of IMD; (iv) review the emergence of antibiotic resistance and describe recommended antibiotics for treatment and prophylaxis, and (v) discuss IMD in high-risk groups and recommendations for immunization. The local data included within this article were presented at the meeting, and/or provided by the relevant author shortly thereafter.

The epidemiology and surveillance of IMD, and prevention and control strategies in Eastern Europe

Surveillance of IMD

Implementation of effective surveillance strategies is key to the control of IMD, allowing the detection of cases and outbreaks, confirmation of the epidemiology of disease (e.g. incidence, burden and circulating serogroups), monitoring of strains and antibiotic susceptibility, as well as determination of the impact of control measures on disease.[6,9]

IMD surveillance is in place in the majority of countries represented at the meeting, with the exception of Azerbaijan, where there is a general surveillance program for infectious diseases. Surveillance systems generally involve confirming cases through polymerase chain reaction (PCR) testing and/or culture, and reporting suspected cases of IMD at a national level. In some countries, isolates are further characterized. For example, in the Czech Republic, multilocus sequence typing (MLST) and more recently, whole genome sequencing (WGS), are used in surveillance.[10,11] In Hungary, finetyping, MLST and WGS (the latter during outbreak investigations) are used to further characterize strains, with phenotypic testing to determine antimicrobial susceptibility to rifampicin.

Differences in surveillance systems were noted. In Georgia, sentinel surveillance of IMD is in place, with data submitted to the World Health Organization (WHO) on a monthly basis. Conversely, in Latvia and Romania, only passive surveillance of IMD is undertaken, while in Serbia, both passive and active surveillance of possible cases is performed. In most Eastern European countries, cases of IMD are reported to the European Centre for Disease Prevention and Control via the European Surveillance System (TESSy).[4,12]

Incidence of IMD

The incidence of IMD has declined over recent decades across many Eastern European countries.[13–16] Incidence is similar and generally <1 case per 100,000 persons per year (Table 1), ranging from 0.14 cases per 100,000 persons per year in Azerbaijan (although, due to a lack of robust statistics, incidence is expected to be higher) to 1 case per 100,000 persons per year in Croatia.[13–18] Notably, incidences of IMD and acute bacterial meningitis due to Nm have previously been documented at 2.45 and 1.9 cases per 100,000 persons per year in Kazakhstan (2005) and Turkey (2005–2006), respectively.[13,16] Incidence of IMD is highest among children <5 years old, particularly in those <1 year old, with incidences of 10.65, 5.4–38.7 and approximately 11 cases per 100,000 persons per year in Poland (2018),[18] the Czech Republic (1993–2018)[13] and Latvia (2008–2018),[13] respectively. Gender differences have been reported in Latvia and Croatia, with greater incidence of IMD recorded in males compared with females.[13]

Case fatality rates (CFRs) range from approximately 3% to 30% both within and across the Eastern European countries represented.[13,17,18] In Poland, the greatest CFR (44%) was noted in individuals aged >65 years, while in the Czech Republic and Hungary, mortality is greatest among infants (16.4% and 11–29% for serogroups B and C among children aged ≤5 years, respectively).[13] In Kyrgyzstan, deaths from bacterial meningitis have declined in recent years (from 12.4% in 2015 to 4.7% in 2018) due to the introduction of guidance on surveillance, anti-epidemic measures, diagnosis and treatment of bacterial meningitis in 2015, and the provision of training to physicians on the diagnosis and treatment of patients (Table 1).[13]

Serogroup distribution

In the Eastern European countries participating in the meeting, the predominant serogroups of Nm were serogroup B (accounting for approximately 60–90% of cases) and serogroup C (re-emerging in a number of countries and accounting for up to 30% of cases), followed by serogroup A (Table 1).[13–22] Cases of serogroup A disease are still reported in Romania,[14] the Republic of Belarus (5%

Table 1
Overview of the epidemiology of IMD and available vaccines in Eastern European countries.

Region/country	Incidence of IMD (cases/100,000 persons/year)	CFR	Serogroup distribution	Control strategies (vaccines)
Poland	• 0.45 (2018)[18] • 10.65 (infants <1 year old)[18]	• 14% (2013–2017)[18] • Increased in: • People aged 65+ (44% 2013–2017)[13] • 2016–2017 compared with earlier years (from 12.5% in 2013 to 18.8% in 2017)[13] • Cases of serogroup W disease (38.5% 2013–2017)[18]	• Stable 2014–2018, with ~70% B and 25–30% C[18] • Increase in serogroup W observed in 2018 (9.8%) relative to 2014–2017 (2.2–4.4%)[18]	• Vaccines recommended but not reimbursed[30]
Czech Republic	• 0.4 to 2.2 (1993–2018); declining since 2003[13] • 5.4–38.7 (infants <1 year old)[13]	• 4.7–16.4%[13] • Highest rate seen in infants[13]	• Serogroup B most prevalent and highest in infants <1 year old[13] • Serogroup C re-emerging, particularly since 2011 [13] • Few cases of serogroup W disease observed (22 cases from 1984 to 2017)[26]	• Vaccines recommended but not included in the NIP[27] • Combination of conjugate tetravalent vaccine and MenB vaccine is recommended • Some insurance companies reimburse vaccination • Vaccination is free of charge for patients with underlying diseases since January 2018
Hungary	• 0.4 (1988–2018)[13] • Serogroup C outbreaks 1999–2000 and 2010–2011 [13]	• Average >10% (2006–2018)[13] • 11–29% in children aged <5 years old[13] • High for serogroups B and C[13] • 17–31% in individuals with serogroup C disease aged 10–24 years[13]	• Serogroup B most prevalent (~60% of all cases 2009–2018), followed by C, with cases of serogroup W (9.3% of cases in 2016; 2.4% in 2017–2018) and Y (8.7% of cases in 2013; 1% in 2014–2018) reported[19] • Incidence highest in infants <1 year old and adolescents aged 15–19 years old[13]	• Vaccination recommended but not mandatory[29] • Recommendations include:[29] • Vaccination from 2 to 3 months, maintained up to 25 years old (MenC conjugate vaccine (freely available to children <2 years old) • Quadrivalent conjugate and MenB vaccine for international travellers, high-risk groups and special populations
Croatia	• 1 (1985–2017)[13]	• ~10%[13]	• Serogroup B most prevalent (~90% of cases 2008–2012); however, in 2017–2018, it accounted for 57%, C for 23% and Y for 11–13% of cases[13] • Serogroup W reported (4 cases from 2009 to 2018;[25] 1 case in 2019)[13] • Serogroups B and C predominate in infants and children ≤5 years old; serogroups C and Y account for the majority of cases in adolescents and adults >15–25 years old[13] • Incidence higher in males (69%) compared with females in 2018 [13]	• Meningococcal vaccine included in the NIP for high-risk groups • Conjugate MenACWY and MenB vaccines are available
Georgia[13]	• From 2010–2018, incidence varied from 0.32 (2016) to 0.67 (2011)	• Data not available	• Available data indicate that cases are largely attributable to serogroups B and C, with cases of serogroup W disease also reported (3 cases from 2015 onwards)	• Pneumococcal vaccine PCV10 introduced December 2014 • Meningococcal vaccine not included in the NIP; although MenACWY conjugate vaccine is available if needed
Romania	• ~0.5 (2008), declining to just over 0.3 (2017)[14] • Highest number of cases in 0–4-years (30 cases) and 15–19-years age groups (<10 cases) in 2017 [14]	• Data not available	• Serogroup B predominates, with cases of serogroup W and A disease reported[14]	• No meningococcal vaccines are available in the NIP • MenACWY conjugate vaccine approved in 2018 and available upon request
Serbia[13]	• 0.17 (12 reported cases in 2017)	• 6.45% • Serogroup B: 5.76% • Serogroup C: 10%	• From 2009–2018, the majority of confirmed cases serogroup B, except in the 25–49-year group, where serogroups B and Y are equally predominant (each accounting for ~40% of cases) • From 2008–2018, 2 cases of serogroup W disease and 4 cases of serogroup Y disease were reported	• Vaccination recommended but not mandatory • MenACWY conjugate vaccine for high-risk groups

