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Global Meningococcal Initiative: Insights on antibiotic resistance, control strategies and advocacy efforts in Western Europe

Running title: Meningococcal disease in Western Europe

Ray Borrow,[1] Helen Campbell,[2] Dominique A. Caugant,[3] Abdessalam Cherkaoui,[4] Heike Claus,[5] Ala-Eddine Deghmane,[6] Ener Cagri Dinleyici,[7] Lee H. Harrison,[8] William P. Hausdorff,[9] Paula Bajanca-Lavado,[10] Corinne Levy,[11] Wesley Mattheus,[12] Claudia Mikula-Pratschke,[13] Paula Mölling,[14] Marco AP Sáfadi,[15] Vinny Smith,[16] Nina M. van Sorge,[17] Paola Stefanelli,[18] Muhamed-Kheir Taha,[6] Maija Toropainen,[19] Georgina Tzanakaki,[20] Julio Vázquez,[21]

[1]UK Health Security Agency, Meningococcal Reference Unit, Manchester, UK; [2]Immunisation Division, UK Health Security Agency, London, UK; [3] Norwegian Institute of Public Health, Oslo, Norway; [4] National Reference Center on Meningococci, Laboratory of Bacteriology, Geneva University Hospitals, Geneva, Switzerland; [5]German National Reference Center for Meningococci and *Haemophilus influenzae*, Institute for Hygiene and Microbiology, University of Würzburg, Würzburg, Germany; [6]Institut Pasteur, Invasive Bacterial Infections Unit and National Reference Centre for Meningococci, Paris, France; [7]Eskisehir Osmangazi University Faculty of Medicine, Eskisehir, Turkiye; [8]Center for Genomic Epidemiology, University of Pittsburgh, Pittsburgh, USA; [9]Center for Vaccine Innovation and Access, PATH, Washington, DC, USA and Université Libre de Bruxelles, Brussels, Belgium; [10] National Reference Laboratory for *Neisseria meningitidis*, Department of Infectious Diseases, National Institute of Health Doutor Ricardo Jorge, Lisbon, Portugal; [11]French Paediatric Infectious Disease Group (GPIP), Créteil, France; [12]National Reference Centre for *Neisseria meningitidis*, Sciensano, Brussels, Belgium; [13]Institute of Medical Microbiology and Hygiene, Austrian Agency for Health and Food Safety, Graz, Austria; [14]National Reference Laboratory for *Neisseria meningitidis*, Department of Laboratory Medicine, Clinical Microbiology, Faculty of Medicine and

Health, Örebro University, Örebro, Sweden; [15]Santa Casa de Sao Paulo School of Medical Sciences; [16]Meningitis Research Foundation, Bristol, UK; [17]Netherlands Reference Laboratory for Bacterial Meningitis, Amsterdam University Medical Centre location AMC, Department of Medical Microbiology and Infection Prevention, Amsterdam, Netherlands; [18]Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy; [19]Finnish Institute for Health and Welfare, Department of Public Health, Helsinki, Finland ; [20]National Meningitis Reference Laboratory, Department of Public Health Policy, School of Public Health, University of West Attica, Athens, Greece ; [21]Institute of Health Carlos III, Madrid, Spain.

*** Corresponding author**: Ray Borrow (ray.borrow@ukhsa.gov.uk)

SUMMARY

In Western Europe, many countries have robust and well-established surveillance systems and case reporting mechanisms. IMD incidence across Western Europe is low with a predominance of meningococcal serogroup B (MenB). Case confirmation and antimicrobial susceptibility testing is often standardised in this region, with many countries also having robust vaccination programmes in place. Both MenB and MenACWY vaccines form part of National Immunisation Programmes (NIPs) in most European countries, with Sweden only offering vaccination in special circumstances. Despite these established programmes, there remains a critical need for advocacy efforts in affecting change in diagnosis, testing, and treatment. Recent campaigns, such as the World Meningitis Day digital toolkit, have helped raise awareness and draw attention to meningococcal disease. Awareness around antibiotic resistance has also led to the identification of antibiotic-resistant meningococcal strains, with an increase, albeit small, in these strains noted across the region. Countries such as Spain, Portugal, Germany, Switzerland, and France have either reported strains resistant to penicillin, ciprofloxacin and/or isolates with a reduced susceptibility to third-generation cephalosporins.

Keywords: meningococcal disease, serogroup, Europe, vaccination, surveillance

INTRODUCTION

Neisseria meningitidis is a Gram-negative bacterium [1], that colonises up to 10% of the general population asymptomatically in their nasopharynx [2], but is also responsible for causing invasive meningococcal disease (IMD). This disease mainly manifests as septicaemia and/or meningitis [3]. The principal virulence factor of *N. meningitidis* is its polysaccharide capsule and differences in the polysaccharide composition have led to the identification of 12 serogroups. Six of these (MenA [meningococcal serogroup A], MenB, MenC, MenW, MenX and MenY) serogroups are responsible for a most of IMD cases worldwide, with epidemiological variations by geographical region, as well as over time [4].

The Global Meningococcal Initiative (GMI) helps to raise awareness of this communicable disease both through education and research [5]. Each year the GMI invites researchers, public health specialists and healthcare professionals from a particular region to discuss the latest insights in meningococcal disease. As part of this annual meeting, each attendee presents IMD epidemiological data from their respective country, as well as current control strategies and surveillance networks. Wider issues in meningococcal disease are also discussed, with GMI Steering Committee members highlighting global trends in vaccine research and disease epidemiology in specific sub-populations.