(*continued on next page*)

Table 1 (*continued*)

Region/country	Incidence of IMD (cases/100,000 persons/year)	CFR	Serogroup distribution	Control strategies (vaccines)
Republic of Belarus	• 0.6 (2018), with a decline noted over the last 20 years[13]	• During 1997–2018, deaths peaked in 1999–2004 and 2011–2016 [13]	• Predominant serogroups are B (65%), followed by C (11%), W (9%), A (5%) and Y (4%) (2011–2018)[20] • Increased detection of isolates belonging to serogroups W and Y from 2015 to 2018 [13]	• No meningococcal vaccines are available in the NIP • MenB vaccine registered and will soon be available
Latvia[13]	• 0.4 (2018), with incidence declining since 1970 • ~11 (infants <1 year old)	• 12.5% (2018) • 28.57% (2013)	• Most common serogroup is B	• No meningococcal vaccines are available in the NIP • Registered vaccines are 4CMenB and MenACWY conjugate, but vaccination is voluntary
Russia	• Last outbreak in 1996, caused by serogroup A[145] • Incidence decreased over 2010–2016, but has increased recently (0.45 in 2016 to 0.48 in 2017)[17]	• 19% (2017)[17]	• In 2017, serogroup B predominated (27%), followed by serogroups C (14%), A (11%) and W (8%)[17] • In 2018, serogroup A was the predominant cause (41%), followed by serogroups W (25%), B (17%) and C (14%) at the 2nd Hospital for Infection Disease (Moscow)[13]	• Mass vaccination is not carried out during non-epidemic periods, except is high-risk groups[28] • Licensed vaccines are: • MenA polysaccharide • MenC conjugate • MenAC polysaccharide • MenACWY conjugate • MenACWY polysaccharide
Kazakhstan[146]	• 2.45 (2015)[95] • Outbreaks of IMD in spring/summer 2016–2018	• Despite the decline in incidence since 2015, fatal cases have risen (from 4.9% in 2015 to 22% for 2018)	• In 2018, 63% of cases in Almaty were serogroup A • In 2017, 18.4% of cases were serogroups W, X and Y • In 2013–2017, 63.3% of cases were in children aged <14 years; serogroup B predominated (2009–2015)	• No vaccine against IMD is included in the NIP • MenACWY conjugate is available, but vaccination is voluntary • Pilgrims travelling to Saudi Arabia can pay to receive the vaccine at a medical institution
Azerbaijan[13]	• 0.14 (2015) • Incidence varies: one case in 2009 and 2010, up to 14 cases in 2015; three cases in 2018 • In children <5 years old, incidence ranges from 14 cases in 2011 to one case in 2018	• Data not available	• Serogroup A (7 cases), B (33 cases, C (21 cases), W (11 cases) and X (1 case) reported from 2010 to 2018 in children <5 years old	• No meningococcal vaccines available • MenACWY conjugate registered in 2018
Kyrgyzstan[13]	• Peak incidences 12.5 (1997) and 6.6 (2015) • 0.36 (2018)	• Declined from 12.4% (2015) to 4.7% (2018)	• Data not available	• Meningococcal vaccinations not included in the NIP, but individuals (e.g. pilgrims travelling to Saudi Arabia) can pay to receive a vaccine at a medical institution
Turkey	• 3.5–4.0 in children <5 years old (2005), with the majority of cases in those aged <1 year[a],[16] • 1.9 (2005) decrease to 0.9 (2014)[a],[15,16]	• 3.2% (2014)[a], [13]	• Serogroups W and B responsible for the majority of cases in 2005–2017[15,16,21] • Large increase in serogroup B disease in 2017 (65% of cases), with cases of serogroups A (<10% of cases), W (<10% of cases) and X (<5% of cases) also reported[15,16,21]	• A NIP is in place, but does not include the conjugate quadrivalent (MenACWY) or MenB (4CMenB) vaccines available • MenACWY for military personnel and Hajj pilgrims • MenACWY (routine) and 4CMenB (since 2019) for patients receiving eculizumab • Vaccination recommended for other high-risk groups

4CMenB = multicomponent meningococcal serogroup B vaccine; CFR = case fatality rate; IMD= invasive meningococcal disease; MenA= meningococcal serogroup A; MenAC = meningococcal serogroups A and C vaccine; MenACWY = meningococcal serogroups A, C, W and Y vaccine; MenB = meningococcal serogroup B; MenC = meningococcal serogroup C; NIP = National Immunization Program; PCV10 = pneumococcal conjugate vaccine.

[a] Incidence of/CFR for acute bacterial meningitis due to *Neisseria meningitidis*.

of cases from 2011 to 2018),[20] Russia (11% of cases in 2017),[17,23] Azerbaijan (seven cases from 2010 to 2018 in <5 year olds)[13] and Turkey (<10% of cases since 2005).[16]

Cases attributable to serogroup W, Y and X are also emerging.[24] Serogroup W disease has been documented in Poland (9.8% of cases in 2018),[18] Croatia (four cases from 2009 to 2018; one case in 2019),[13,25] the Czech Republic (11 cases from 2010 to 2017),[26] Hungary (seven cases from 2016 to 2018),[19] Georgia (three cases since 2015),[13] Romania (one case in 2011),[14] the Republic of Belarus (9% of cases from 2011 to 2018),[20] Kazakhstan (18.4% of cases [serogroups W, X, Y] in 2017),[13] Russia (8% of cases in 2017),[17] Serbia (two cases from 2008 to 2018), Azerbaijan (11 cases from 2010 to 2018 among <5 year olds)[13] and Turkey (<10% of cases in 2017).[14-16,21] Available data indicate that ST-3342 (cc865) has been recorded in the Czech Republic since 2010, as well as in Poland during 2013–2014.[13,26]

Cases of serogroup W disease (including ST-9316 and cc11) have recently increased in Poland (from 2.2% in 2014 to 9.8% in 2018),[18] Russia (8% of cases in 2017)[17] and Kazakhstan (from 2.6% in 2015–2016 to 18.4% in 2017 [serogroups W, X, Y]).[13] Conversely, the proportion of serogroup W cases in Turkey has declined following peaks in 2009–2010 and 2011–2012 (from >50% to <10% of cases in 2017),[21] together with cases in Hungary (from 9.3% of cases in 2016 to 2.4% in 2017–2018).[19] In Poland, cases of serogroup W disease are more common in males <3 years of age and in females aged 25–65 years of age or above, with a CFR of 38.5% in 2013–2017.[13,18]

Cases of serogroup Y disease appeared in Croatia in 2011 and accounted for 11–13% of cases in 2017–2018 while in Serbia, four cases were reported from 2008 to 2018, with serogroup Y and serogroup B disease equally prominent among individuals aged 25–49 years (each accounting for approximately 40% of cases from 2009 to 2018).[13] Cases of serogroup Y disease have also been documented in Hungary (from 2013 onwards; 8.7% of cases in 2013 and 1% of cases 2014–2018),[19] Kazakhstan[13] and the Republic of Belarus (4% of cases from 2011 to 2018).[20] Since 2017, one case of serogroup X has been recorded in both Turkey (2017) and in Poland (2018), while one case was documented in Azerbaijan in 2011.[13,18,21]

Prevention and control strategies

Prevention and control strategies available across Eastern European countries encompass vaccination and antimicrobial prophylaxis. In the event of an outbreak, close contacts of cases of IMD are closely monitored and/or chemoprophylaxis is provided,[27,28] with vaccination as appropriate and increased epidemiological and laboratory surveillance undertaken. Both conjugate and polysaccharide vaccines are available, although not provided via National Immunization Programs (NIPs) in the majority of countries (Table 1). Generally, Eastern European countries provide vaccination to high-risk populations (e.g. immunocompromised individuals) and special populations (e.g. military recruits, the elderly, travelers) only.[27–29] However, in many countries, vaccination is recommended, but not mandatory and/or not reimbursed.[27,29,30]

Barriers to implementation of vaccination strategies include the low incidence of IMD, high cost of meningococcal vaccines, lack of universal vaccines against all meningococci and absence of effect on carriage for current MenB vaccines. Potential solutions include provision of additional vaccination recommendations, reduction of the price of vaccines, inclusion of additional vaccines in NIPs and implementation of educational initiatives to change current attitudes towards vaccination.

Meningococcal immunization: overview, recent developments and predicting coverage

Conjugate vaccines and the prevention of IMD

Conjugate vaccines, formed by binding the polysaccharide antigen of interest to a carrier protein that will induce a T cell-dependent immune response (e.g. the tetanus toxoid protein), have several advantages when compared with pure polysaccharide vaccines, including an ability to induce immunological T cell memory and consequently high response to boosters, as well as a lack of hypo-responsiveness following repeated dosing.[7,31–33] Importantly, conjugate vaccines also infer indirect (herd) protection through hindering the acquisition of carriage.[34] As such, the GMI recommends that conjugate vaccines replace plain polysaccharide vaccines whenever cost, availability, licensing, and immunization policy allow.[9] A number of conjugate vaccines are available worldwide, although it should be noted that their availability varies from country to country.[9]

As discussed previously,[9] introduction of the conjugate meningococcal serogroup C (MenC) vaccine in the UK infant immunization schedule in 1999, with a catch-up program for all children and adolescents under the age of 18 years, led to a rapid decline in the incidence of MenC disease, with reductions observed in carriage (Fig. 1(A)).[34,35] Similarly, the introduction of the meningococcal serogroup A (MenA) conjugate vaccine in Africa in 2010 has eliminated carriage of MenA (Fig. 1(B)).[36–39] Multivalent conjugate vaccines that provide protection against meningococcal serogroups A, C, W and Y (MenACWY) are also proving effective. For instance, prevention of the acquisition of carriage of serogroup Y has been shown following the administration of the MenACWY vaccine among university students in the UK.[40] Further, following an outbreak of meningococcal serogroup W (MenW) disease in the UK, direct protection was reported among the MenACWY-vaccinated cohort of adolescents aged 14–18 years, as observed through a reduction in cases of MenW (Fig. 2).[41] However, further research is required to understand the impact of vaccine implementation on carriage of serogroup W. Currently, a pentavalent ACWXY conjugate vaccine that will potentially be targeted at individuals aged 9 months to 29 years in sub-Saharan Africa is in clinical trials; the Phase I trial has been completed[42] and Phase II trials are ongoing. While time-consuming, expensive and difficult to undertake, carriage studies will help us to support and guide the introduction of conjugate vaccines and measure the indirect impact of their addition to vaccination programs.[34]

Meningococcal serogroup B vaccines

Unlike other meningococcal serogroups, it is not possible to create vaccines that target the capsular polysaccharide of meningococcal serogroup B (MenB) as the polysialic acid component of the capsule is homologous to an adhesion molecule found on the surface of human neural cells.[43] As such, this polysaccharide would be poorly immunogenic, with the potential to induce an autoimmune response.[44] Major breakthroughs in the development of vaccines for MenB were (i) the development of outer membrane vesicle (OMV) vaccines, which have previously been used to control local and clonal outbreaks in countries such as New Zealand, Norway, Cuba and France, and are still used in Cuba,[45,46] and (ii) the development of vaccines including recombinant surface proteins.[47]

Currently, two vaccines targeting MenB are licensed in Europe: (1) a multicomponent vaccine (4CMenB [Bexsero®]); licensed since 2013; including four main surface proteins (factor H-binding protein [fHbp], *Neisseria* adhesin A [NadA], Neisserial Heparin Binding Antigen [NHBA] and Porin A [PorA]); and (2) a bivalent MenB vaccine (MenB-fHbp [Trumenba®]); licensed in May 2017; composed of two variants of fHbp.[48,49] Broadly speaking, 4CMenB provides protection against isolates expressing variant 1 peptides of fHbp, variant NadA-1 and NadA-2/3 peptides of NadA, NHBA and/or PorA 1.4, with a gradient of protection observed according to how homologous the respective peptide subvariants are to the antigens in the vaccine and the level to which they are expressed.[50] Given that the distribution of the peptide subvariants differs according to region and age, the coverage of these vaccines against circulating MenB strains is not certain, but can be predicted using assays such as the Meningococcal Antigen Typing System (MATS; 4CMenB) and Meningococcal Antigen Surface Expression (MEASURE; MenB-fHbp; see following section for further detail) assay. The predicted coverage of 4CMenB differs across countries, ranging from 66% in Canada to 91% in the US, while the predicted coverage of MenB-fHbp is 91%, based on 1923 isolates from the US, the UK, France, Norway, the Czech Republic,