This most recent meeting took place virtually on March 19 and 20, 2024 and was attended by delegates from most countries across Western Europe. The principal objectives were: (i) to determine current trends in epidemiology, vaccination and other control strategies for IMD in Western Europe; (ii) to understand trends in antibiotic resistance; (iii) to learn about IMD due to rare serogroups such as E and X, as well as the carriage rates among individuals after the COVID-19

pandemic and (iv) to obtain an overview on the progress with pentavalent vaccines, both ACWYX and ABCWY.

This article acts a meeting consensus, summarising the key points raised during the presentations, as well as offering a broad overview of the epidemiology, surveillance and control of IMD in Western Europe. Equally, this report also highlights global trends in IMD and immunisation research.

The epidemiological data identified in this article, as well as insights on vaccination and control strategies across Europe, were taken from delegate presentations. Data were generally sourced from relevant public health authorities in these presentations or from a delegates' own research on epidemiological trends in their country of practice. A more comprehensive epidemiological data set can be accessed through the European Centre for Disease Prevention and Control (ECDC) [6].

The surveillance, epidemiology and prevention of IMD in Western Europe

Surveillance of IMD

There is an ongoing need for continuous surveillance of IMD cases [7, 8] to ensure the rapid detection of outbreaks, monitor disease trends, as well as shape and support public health strategies [9].

IMD occurs in the majority of countries in Western Europe; however, incidence rates have remained low in recent years at less than 1 case per 100,000 people on average [6]. This is mainly due to vaccination programmes that have been implemented.

These established surveillance networks and reporting channels are present in all European countries, with IMD reporting being a mandatory requirement under legislation. For example, in Austria, hospitals, physicians, and laboratories have to report suspected and confirmed cases to through the electronic Epidemiological Reporting System, and isolates must be sent to the reference

centre for serogroup determination and further typing. IMD cases will subsequently be divided into sporadic cases or a cluster, and are managed by local authorities.

In Germany, suspected and confirmed IMD case reporting is mandated under law within the provisions of the German Infection Protection Act. Under this legislation, any case report needs to be sent to the local health authorities responsible for a patient's residence within 24 hours [10] and subsequently to the Robert Koch institute, with case data matching taking place with the National Reference Centre for Meningococci and *Haemophilus influenzae* (NRZMHi). Laboratory surveillance is based on non-mandatory submission of IMD isolates and clinical samples to the NRZMHi.

IMD is also a notifiable disease in England under the Health Protection Notification (2010), with diagnosis performed at a local hospital and any clinically diagnosed IMD case being reported to the Health Protection Teams (HPTs) responsible for public health action. Positive cases are referred to the UK Health Security Agency (UKHSA) Immunisation Division to undertake enhanced surveillance, provide advice in cluster and outbreak cases, monitor the phenotypic and genetic characteristics of invasive meningococcal strains, describe the clinical characteristics, risk factors and outcomes of IMD, and monitor vaccine safety and the impact and effectiveness of the vaccination programmes. Positive meningococcal samples must also be notified to the UKHSA and laboratories are are also encouraged to submit these to the UKHSA Meningococcal Reference Unit (MRU). The MRU offers effective case confirmation support and characterisation through testing and grouping of isolates. The unit also offers case guidance and contributes to outbreak investigations [11].

Similarly, in Finland, the notification and surveillance of IMD involves both the clinical microbiology laboratory and the treating physician reporting a new laboratory-confirmed case to the National Infectious Disease Register. Upon receipt of the meningocccal isolate, the Expert Microbiology Unit of the Finnish Institute for Health and Welfare (THL) performs species confirmation, serogrouping and molecular typing. THL also offers guidance and participates in the investigation and control of outbreaks where necessary.

In Portugal, notification of all IMD cases is mandatory, with case definition aligned with the European Commission' guidelines (EU Commission Decision 2018/945 of 22 June 2018). Notifications are submitted through an online platform, reaching both local and national public health authorities. Biological samples from suspected IMD cases, as well as *N. meningitidis* isolates, are sent to the National Reference Laboratory for *N. meningitidis* for confirmation and/or molecular characterisation.

Additionally, all represented countries report national data annually to The European Surveillance System (TESSy, ECDC).

Incidence of IMD

The incidence of IMD across Western Europe remains low (Table 1). In 2023, IMD incidence in the region was on average less than 1 case per 100,000 people [9, 12], with countries such as Italy having an incidence in 2022 of 0.1 per 100,000 people [9].

There was a notable decline in the incidence of IMD during the COVID-19 pandemic. However, since the easing of COVID-19 lockdown restrictions and other public health measures, IMD levels have been increasing, albeit not to pre-pandemic levels in most cases. In Finland, whilst there were only two IMD cases reported in 2021, the number of reported cases increased to 10 in 2023 (there were 16 cases in 2019). In Switzerland, 44 IMD cases were reported in 2019, 8 in 2021, 17 in 2022, and 34 in 2023. The IMD incidence was 0.51, 0.09, and 0.38 cases per 100,000 in 2019, 2021 and 2023, respectively (Table 1).