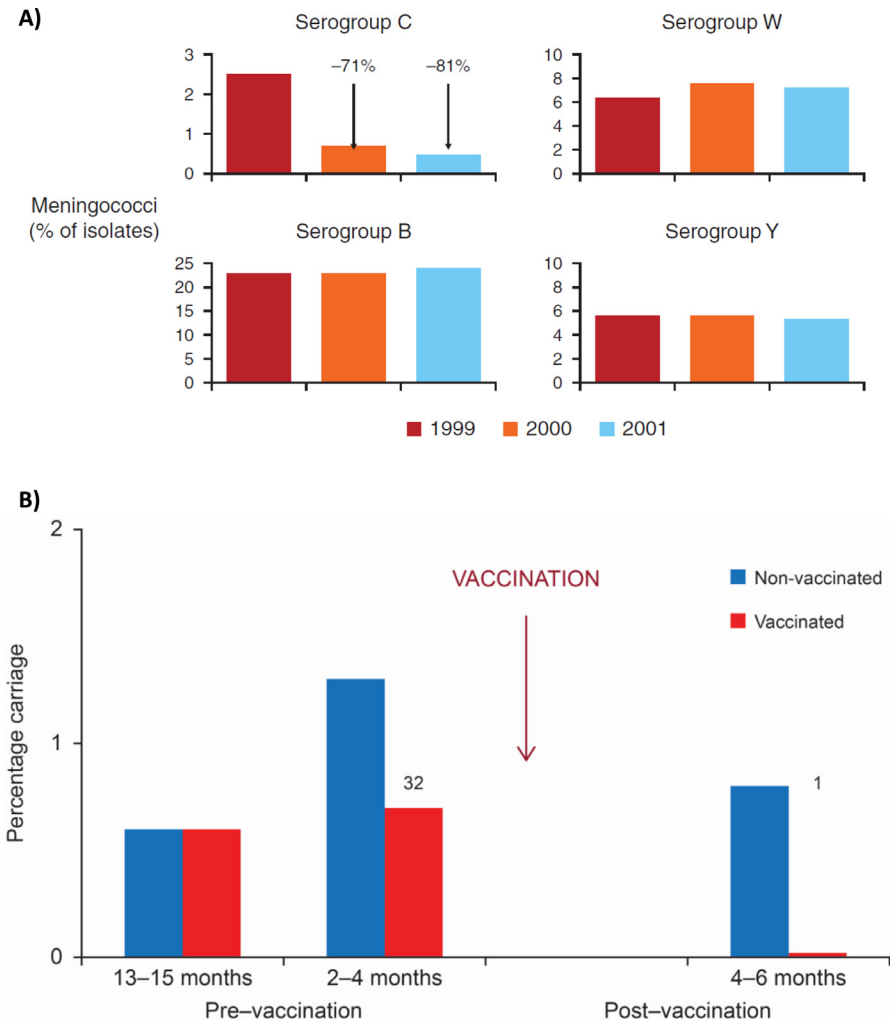

Fig. 1. Reductions in carriage of (A) serogroup C, in contrast to other serogroups, and (B) serogroup A following the introduction of MenC and MenACWY, in the UK and Africa, respectively.[34,36] MenC = meningococcal serogroup C; MenACWY = meningococcal serogroups A, C, W and Y vaccine.

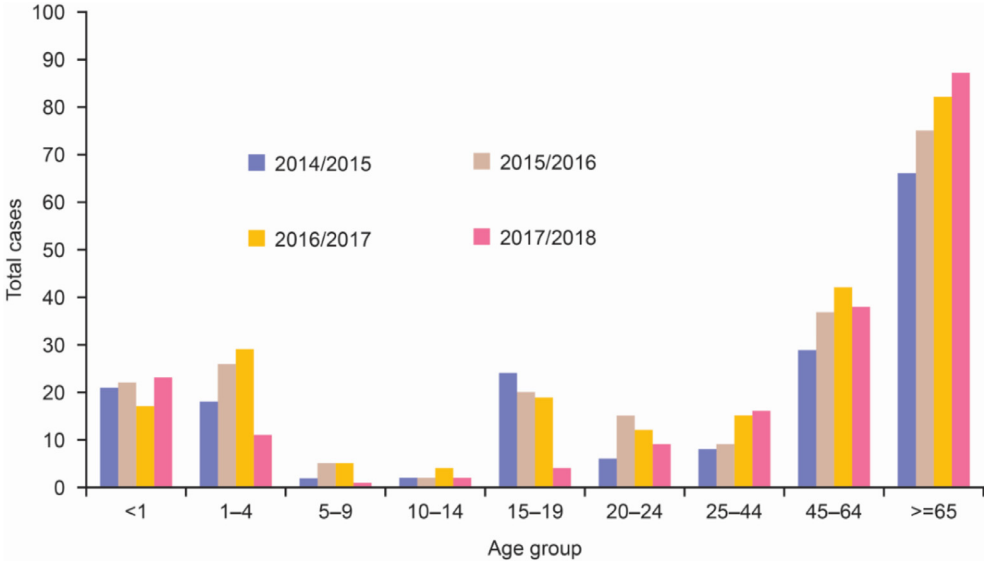

Fig. 2. Age distribution of MenW cases in the UK following immunization of adolescents aged 14–18 years with conjugate MenACWY vaccine, which commenced in 2015.[41] MenW = meningococcal serogroup W; MenACWY = meningococcal serogroups A, C, W and Y vaccine.

Table 2
Reductions in the carriage prevalence of *N. meningitidis* in subjects who received 4CMenB versus those who received control vaccination (Japanese Encephalitis vaccine) (adapted from Read et al.[40]).

N. meningitidis serogroup(s)	Odds ratio (95% CI)	Carriage reduction (95% CI)
All NmB	0.8 (0.6–1.1)	15.6% (–11.0 to 35.9)
Disease associated MenB	0.9 (0.7–1.2)	12.6% (–15 to 34.1)
BCWY	0.7 (0.6–0.9)	26.6% (10.5 to 39.9)
CWY	0.7 (0.5–0.9)	29.6% (8.1 to 46.0)

4CMenB = multicomponent meningococcal serogroup B vaccine; BCWY = capsular group B, C, W, Y; CI = confidence interval; CWY = capsular group C, W, Y; MenB = meningococcal serogroup B; NmB = *Neisseria meningitidis* serogroup B.

Table 3
Summary of ongoing studies to determine the impact of serogroup B vaccination on carriage.

Study (country)	Participants	Study arms	Primary endpoint	Initial findings and/or estimated completion
Be on the Team (UK)[13]	~24,000 adolescents (16–18 years) from schools/colleges across the UK	• 4CMenB at 0 and 6 months • MenB-fHbp at 0 and 6 months • 4CMenB at the end of the study period	Rate of oropharyngeal carriage prevalence of pathogenic meningococci (capsular groups B, C, W, Y, X) following immunization	October 2020 (estimated completion of data collection)
B Part of It (Australia)[57,58]	34,483 adolescents (16–18 years; mean age 16 years) from 235 schools in South Australia	• 4CMenB at baseline and 1–2 months following • 4CMenB at study completion (12 months)	Rate of oropharyngeal carriage prevalence of pathogenic meningococci (capsular groups A, B, C, W, Y, X) following immunization	Carriage rates were: • Lower than expected (4.9% in Year 12 students, 3% in Year 11 and 1.9% in Year 10 ($p < 0.001$ [Year 12 versus Year 10]) • Higher in students with a current cold/sore throat (4.0% compared with 2.9% [$p = 0.001$]) • Higher in cigarette, e-cigarette and water pipe users compared with non-users (13.7%, 9.8% and 9.9%, respectively) • Highest in Aboriginal students, followed by Caucasian students (5.3% versus 3.3%; $p = 0.05$) June 2020 (estimated completion)

4CMenB = multicomponent meningococcal serogroup B vaccine; MenB-fHbp = meningococcal serogroup B vaccine.

Spain and Germany.[50–55] While these assays may provide reasonable estimates of predicted coverage, this may differ in a real-life setting. Further, data are needed to determine the impact of these vaccines on established carriage and on acquisition of carriage, in addition to the protection provided against other meningococcal serogroups. For instance, data have shown that 4CMenB may not be effective against acquisition of carriage of serogroup B, although, reductions in carriage of capsular groups BCWY and CWY has been demonstrated (Table 2).[40] Similarly, vaccination with MenB-fHbp has not been shown to reduce meningococcal carriage or to prevent the acquisition of carriage of serogroup B.[56] Ongoing studies in the UK and South Australia (Table 3) will fully answer the question of whether serogroup B vaccination affects carriage, thus providing essential information for devising immunization schedules.[13,57,58]

Both 4CMenB and MenB-fHbp have exhibited immunogenicity, although some concerns in relation to fever, seizures and Kawasaki disease were initially identified for 4CMenB.[59–61]

In September 2015, the UK added 4CMenB to the infant immunization schedule with a 2, 4 and 12-month regimen. Reductions in the number of cases of MenB have been observed, particularly in children aged <1 to 2 years, following the implementation of 4CMenB, with primary doses administered at 2 months and 4 months (and an opportunistic catch-up for 3- and 4-month olds).[62] When considering all MenB disease, effectiveness of two doses of vaccine has been estimated at 82.9%.[62] No safety concerns have been observed following the vaccination of 1.29 million children aged 2–18 months with 3 million doses of 4CMenB;[63] however, further studies are required to determine the need for boosters and their frequency.

Recently, pentavalent ABCWY vaccines have been developed, with promising results in Phase II trials,[64] although additional data are required to identify the value of these vaccines compared with targeted co-administration of ACWY and MenB vaccines.

Determination of strain coverage of serogroup B vaccines

Determining the predicted coverage of serogroup B vaccines can help to inform vaccine effectiveness and immunization schedules at the country level.[65] To predict strain coverage, MATS (for 4CMenB) and MEASURE (for MenB-fHbp) assays have been developed.[52,66]

The MATS assay comprises (i) genotypic characterization of PorA and (ii) phenotypic characterization of fHbp, NHBA and NadA. For the latter, detergent lysates of test and reference isolates are applied to three enzyme-linked immunosorbent assay (ELISA) plates, one per antigen. The resulting test and reference curves are then compared to provide a relative potency (RP) for each antigen

for each isolate. If a test isolate has PorA P10.4 and/or any single RP exceeds a threshold level, known as the positive bactericidal threshold (PBT), the isolate is considered MATS-positive and therefore likely covered by the vaccine. Thus, the RP is determined by a combination of antigenic expression and antigenic similarity to the vaccine antigen variant against which the ELISA antisera were raised.[66]

Since the introduction of 4CMenB to the UK infant immunization program, MATS has formed an important part of enhanced surveillance. For example, up until the end of December 2017, surveillance data from England revealed that there were a total of 202 laboratory confirmed cases of IMD in infants born from May 1st 2015. Of these, 177 were eligible for vaccination, of which MenB accounted for 116 (66%) cases. Of the eleven vaccine-eligible MenB cases that had received three doses of vaccine, five were culture confirmed and two were MATS positive (unpublished data).

To determine MenB-fHbp coverage via MEASURE, flow cytometry is used to determine fHbp expression, with mean fluorescence intensity calculated to assess strain coverage.[52] Protein expression with a mean fluorescence intensity of above 1000 arbitrary units (corresponding to 30 pg of fHbp/μg of cell extract) predicts with 91% accuracy that a MenB isolate would be killed by antibodies induced by the MenB-fHbp vaccine.[52] Currently, MenB-fHbp has not been used as part of a NIP. As such, population-based MenB-fHbp effectiveness data are not available.

The use of MATS and MEASURE assays to estimate the strain coverage of MenB vaccines has a number of limitations, such as the inability to evaluate non-culture cases and limited availability for reference laboratories to be able to perform the assays. As a result, Genetic Meningococcal Antigen Typing System (gMATS)[67] has been developed to assess strain coverage of 4CMenB in culture and potentially non-culture cases. gMATS was developed using a large international genotypic/MATS dataset (n = 3481 isolates) to assign antigen peptides to covered, not covered or unpredictable (half of which are considered covered within national strain panel datasets). The Bexsero Antigen Sequence Type (BAST) scheme provides a reproducible method for collective typing of 4CMenB vaccine antigens whereby each unique combination of fHbp, NHBA, NadA, PorA-VR1 and PorA-VR2 is assigned a unique arbitrary identification number or 'BAST'. BASTs can be used in conjunction with predictors of antigenic coverage such as MATS data to aid prediction of coverage for, and comparisons between, genotypic datasets. When used in this way, it is important to define the basis on which a given BAST is considered covered/not covered.[68]

While gMATS and seven-locus MLST (used to demonstrate the utility of genotype-phenotype association) have previously exhibited 92%[67] and 80%[68] prediction accuracy versus MATS, respectively, both relied on correlation with MATS data for identifying cross-reactive variants. Data suggest that gMATS can accurately complement MATS in predicting 4CMenB strain coverage in England and Wales in 2007–2008, with coverage estimated at 70% via MATS and 72–73% via gMATS, compared with 88% killing in the human complement serum bactericidal antibody assay.[67,69] Consequently, gMATS may constitute a reliable alternative to MATS; however, ongoing MATS analysis is likely to be necessary to maintain a relevant gMATS dataset (e.g. accounting for novel peptides or peptides expanding in their frequency among IMD cases).