In other countries, however, IMD case numbers have returned to levels comparable to those reported prior to the pandemic. In France, the number of cases increased from 117 in 2021 to 525 in 2023, marking an increase in the incidence from 0.2 in 2021 to 0.8 cases per 100,000 people in 2023 (there were 214 cases in 2020). In Greece, the reported incidence was 0.3 cases per 100,000 in 2019 [13], it dropped to 0.04 per 100,000 people in 2021 and increased to 0.2 cases per 100,000 people in

2023 (Table 1). In Germany, the IMD incidence was 0.3 cases per 100,000 in 2023, reaching pre-pandemic levels (2019: 0.31 cases per 100,000) following a low of 0.09 cases per 100,000 in 2021. In Portugal, the incidence of IMD was 0.27 cases per 100,000 inhabitants in 2023. COVID-19 measures have reduced *N. meningitidis* strain circulation, leading to a decline in the incidence rates of IMD over the years from 0.55 in 2019 to 0.36 in 2020, 0.09 in 2021, and 0.14 in 2022. The 2023 incidence, whilst increasing, did not reach the levels reported in the years before the COVID-19 pandemic [14].

Despite these recent trends, there has been an overall long-term decline in IMD incidence. In England, the IMD incidence decreased from 2 cases per 100,000 during 2006–2007 to 1 case per 100,000 during 2011–2012 and was <1 case per 100,000 in 2023 [15]. In Finland, IMD has also declined. In 2017 the incidence was 0.29 cases per 100,000; however, the incidence was higher in infants under one year (1.39 cases per 100,000) and in adolescents aged 15-19 years (1.12 cases per 100,000) (Table 1).

IMD incidence has also decreased from 2017 onward in Italy, albeit with higher proportions of infants being diagnosed, in a similar trend with other countries [16]. The annual incidence of IMD cases decreased from 0.33 per 100,000 in 2017 to 0.10 cases per 100,00 people in 2022, with children <1 years being the most affected age group from 2017 to 2022, with an incidence of 2.5 cases per 100,000 (reported in 2022).

This trend of higher IMD incidence in younger age groups is also evident in other European countries, with the highest incidence in infants aged <1 year in a recent analysis performed in eight European countries [17]. The reported incidence was 7.24 cases per 100,000 during 1999–2019. This was followed by toddlers with an incidence of 2.0 cases per 100,000 and a second peak observed with young persons at 0.88 cases per 100,000 [17].

Serogroup distribution

The majority of IMD cases in Europe are caused by serogroups B, W and Y [18]. MenB is the most common serogroup accounting for more than 50% of IMD cases across the region (2008–2017) [18] ; however, there has been a clear decline over time across Europe with a 56.1% decrease in MenB prevalence, from 71.5% to 48.0% between 2008 and 2017 [7]. In Belgium, MenB also remains the most frequent serogroup, accounting for 42% of cases in 2023. On the other hand, MenB is the most prevalent serogroup in the overall population in Italy and the Netherlands and the proportion of IMD cases due to MenB increased from around 40% in 2017 to 80–90% in 2022. The Netherlands vaccinates with MenACWY but not MenB through the National Immunisation Programme (NIP). In England, MenB cases have fallen, especially since the introduction of a MenB infant vaccination programme from 2015, but with a successful MenACWY teenage vaccine programme imparting herd protection, MenB remains the predominant causative serogroup accounting for over 90% of cases during 2023. In Portugal, MenB also constituted a significant portion of cases, comprising 65% of cases from 2012 to 2023. The MenB (Bexero) vaccine became available in Portugal in 2014 and was integrated into the NIP in 2020. Following its inclusion, there was a marked decline in MenB cases to 47.8% overall, and 28.6% in children. From 2001 to 2019, the IMD incidence in Germany steadily decreased, due to lower cases of serogroups B and C following the introduction of MenC vaccination. However, cases due to serogroups W and Y have increased [19].

There has been a similar trend in France with MenB IMD cases. Although MenB has been the cause of 44% of IMD diagnoses in France in 2023, the occurrence of MenW (29%) and MenY (23%) cases increased sharply in 2023 from approximately 10% and <10% of cases in 2017, respectively. MenW or MenY vaccination does not form part of the NIP in France. There has also been a rebound of IMD MenB cases in 2022 in France due to specific situations arising between September 2021 and December 2022 [20]. One such situation occurred in Chambery and East Lyon (September 2021–December 2022), where an outbreak involved 16 MenB cases (aged 16–21 years). Another outbreak occurred in Strasbourg during November to December 2022 with a cluster of six MenB cases in people (aged 23–33 years) who frequented social venues such as pubs and bars in Strasbourg.

In Switzerland, MenY was the most predominant serogroup (42%) in 2023, followed by MenB (35%), and MenW (23%). In 2018, MenW was the predominant serogroup (41%), followed by MenB (27%), MenY (21%), and MenC (11%). The most common types of meningococcal infection related to MenW from 2010 to 2016 were sepsis (58%), meningitis (23%) and rarely, arthritis (10%) [21].

Prevention and control strategies

The primary treatment for IMD is the administration of antibiotics to the patient. Furthermore, post-exposure prophylaxis is recommended for close contacts [22]. While antibiotic prophylaxis is effective in reducing the occurrence of secondary cases, a future public health concern could be the rise of antimicrobial resistance in *N. meningitidis* both in IMD cases and in asymptomatic carriers worldwide (see section on antibiotic resistance) [23].

There are vaccines currently available that address serogroups A, B, C, Y and W. In certain European Union/European Economic Area member states, vaccination against IMD is part of the NIPs (Table 1) [24, 25]. Recommendations often advise vaccination of infants, children, and adolescents, as well as in high-risk categories as a safe and effective way of reducing IMD and associated sequelae. However, vaccination policies are not uniform among European countries with different vaccines and schedules in routine programmes, and immunisation being offered in specific risk groups in different countries. Irrespective of strategic imperatives, there are several vaccines available in Europe, including: MenC conjugate, quadrivalent MenACWY conjugate and MenB protein-based vaccines [26–28].