Challenges in the management and surveillance of IMD: the emergence of antibiotic resistance and of new strains of *Neisseria meningitidis*

Antibiotic resistance

The emergence of antibiotic resistance is a growing problem worldwide.[9] Nm is generally susceptible to the antibiotics used in the treatment and prevention of IMD. However, isolates with reduced susceptibility to penicillin are increasing[9,70] and can arise through alterations of penicillin binding protein 2 (PBP2) involved in cell wall synthesis or from the production of beta-lactamase (an enzyme that inactivates beta-lactams).[70] Rare beta-lactamase-producing (penicillin resistant) Nm strains were described in Canada, South Africa and Spain in the 1980s and were thought to arise through transfer of beta-lactamase-encoding plasmids from *Neisseria gonorrhoeae* (Ng).[71–76] In recent years, isolates from France, Canada, the UK and Germany have been found to produce beta-lactamase.[77–79] These isolates belonged to serogroup Y cc23 and possessed the ROB-1 gene that encodes beta-lactamase, which was likely acquired through transformation from *Haemophilus influenzae*.[77,78]

In terms of modifications of PBP2, mutations within the portion of the *penA* gene that encodes transpeptidase activity have been reported in isolates that demonstrate reduced susceptibility to penicillin G and amoxicillin Y yet remain susceptible to third-generation cephalosporins.[70] These altered *penA* alleles have been documented across a number of countries and it is thought that approximately 33% of isolates possess altered *penA* conferring reduced susceptibility to penicillin, although, this varies from country to country (e.g. 88% in Italy versus 6% in Sweden).[80]

Of concern, isolates harboring the *penA327* allele that demonstrate reduced susceptibility to penicillin and third-generation cephalosporins were identified in 2012. The *penA327* allele was found to originate from Ng[81] and has been observed in isolates from men who have sex with men (MSM) in France, as well as urethritis cases.[81] These isolates demonstrate intermediate susceptibility to cefotaxime and as such, should be kept under surveillance.

Isolates that are resistant to rifampicin and ciprofloxacin are rare; however, close surveillance is warranted. Resistance to rifampicin, which inhibits transcription by interacting with the beta subunit of RNA polymerase, arises from alterations in the *rpoB* gene.[82] Ciprofloxacin inhibits DNA topoisomerases to inhibit DNA replication, with ciprofloxacin resistance resulting from mutations in the *gyrA* gene that were likely acquired through horizontal gene transfer from other *Neisseria* species.[83] Isolates with modified *rpoB* have been documented in Europe,[84] while isolates resistant to ciprofloxacin have been found in France, Italy, Spain and Sweden,[83] with a recent outbreak (serogroup A) in India.[85–87] Ciprofloxacin-resistant isolates belonging to different serogroups (A, B, C, E, W and Y) and possessing different *gyrA* alleles have also been recorded in Shanghai.[88,89] Global surveillance of antibiotic resistance is therefore required to identify changes in antibiotic susceptibility of Nm to ensure that both cases and outbreaks of IMD can continue to be managed effectively, and appropriate prophylaxis can be utilized where indicated.

Monitoring outbreak progression, international spread and the emergence of new strains of Neisseria meningitidis

The general advantages of genotypic analyses include their relative simplicity, portability of data, utility in non-culture cases, sensitivity to detect and characterize broad variation, and relative resolving power. The superiority of genome-based high-resolution core genome multilocus sequence typing (cgMLST) over standard seven locus MLST in resolving population structure, identifying emergent strains and tracing outbreak progression, both nationally and internationally, has been demonstrated for the ST-11 complex (cc11).[90] This includes (i) the progression of a MenW ccc11 outbreak that originated in South America before spreading to Europe, Australia and North America,[26,77,90–93] (ii) the current expansion of two unique serogroup C cc11 strains in the UK,[94] and (iii) the heightened potential for cc11 lineage 11.2 meningococci to

escape MenB vaccine immunogenicity.[95] The well-established Meningitis Research Foundation meningococcus genome library, containing genome sequences for all invasive meningococcal isolates received by the Public Health England Meningococcal Reference Unit since July 2010,[94] is a forerunner to a proposed Global Meningitis Genome Library, to include Nm, *Streptococcus pneumoniae, H. influenzae* and *Streptococcus agalactiae*. This is in the early stages of planning and is intended to support the new WHO Global Roadmap to defeat Meningitis by 2030.[96]

Emergence of the US Neisseria meningitidis non-groupable urethritis clade

Diverse Nm have been reported within the ano-genitourinary tract for decades, with a recent study documenting urethritis isolates among individuals from a number of countries spanning Europe, Asia and North America from 2002 to 2016.[97] Since 2001, outbreaks of IMD due to cc11 lineage 11.2 have been recorded among MSM in North America and Europe.[90,98–102] Since 2015, increased numbers of cases of Nm urethritis have been documented across sites in the US, predominantly involving heterosexual males who were recent oral sex recipients.[103,104] Comparison with geotemporally diverse cc11 isolates revealed that a single clade within lineage 11.2 was responsible for the increased reports of urethritis; the so-called United States of America (US) Nm non-groupable urethritis clade (US NmNG urethritis clade).[105]

The US NmNG urethritis clade is thought to have emerged around 2011, before expanding across at least 13 states in the East of the US from 2013 to 2016.[106] With suspected transmission during oral sex, this strain is a potential conduit between Ng and 'nasopharyngeal' Nm. The strain possesses gonococcal *aniA* (nitrite reductase) and *norB* (nitric oxide reductase) genes, enabling anaerobic growth.[105] It is stably acapsulate[107] due to loss of several capsular synthesis genes, which may lead to difficulties for non-culture diagnosis of IMD cases. Since its emergence, isolates within the clade have continued to acquire gonococcal DNA, with one isolate acquiring a gonococcal-like *mtrR* sequence, associated with reduced susceptibility to azithromycin.[106,108] Further, heteroresistant sub-populations with resistance to antimicrobial peptides polymyxin B and colistin, and reduced susceptibility to other antibiotics such as penicillin G, have been reported.[109] In addition to evolving antibiotic resistance, the strain has caused invasive disease in four males (including two MSM) and one female for whom immune status is not known.[106]

In terms of prevention, existing subcapsular vaccines could provide coverage; however, fHbp, NadA and NHBA are considered non-essential genes elsewhere within lineage 11.2 and, as such, may be dispensed with.[95,105,106] Consequently, the clade could escape MenB vaccine immunogenicity. However, current data[106] are promising, with 191 of 209 (91.4%) US NmNG urethritis clade isolates potentially covered by three antigens – fHbp, NHBA and NadA, and the remaining 18 isolates potentially covered by two antigens – fHbp and NHBA, or NHBA and NadA (Fig. 3). Furthermore, MATS analysis for several related MenB lineage 11.2 isolates with matching NHBA (peptide 20) is encouraging, with all isolates potentially covered for at least this antigen.[95] However, several US NmNG urethritis clade isolates were found to possess frameshifted *fHbp* and disrupted *NadA* alleles (two and 16 isolates, respectively), and PorA was mismatched across all of the isolates. Thus, unless NHBA serves a crucial function for colonizing the genitourinary tract, it seems likely that the US NmNG urethritis strain is as susceptible to escaping the licensed MenB vaccines as the rest of lineage 11.2. This is a concern, particularly for immunocompromised individuals on antibiotic prophylaxis. As such, ongoing surveillance and characterization of this and other potentially emerging Nm strains is warranted.