As an example of evolving and responsive vaccination schedules, the UK's meningococcal immunisation programme has significantly changed over the past two decades. In 1999, the UK introduced MenC conjugate vaccine at 2, 3, 4 months of age with a catch-up campaign up to 21 years of age. In 2015, the MenC conjugate vaccine administered at 13/14 years of age was changed

to a MenACWY vaccine with catch-up started for all 13- to 18-year-olds. Within the same year, the UK was the first country to introduce MenB vaccination at 8 weeks, 16 weeks and 12 months of age [18]. The current IMD vaccine schedule includes, in addition to MenB (Bexsero); Hib/MenC (Menitorix) at 1 year and MenACWY (Nimenrix) at 13–14 years (or school year 9). All vaccines are offered free of charge as part of the NIP.

IMD epidemiology, NIPs, and vaccination coverage rates in children and adolescents have recently been assessed in eight European countries, Belgium, Germany, Spain, France, Italy, Portugal, the Netherlands and the UK [17]. Several vaccination strategies and programme amendments have been implemented since 1999 in these countries, with Germany not changing their schedule since 2006. With the introduction of MenC vaccination at the turn of the millennium, there was a sharp decline in MenC IMD notification rates in many of these countries. Equally, MenB vaccination was introduced in the UK in 2015 decreasing the MenB-related IMD incidence.

IMD and vaccination in high-risk groups

When considering vaccination strategies, there are several groups at a higher risk of contracting IMD. These include people with functional or anatomic asplenia; those who are complement deficient; people living with human immunodeficiency virus (HIV); men who have sex with men (MSM); and laboratory workers.

The likelihood of infection varies between these groups, with individuals who are complement deficient at a 1,000-fold increased risk of contracting IMD. Complement inhibitors, such as eculizumab or ravulizumab, are commonly used in treating rare diseases such as paroxysmal nocturnal haemoglobinuria and inhibit complement factor C5 and subsequently the formation of the membrane attack complex, leaving patients vulnerable to IMD. In one study, 14 out of 16 patients receiving eculizumab who were diagnosed with IMD had previously received a meningococcal vaccination [29]. IMD in this population is often associated with rare serogroups (X, Z and E) or

unencapsulated isolates, which are otherwise considered relatively non-pathogenic [29, 30]. Owing to this increased risk of IMD, antibiotic chemoprophylaxis is recommended by experts in the United States for the duration of eculizumab or ravulizumab treatment.

Another group that may be vulnerable to IMD are MSM, with several IMD outbreaks associated with a serogroup C sequence type 11 strain being documented in the United States in this population. During 2012–2015, 74 IMD cases were reported in MSM, with an incidence of 0.56 cases per 100,000 people [31]. This is compared with 0.14 cases per 100,000 people in the non-MSM population. Much of the increased risk of IMD among MSM appears to be due to HIV infection (relative risk [RR] [95% CI]: 16.3 [11.7, 22.7] for MSM with HIV infection versus RR [95% CI] 1.6 [1.1, 2.4] for MSM without HIV infection) [31]. IMD cases among MSM have also been reported in Europe [32].

Laboratory technicians who work with live *N. meningitidis* are also at an increased risk of IMD; working with the organism on an open laboratory bench appears to be the major risk factor for infection. Therefore, such workers should work in microbiological safety cabinets, receive in-depth training about safe laboratory practices and education about the signs and symptoms of IMD, receive appropriate immunisation and boosters, as well as be aware of the need for antimicrobial prophylaxis following high-risk exposures [33].

Advocacy and the role of meningitis charities

National Immunisation Technical Advisory Groups (NITAGs) continue to play a key role in reviewing scientific evidence and making informed decisions on vaccination policy. Alongside these groups, charities and other advocacy organisations can have a tangible and central role in advocating for patients and families. For example, the introduction of MenB vaccination in the UK may be partly attributed to advocacy efforts in driving change with policy makers. The Meningitis Research Foundation (MRF) played a central role in these endeavours. A patient advocacy group set up in

1989, the MRF's original objective was to raise key funds for research and education. Since 2021, the MRF merged with the Confederation of Meningitis Organisations (CoMO) – a worldwide membership network dedicated to eradicating meningitis.

These organisations' advocacy work is routed in finding parent–patient advocates, health experts and key opinion leaders who are willing to share their stories, perspectives and expertise. In combination, these various advocates can help to drive opportunities for change in IMD management and prevention, globally.

There have been several notable successes in recent years in raising awareness of meningitis. Since its inception in 2009 through CoMO, World Meningitis Day has highlighted the disease's impact and fostered action through driving investment and political support. Following CoMO's integration with the MRF in 2021, the day was moved to October 5th. As part of the day in 2023, there was activity in 126 countries, with #WorldMeningitisDay trending organically on X (formerly Twitter).

Equally, the digital toolkit, co-created with CoMO members, has been utilised by multiple organisations through World Meningitis Day. The toolkit is a resource containing key campaign messaging and facts on meningitis. Available in multiple languages, the toolkit also provides critical information on meningitis signs and symptoms, and can be utilised on social media platforms. In 2023 (1st June to 31st October), people in 77 countries downloaded the toolkit (6,925 individual downloads), with a 200% year-over-year growth in its use. Between 31st October and the following February, the number of resource downloads had doubled to over 17,000.

Long-term sequelae associated with IMD in children

The drive for change through advocacy efforts is underpinned with the knowledge that IMD is a potentially life-threatening disease that may lead to short- or long-term complications in surviving individuals [34, 35]. A recent analysis of a German claims database highlighted this, with at

least 23.5% individuals discharged from hospital following IMD experiencing a short-term sequelae; the most frequent of which was renal failure [36]. Thus, understanding the impact of IMD is an important consideration to help structure follow-up in practice. Despite such aforementioned studies assessing short-term complications, the impact of long-term sequelae remains poorly understood.

Sequelae can present in various forms as cutaneous, neurological, and psychological complications [37]. In two studies among Australian and French children, neurological sequelae were frequent, along with skin necrosis in the former trial [38,39].

In an effort to assess long-term IMD sequelae in children and adolescents, the SEINE study was designed as an interventional trial in France, which would also evaluate the psychological impact of IMD on parents [40]. Children from birth to 15 years old, who were diagnosed with IMD between 2010 to 2022 in the Paris area, were included in the trial.

The trial has opened specific opportunities for parents, having access to specialists without incurring an increased financial burden, and also raises important issues on long-term follow-up in practice [40, 41].

Antibiotic resistance update

Antibiotic treatment is critical in IMD management [42-46]. However, antibiotic-resistant strains of *N. meningitidis* have emerged.

A penicillin-resistant *N. meningitidis* strain (clonal complex (CC) 23) containing the ROB-1 β-lactamase gene (bla_{ROB-1}) has been detected in Europe, Mexico and Canada [43]. Equally, resistance to antimicrobials used for chemoprophylaxis has been identified in invasive strains in the United States and El Salvador owing to genetic mutations [42-44]

Reduced penicillin susceptibility is due to alterations of the penicillin-binding protein 2 (PBP2) encoded by the *penA* gene [19]. *penA* alleles can be categorised into two groups: wildtype (WT) and mosaic, associated with penicillin non-susceptibility. This phenotype has been linked to five critical mutations in PBP2. These mutations are due to altered mosaic *penA* alleles, which have multiplied worldwide [45]. Data from France during 2017–2021 showed that the penicillin minimum inhibitory concentration (MIC) of isolates with mosaic *penA* alleles rose above the threshold of 0.125 mg/L. The same trend can be seen in England, Wales and Northern Ireland during 2010–2011 and 2018–2019 where both MIC_{50} and MIC_{90} rise above the MIC threshold of 0.125mg/L. The *penA* sequence provides a reliable way of predicting penicillin susceptibility [45].

In the above-mentioned French study of 1255 IMD isolates an increasing trend of penicillin non-susceptible IMD isolates was found from 36% in 2017 to 58% in 2021 [45]. The *penA9* was the most frequent mosaic allele in those isolates non-susceptible to penicillin, with the *penA327* allele being present in isolates that also showed reduced susceptibility to third-generation cephalosporins [45].

The growing resistance of IMD isolates to ciprofloxacin is also an important concern. In a study performed in China, almost all isolates collected were susceptible to penicillin, ampicillin and ceftriaxone, but a high proportion (MenA and MenC isolates, in particular) were resistant to ciprofloxacin [5].

Resistance to both beta-lactams and ciprofloxacin is another emerging trend globally, with recent data in the United States during 2013–2020 highlighting multi-resistant *N. meningitidis* strains. In a recent study characterising *N. meningitidis* in Southern Vietnam between 2012 and 2021, seven IMD isolates were resistant/non-susceptible to at least two different antibiotics [46]. Multi-resistance is a growing phenomenon and should be kept under surveillance.

Progress with pentavalent ACWXY vaccines

Meningococcal vaccine development has focussed on targeting specific epidemiological situations owing to financial and supply issues [47].

One such example of targeted vaccination is the MenAfriVac™ vaccine, which was produced for Africa as an affordable MenA conjugate vaccine. The vaccine was introduced across all 26 countries in sub-Saharan Africa, with an epidemiological study in Chad showing the impact on MenA IMD and carriage [48]. As MenA cases declined in the vaccinated populations, IMD due to MenA was still endemic in those areas where MenAfriVac™ had not been introduced. Following widespread vaccination in 2012, MenA IMD has virtually disappeared in Chad [48].

Since the introduction of the MenA conjugate vaccine across the meningitis belt, MenA cases appear practically eliminated in the whole region, similar to the situation in Chad. However, IMD cases due to other serogroups (namely MenW, MenX and MenC) are still present in appreciable numbers and cause outbreaks. Therefore, a multivalent conjugate vaccine that can be widely distributed at a suitable cost to countries is necessary, particularly in this region of Africa [48]. A MenACWXY (Nm-CV5) vaccine (comprised of a mixture of conjugates employing tetanus toxoid and/or the diphtheria toxoid variant CRM_{197} as carrier proteins) is a more attractive vaccine option in this setting with vaccines MenFive® (SIIPL) and EuNmCV-5 (EuBiologics) being developed. In a phase 3 study comparing NmCV-5 with MenACWY-D (Menactra®) among 1,800 individuals in Mali and Gambia (2–29 years), NmCV-5 was non-inferior to MenACWY-D in terms of seroresponse across all serogroups, with the former also eliciting a robust immune response to MenX [47]. Other studies in the same countries have demonstrated acceptable safety and immunogenicity in toddlers [49] and infants [50]. Currently, MenFive (SIIPL) is licensed in India and is in the process of seeking regulatory approval in multiple countries in the meningitis belt. In 2024, the International Coordinating Group (ICG) approved over 1 million doses of SIIPL MenFive to be administered in Nigeria as part of a MenC epidemic response. In 2023, the WHO granted pre-qualification (PQ) for use as a single dose at 1 year of age, with infant PQ (at 9 months), subsequently received in the first quarter of 2024. The

current WHO Strategic Advisory Group of Experts on immunisation (SAGE) recommends that "all countries in the African meningitis belt introduce [NmCV-5] in their routine immunisation programmes. In high-risk countries and countries with high-risk districts, a preventive vaccination campaign [1-19 years of age] should be conducted when the vaccine is introduced at the national or subnational level." [51]. In December 2023, the Vaccine Alliance (Gavi) Board approved the expansion of the meningococcal programme to include support for multivalent meningococcal conjugate vaccines containing at least serogroups A, C and W, and countries are expected to start applying for funding in mid-2024.