Expanded use of genomic analyses worldwide will further inform outbreak analyses and strain determination. The proposed Global Meningitis Genome Library and WHO initiatives, such as the Global Roadmap and Vaccine Preventable Disease Surveillance Standards documents, will also support disease surveillance to reduce the burden associated with this disease.

The Global Roadmap to defeat Meningitis by 2030

The Global Roadmap is being developed by the WHO, in collaboration with organizations such as the Meningitis Research Foundation, technical partners and stakeholders at the regional, national and global levels, with the aim of achieving a world in which meningitis is no longer an ongoing public health threat by 2030.[96] Specific goals are to eliminate meningitis epidemics, reduce cases and deaths from vaccine-preventable meningitis and decrease the impact of sequelae.[96] The Global Roadmap will describe the initiatives and planned steps that countries, organizations and communities need to take to achieve these goals, with a focus on the prevention of cases and deaths due to organisms responsible for the majority of non-tuberculous bacterial meningitis, i.e. Nm, *S. pneumoniae, H. influenzae* and *S. agalactiae*.[96] As well as a pillar on prevention and epidemic control, four other pillars include: diagnosis and treatment; disease surveillance; support and aftercare for people affected; and advocacy and information,[96] and these will seek to address issues more broadly than the four main pathogens. It is anticipated that the Global Roadmap will be presented to the World Health Assembly by 2020, for adoption at the global level.[96]

WHO Vaccine Preventable Disease Surveillance Standards

In order to improve regional monitoring and estimation of disease burden, and to achieve the goals of the roadmap, there is a need to strengthen surveillance and improve disease data reporting at the international level. WHO Vaccine Preventable Disease Surveillance Standard documents have been developed to provide global guidance for disease-specific surveillance, including outbreak investigation and response, based on available vaccines, current thinking and the latest laboratory techniques. Chapters are available for meningococcus, pneumococcus and *H. influenzae*.[110] In terms of IMD, surveillance objectives include: (i) detect and confirm cases (via culture and/or PCR), (ii) detect and confirm outbreaks, (iii) determine the epidemiology of disease, (iv) identify the impact of control measures and (v) establish populations and/or geographical areas at risk.[111] It is recommended that surveillance should be nationwide, case-based and carried out across all age groups.[111] Case definitions, and guidance in terms of laboratory investigations, data collection and reporting of cases are provided.[111]

Meningococcal carriage and disease: risk factors and recommendations for the prevention and control of IMD in at-risk groups

Risk factors for meningococcal carriage and disease

Meningococcal colonization of the respiratory tract (carriage) enables the microorganism to be transmitted from one person to another.[112] Transmission of bacterial infection primarily occurs among adolescents and young adults (15–25 years),[113] with several studies demonstrating the highest carriage rate in adolescents.[114–116] Key risk factors for the transmission/colonization of meningococci are invasive respiratory tract infections, and smoking and overcrowded living conditions and specific adolescent social behavior are risk factors for the local and global spread of meningococcal disease.[117–121]

Antigen	Potentially covered	Not covered
fHbp (4CMenB and MenB-fHbp)	Peptide 1.896 (*n* = 205) Peptide 1.456 (*n* = 1) Peptide 1.915 (*n* = 1)	Frameshift (*n* = 2)
NHBA (4CMenB)	Peptide 20 (*n* = 209)	n/a
NadA (4CMenB)	Peptide 2 (*n* = 193)	Insertion (*n* = 13) Frameshift (*n* = 3)
PorA (4CMenB)	n/a	P1.10-8 (*n* = 198) P1.10-1 (*n* = 9) P1.10-22 (*n* = 1) P1.9 (*n* = 1)

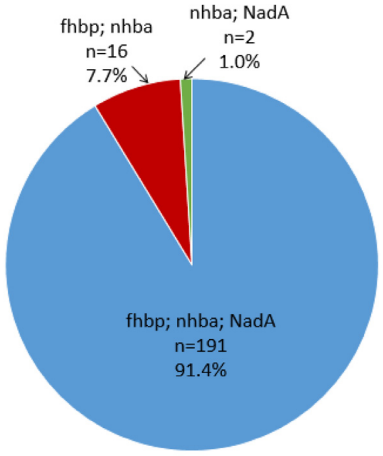

Fig. 3. 4CMenB antigen distribution and potential coverage among US NmNG urethritis clade isolates (n = 209). Adapted from Retchless et al.[106] 4CMenB = multicomponent meningococcal serogroup B vaccine; fHbp = factor H-binding protein; NadA = *Neisseria* adhesin A; NHBA = Neisserial Heparin Binding Antigen; PorA = Porin A; US NmNG urethritis clade = US *Neisseria meningitidis* non-groupable urethritis clade.

Upon acquisition, the first barrier against meningococcal infection is a functional complement system. As such, factors predisposing individuals to IMD include inherited deficiencies of the terminal complement pathway (e.g. deficiencies in complement components C5–C9) and medical conditions or treatment that may lead to acquired or secondary complement deficiency, such as treatment with eculizumab, a terminal complement pathway inhibitor.[122–125] For instance, individuals with terminal complement pathway deficiencies are thought to have a 7000- to 10,000-fold higher risk of IMD versus the general population.[122] Other populations at increased risk of IMD include laboratory workers and Human Immunodeficiency Virus-positive individuals, who have an estimated 184-fold[126,127] and 5-fold greater risk of IMD compared with the general population,[128] respectively, as well as migrants and refugees, who live in overcrowded conditions with poor sanitation.

Complement deficiencies and meningococcal disease

The complement system plays a major role in innate immunity; it is composed of complement proteins, activation of which results in cascade reactions to eliminate targeted cells or invaders.[129] The complement system therefore provides pivotal protection against meningococcal infection, with deficiencies in late components of the complement system (proteins C5–C9), and in regulatory proteins including factor D and properdin, linked to IMD.[130]

While complement deficiencies are primarily inherited as autosomal recessive traits[131] and as such, are rare, IMD is common in this population. Cases of IMD in patients with complement deficiency indicate that these patients are prone to repeated infections from identical or different isolates, with a theoretical risk for recurrent infection of 40–50%.[130,132] Further, in patients with inherited complement deficiency, data suggest that capsular group Y predominates.[132] Conversely, patients receiving eculizumab develop IMD due to more diverse capsular groups, including non-encapsulated strains. Vaccination with the ACWY conjugate vaccine is therefore recommended in individuals with complement deficiencies, including patients receiving eculizumab, with boosters every 5 years. Immunization with a vaccine targeting serogroup B isolates is also recommended, but the administration of boosters has not yet been defined. In addition, vaccination of household contacts of subjects with complement deficiencies (cocooning vaccination) may be beneficial. Penicillin V is recommended as the first-line antibiotic prophylaxis treatment; however, risk assessment should inform the optimal approach.

Further research is needed to determine the distribution of complement deficiencies, which are thought to vary according to region and population,[130,133,134] as well as typical characteristics for each complement deficiency, such as patient age and clinical presentation. Further studies of isolates from patients with complement deficiencies are warranted, including typing, vaccine coverage and susceptibility to penicillin.

Laboratory workers

Working with meningococci can lead to laboratory-acquired infections if appropriate safety precautions are not taken.[135] Indeed, review of laboratory-acquired cases of IMD has identified acquisition of infections outside of a safety cabinet.[126,135,136] Further, case reports of laboratory workers who have become critically ill or have died following exposure to meningococci confirm the importance of safe working practices when working with suspensions of meningococci.[135]

Guidance recommends that a safety cabinet is always used when performing microbiological work with meningococci, which should be reflected in local risk assessments.[135] Training on the signs and symptoms of meningitis, safe working practices and emergency procedures should be provided on a regular basis.[135] In addition, laboratory workers who may be exposed to Nm should receive available vaccines and boosters in-line with local immunization programs.[135] Further, antimicrobial prophylaxis (e.g. ciprofloxacin) should be prescribed in conjunction with relevant guidance if there has been a credible risk of exposure to live meningococci.[135]

Refugees and migrants

In addition to the groups at high risk of IMD previously mentioned, attendance at mass gatherings and international travel are known to increase the likelihood of Nm transmission.[137] Data suggest that there are approximately 5.2 million refugees and 1.4 million asylum seekers in the European Region.[138] These groups are at increased risk of meningococcal infection compared with the overall population due to overcrowded living conditions with poor sanitation and the undertaking of long and dangerous journeys. In addition, available health services can be sporadic or poor-quality

during travel to and/or within host countries, coverage of vaccinations is low among these individuals and antibiotic resistance is becoming a growing problem within crowded camps with poor hygiene.

Outbreaks of meningococcal disease in refugee camps have been successfully controlled through the implementation of timely and high-coverage vaccination campaigns, as demonstrated following an outbreak of serogroup A disease in a large refugee camp in Zaire in 1994.[139] Further, individual cases of IMD have been effectively managed through chemoprophylaxis (e.g. with rifampicin or ciprofloxacin) for cases and persons directly exposed to them, as shown following unrelated cases of meningococcal serogroup X and MenB among migrants and refugees in Italy and Turkey, respectively.[140–142] Consequently, early diagnosis, treatment and prophylaxis are key to protect these vulnerable populations, as well as host communities. However, surveillance is needed to determine the prevalence of carriers of Nm and of circulating serogroups among these populations in order to inform vaccine recommendations. In addition, challenges relating to the vaccination of migrants and refugees, such as refusal of vaccination for fear of legal consequences and lack of information on immunization status, and of co-ordination among public health authorities of neighboring countries[143] need to be addressed to facilitate the implementation of effective prevention and control strategies.

Conclusions

Effective surveillance strategies are key to the control of IMD, allowing the detection of cases and outbreaks, confirmation of the epidemiology of disease, monitoring of strains and antibiotic susceptibility, as well as determination of the impact of control measures, such as vaccination, on control of disease.[6] IMD surveillance is in place in the majority of Eastern European countries represented at the recent GMI meeting. Across these countries, the incidence of IMD has declined in recent decades and is generally <1 case per 100,000 persons per year. Predominating serogroups of Nm are B and C, followed by serogroup A; exploration of the genetic relationships between the serogroup A isolates and recent isolates from the meningitis belt is required. Cases attributable to serogroups W, X and Y are emerging. In terms of prevention, available vaccinations include both conjugate and polysaccharide vaccines, although, generally, these are not included in NIPs and are provided to high-risk populations only.

It is recognized that conjugate vaccines have a number advantages when compared with polysaccharide vaccines, including inferring both direct and indirect (herd) protection through the interruption of the acquisition of carriage, as has been demonstrated for serogroups A, C and Y.[34,39,144] However, further research is needed to understand the impact of vaccination on carriage of serogroup W, as well as if/how protein-based MenB vaccines affect carriage and/or protect against other meningococcal serogroups. These data, in addition to the predicted coverage of vaccines, can inform estimates of vaccine effectiveness and immunization schedules at the country level.

With the emergence of new strains of Nm and growing concern of antibiotic resistance, it is recommended that effective prevention and control strategies also be informed by monitoring outbreak progression, international spread of Nm and antibiotic resistance, as well as trends in risk factors. Expanded use of genomic analyses and implementation of WHO initiatives worldwide are expected to strengthen surveillance of IMD and reduce the burden of disease. Further, identification of individuals at high-risk of infection, such as those with complement deficiencies, laboratory workers and migrants and refugees, and the implementation of appropriate prophylactic measures within these populations, is essential for the prevention of outbreaks of IMD.

Declaration of Competing Interest

R Borrow, J Lucidarme and X Bai perform contract work for Public Health England on behalf of GSK, PATH, Sanofi Pasteur and Pfizer.

EC Dinleyici performs contract work for the Eskisehir Osmangazi University funded by GSK, Sanofi Pasteur and Pfizer.

A Skoczyńska has performed contract work for the National Medicines Institute funded by GSK and Pfizer, attended the Advisory Boards of GSK, Pfizer and Sanofi Pasteur and had personal fees from GSK, Pfizer and Sanofi Pasteur.

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MK Taha performs contract work for the Institut Pasteur funded by GSK, Pfizer and Sanofi Pasteur.

JA Vázquez performs contract work for the Institute of Health Carlos III funded by GSK and Pfizer and he has received personal fees from GSK, Pfizer and Sanofi Pasteur.

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CRediT authorship contribution statement

Xilian Bai: Writing - review & editing. **Ray Borrow:** Conceptualization, Funding acquisition, Writing - original draft, Writing - review & editing. **Suzana Bukovski:** Writing - review & editing. **Dominique A. Caugant:** Writing - review & editing. **Davor Culic:** Writing - review & editing. **Snezana Delic:** Writing - review & editing. **Ener Cagri Dinleyici:** Writing - review & editing. **Medeia Eloshvili:** Writing - review & editing. **Tímea Erdősi:** Writing - review & editing. **Jelena Galajeva:** Writing - review & editing. **Pavla Křížová:** Writing - review & editing. **Jay Lucidarme:** Writing - review & editing. **Konstantin Mironov:** Writing - review & editing. **Zuridin Nurmatov:** Writing - review & editing. **Marina Pana:** Writing - review & editing. **Erkin Rahimov:** Writing - review & editing. **Larisa Savrasova:** Writing - review & editing. **Anna Skoczyńska:** Writing - review & editing. **Vinny Smith:** Writing - review & editing. **Muhamed-Kheir Taha:** Writing - review & editing. **Leonid Titov:** Writing - review & editing. **Julio Vázquez:** Writing - review & editing. **Lyazzat Yeraliyeva:** Writing - review & editing.

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