In mid-2024 the EuBiologics NmCV-5 vaccine (EuNmCV-5, utilizing CRM_{197} as the carrier protein for each of the five polysaccharides A, C, W, Y, X) is expected to enter Phase 2/3 trials in Africa, assisted by the Programme for Appropriate Technology in Health (PATH) with support from the Bill and Melinda Gates Foundation and Right Foundation, with the goal of enhancing and sustaining the supply of NmCV-5 vaccine. Irrespective of efforts in pentavalent vaccination, it may be prudent to consider a hexavalent meningococcal vaccine that would also include MenB protection. Although MenB is currently extremely minor in the meningitis belt, it is an important serogroup elsewhere on the continent, and meningococcal serogroup epidemiology is notoriously dynamic. Given the increasingly crowded immunisation schedule [52], the potential for combination of this vaccine with others already forming part of the Expanded Program on Immunisation (EPI) schedule should be an important consideration in future vaccine development.

Progress with pentavalent MenABCWY vaccines

Outside the meningitis belt, MenB is the dominating serogroup causing IMD in Western Europe, as previously stated. This has been addressed in different countries' vaccination schedules, with MenB and MenACWY immunisation typically being recommended for various age groups (or specific high-risk populations) (see Table 1).

However, to reduce the number of injections and simplify schedules, efforts are underway to develop MenABCWY pentavalent vaccines, which would consolidate protection against the five main serogroups in a single formulation. One such pentavalent ABCWY vaccine under investigation combines components of the 4CMenB vaccine (Bexsero®, GSK) and the MenACWY-CRM vaccine (Menveo®, GSK), and is currently in late-stage development. This candidate vaccine, administered in two doses six months apart, successfully met all primary non-inferiority endpoints in a pivotal trial involving over 3,000 participants aged 10-25 years. It showed tolerability and a safety profile in line with the licensed 4CMenB and MenACWY-CRM vaccines and is now being studied in younger age groups, with formulations including new Factor-H binding Protein (fHbp) antigens [53]. A second investigational pentavalent MenABCWY vaccine, developed by Sanofi Pasteur, has just started a phase I/II randomised, descriptive, safety and immunogenicity trial including adolescents and young adults 10-25 years in United States, with study completion estimated to occur in mid-2025 [54].

Another ABCWY vaccine (MenACWY-TT/MenB-FHbp, Penbraya®), that combines the MenB-fHbp vaccine (Trumenba®, Pfizer) and the MenACWY-TT vaccine(Nimenrix®, Pfizer) met all endpoints assessing non-inferiority in clinical trials and has already been approved by the U.S. Food and Drug Administration, for use as a 2-dose series administered 6 months apart in adolescents and young adults 10-25 years for prevention of invasive disease caused by *N. meningitidis* serogroups A, B, C, W, and Y. On October 25, 2023, ACIP recommended that MenACWY-TT/MenB-FHbp may be used when both MenACWY and MenB are indicated at the same visit for the following groups: 1) healthy individuals aged 16–23 years (routine schedule) when shared clinical decision-making supports the administration of MenB vaccine, and 2) individuals aged ≥10 years who are at increased risk for meningococcal disease (e.g., due to persistent complement deficiencies, complement inhibitor use, or functional or anatomic asplenia) [55].

Penbraya is currently not licensed in Europe; though modelling and cost-effectiveness studies are underway to establish whether it could replace either the infant 4CMenB programmes or the adolescent ACWY programmes.

Disease caused by rare serogroups E, X & carriage after the pandemic

MenX was considered as a rare serogroup until outbreaks in Africa were noted, resulting in the development of pentavalent vaccines for the meningitis belt including this serogroup, as described earlier. Aside from MenX, other rare IMD serogroups in circulation are E, H, I, K, L and Z.

Several studies have reported on case and outbreak patterns of MenX in different countries, principally in Africa [56-59]. The emergence of MenX in these countries, including Togo and Burkina Faso, has reiterated the need for a pentavalent vaccine that offers coverage against this serogroup [59]. To further reinforce this point, a recent study assessing the impact of MenAfriVac in Burkina Faso showed that, following the vaccine's introduction in 2011, MenX subsequently accounted for 59% of all 259 confirmed IMD cases [58].

Although MenX cases in Europe have been rare, there have been several reported in Italy during 2015 to 2016 [60]. Each of these cases were associated with refugee camps in Lombardy and Tuscany. In 2015, a single Men X case was reported in a young girl (15 years) in the Lombardy camp. There were subsequent non-linked cases in this camp in 2016 (a man originally from Mali [20 years] and one from Niger [31 years]). In the Tuscany camp, a MenX case was reported in a 24-year-old man from Bangladesh. All case isolates were associated with cc181.

MenX has also been detected among meningococcal carriage isolates. For instance, MenX accounted for 25% of nasopharyngeal samples collected from 1,267 children and adolescents in Turkiye in 2018 [61]. There have been two separate IMD case reports of MenX in Turkiye, with a MenX (ST-767) case being reported in 2010 (Turkish soldier) and an ST-5799 (cc22) case reported in 2018 in a paediatric patient [62,63]. MenX has also been identified in other parts of the world, with

the genomic characterisation of invasive MenX isolates from Brazil (1992 to 2022). Six MenX isolates were recovered where 66.6% were attributed to ST-2888 [64].

Another rare serogroup, MenE, was first identified in 1968, with the serogroup first being recorded in PubMLST in 2000 [65]. In that year, MenE isolates from carriers were predominantly cc60 (33%), cc1157 (26%), cc254, cc178 [66]. In 2024, cc60 and cc1157 were still the predominant clonal complexes. There have also been two IMD isolates in the UK in 2023 and 2024 attributable to MenE (PubMLST) [67]. MenE carrier isolates have been recorded on PubMLST during the same period (n=108), with 37.6% attributed to ST-1157 and 34.6% to ST-60, thus highlighting the increasing importance of this serogroup. There was also a notable proportion of MenE among the 160 carriage isolates (8.3%) identified in Greece among military recruits and university students (N=1,420) (2014–2015). Furthermore, among the non-groupable isolates (n=76), MenZ and MenX were attributable to 1.1% and 3.3% of the carriage isolates in this population, respectively [66].

Following the introduction of MenACWY vaccination in the Netherlands in 2018, a study of meningococcal carriage was conducted among young adults in 2022 [68]. Of the carriage samples, MenB was the most detected serogroup, but also an increase in MenE carriage was observed in comparison to a pre-vaccine carriage study in 2018. Only a small number of meningococcal carriage strains belonged to MenX [67].

Conclusions

There is a low incidence of IMD across Western Europe, with countries having robust and well-established surveillance and case reporting systems. MenB has been and remains the predominant serogroup, although MenY and MenW cases have emerged in some countries in recent years. Case confirmation and antimicrobial susceptibility testing is often standardised, with some countries, such as Switzerland, now establishing fully automated laboratory processes for sample analysis.

Many successful vaccination programmes are already in place. Pentavalent MenABCWY and pentavalent MenACWXY conjugate vaccines have been developed, with one example of each recently licensed in the United States and India, respectively; the latter vaccine has also been prequalified by WHO and recommended for broad use in the African meningitis belt. Introduction of these vaccines into NIPs could occur over the next few years.

In many European countries, there has also been a notable, albeit small, increasing trend in antibiotic-resistant meningococcal strains. Thus, there is a strong impetus to consistently monitor for antibiotic resistance across the region, particularly as multi-resistant meningococci emerge. With the emergence of rare serogroups, such as MenX, a pentavalent vaccine targeting that serogroup (in addition to MenA, C, W and Y) will be appropriate in further controlling the incidence of IMD. Furthermore, a pentavalent MenABCWY vaccine in regions where MenB circulates will reduce the number of injections and simplify schedules.

Underpinning all these research efforts is the need for well-informed NITAGs, with access to appropriate scientific and epidemiological data, and a key role for advocacy. As illustrated through the work of the MRF and CoMO, various initiatives are helping to raise awareness on IMD, as well as to drive change and establish a path to defeat meningitis in the future.

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Table 1: Overview of the epidemiology and prevention of IMD across Western Europe.

Country	Surveillance system (Y/N)	Epidemiology	Control strategies
Austria	Y	- Incidence (2023): 0.18 cases per 100,000 people - Number of cases (2023): 16 cases - Serogroups (2023): MenB (11/16), MenY (2/16), MenC (1/16)	- MenB and MenACWY vaccination recommended for children, teenagers and young adults - Chemoprophylaxis offered to close contacts
Belgium	Y	- Incidence (2023): 0.71 cases per 100,000 people - Number of cases (2023): 83 cases - CFR (2023): 3.6% - Serogroups (2023): MenB (42.2%), MenW (22.9%), MenY (28.9%)	-MenACWY is in the NIP for infants (15 months) (free of charge) - It is also recommended for teenagers (14 years) in Wallonia; although, it is not reimbursed -MenB is not included in the NIP (Although it is recommended for infants on an individual basis by the Health Council)
England	Y	- Number of cases (2021–2022): 205 cases - Serogroups (2021–2022): MenB (87%), MenW (6%), MenY (2%)	- 4CMenB recommended at 8 weeks, 16 weeks and 1 year - Hib/MenC recommended at 1 year - MenACWY recommended at 13 to 14 years
Finland	Y	- Incidence (2023): 0.2 cases per 100,000 people - Number of cases (2023): 10 cases - Serogroups (2023): MenB (60%), MenY (10%), non-groupable (20%), Not known (10%)	- Vaccination established in the armed forces since 1974 - MenACWY and MenB vaccines in the NIP for medical risk groups since 2020 - Chemoprophylaxis and vaccination offered for close contacts of IMD case
France	Y	- Incidence (2023): 0.82 cases per 100,000 people - Serogroups (2023): MenB (44%), MenW (29%), MenY (24%), MenC (1%)	- 4CMenB and MenACWY recently introduced (March 2024) as mandatory in the NIP for infants ≤1 year. - MenACWY recommended at 11 to 14 years
Germany	Y	- Incidence (2023): 0.3 cases per 100,000 people - Serogroups (2023): MenB (40–50%), MenY (40–50%)	- MenC vaccination recommended in infants (12 months) - MenB recommended at 2, 4 and 12 months MenB and MenACWY recommended for individuals with underlying medical conditions; laboratory staff; travellers and pilgrims
Greece	Y	- Incidence (2023): 0.2 cases per 100,000 people - Number of cases (2023): 21 cases CFR (2023): 5.26%	- MenC included in the NIP for those aged 12 months, as well as those at 15 months and 10 years MenACWY part of the NIP for high-risk groups
Italy	Y	- Incidence (2022): 0.1 cases per 100,000 people	- The NIP 2023-2025 recommends MenB vaccination (2 doses in first

		- Number of lab-confirmed cases (2022): 57 cases -Serogroups: MenB (80%) in 2022	year of life and a booster at 13/14 months - MenACWY vaccination recommended (single dose at 12 months of age, booster at 12– 18 years)
Netherlands	Y	- Number of cases (2023): 120 cases - Serogroups (2023): MenB predominant serogroup (87%)	- MenB vaccination is available, but not part of the NIP - MenACWY vaccination recommended at 14 months and 14 years
Norway	Y	- Number of cases (2023): 16 cases; incidence 0.29 per 100,000 people - Serogroups (2023): MenB (7/16), MenY (5/16), MenW (2/16), MenA (1/16), MenC (1/16)	- No meningococcal vaccines are included in the NIP - However, vaccination is recommended in some high-risk groups (e.g., HIV+, complement deficient patients, men who have sex with men, youth [16–19 years])
Portugal	Y	- Incidence rate (2023): 0.27 cases per 100,000 people - Highest incidence rate in children under 12 months (14.6), with a notable decrease in the 1-4 years age group (3.6) and adults ≥45 years (0.25) - Serogroups (2012–2023): MenB (65%), MenY (9.1%), MenW (6.1%) and MenC (5%)	- MenC conjugate vaccine: introduced in the NIP in 2006 - MenB (Bexsero) vaccine: recommended since 2014, and introduced into the NIP in 2020 - MenB (Trumenba) recommended for children older than ten years of age - MenACWY vaccine: recommended for adolescents and /or pilgrims and travellers to the African meningitis belt
Spain	Y	-Incidence (2022/2023): 0.45 cases per 100,000 people - Serogroups (2023): MemB (54.9%), MenC /1.7%), MenW (20.9%), MenY (15.1%)	- MenB vaccination (2, 4 and 12 moths) introduced into the NIP in 2023, along with the already existing MenC (4 and 12 moths) conjugate vaccine and MenACWY (11 or 12 years) conjugate vaccine
Sweden	Y	- Number of cases (2023): 33 cases, incidence of 0.31 cases per 100,000 people, CFR 9.1% -Most cases in the age of 15-24 (n=12) - Equal distribution of cases among gender - Serogroups (2023): MenB (29%), MenY (23%), MenW (23%), MenC (6%), MenX (3%)	- No meningococcal vaccines are included in the NIP - Special situations for considering vaccination; suspected outbreak situations (>2 cases in a defined group), traveling to high-risk areas or to patients with risk factors due to congenital or acquired immunodeficiency
Switzerland	Y	- Number of cases (2023): 34 cases - Incidence (2019 - 2023): 0.51, 0.23, 0.09, 0.19, and 0.38 cases per 100,000 people in each year, respectively. - Serogroups (2023): MenY (42%), MenB (35%), and MenW (23%).	-MenACWY vaccination is recommended for those 2 years and 11–14/15 years -4CMenB vaccination is also recommended for specific high-risk groups

IMD, invasive meningococcal disease; NIP, National Immunisation Program; MenA, meningococcal serogroup A; MenACWY, meningococcal serogroups A, C, W and Y; MenB, meningococcal serogroup B; MenC, meningococcal serogroup C, MenY, meningococcal serogroup Y; MenW, meningococcal serogroup W.

Declaration of Competing Interest

Ray Borrow performs contract research on behalf of UKHSA for GSK, PATH, Pfizer and Sanofi. Heike Claus has received personal fee for scientific presentation for Sanofi. Ener Cagri Dinleyici performs contract work for the Eskisehir Osmangazi University funded by GSK, Sanofi Pasteur and Pfizer. Lee Harrison has served on advisory boards and/or made scientific presentations for GSK, Pfizer, Sanofi, and Merck, for which he does not receive any personal fees. William P. Hausdorff has served on advisory boards for Sanofi, Merck, and Vaxcyte, for which he does not receive any personal fees or reimbursement. Corinne Levy reports personal fees for advisory board and scientific presentations for MSD and Pfizer. Wesley Mattheus reports research grants funded by GSK and Pfizer. Marco A. P. Sáfadi reports research grants and personal fees for advisory boards from GSK, Pfizer, and Sanofi. Vinny Smith works for Meningitis Research Foundation that receives income from grants, sponsorship and consultancy income from GSK, MSD, Pfizer, Sanofi and Serum Institute of India. M.K. Taha performs contract work for the Institut Pasteur funded by GSK, Pfizer and Sanofi. M.K. Taha and A-E Deghmane have a patent NZ630133A Patent with GSK “Vaccines for serogroup X meningococcus” issued. Georgina Tzanakaki reports contract work on behalf of the University of West Attica as participation on advisory boards and scientific presentations for Pfizer, Sanofi and Merck. J.A. Vázquez performs contract work for the Institute of Health Carlos III funded by GSK and Pfizer and he has received personal fees from Pfizer and Sanofi. Nina van Sorge receives fee for service and presentations (directly paid to the institution) from MSD and GSK. Finnish Institute for Health and Welfare has received research funding from Pfizer and GSK for projects in which Maija Toropainen has acted as a researcher without personal remuneration.