Challenges of Unpredictability: Meningitis Prevention Takes Everyone's Continuous Vigilance – Interview with A Key Opinion Leader

Interviewee:

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Interview Summary

Meningitis is rare and unpredictable, with a high case fatality rate and devastating long-term sequelae. Meningitis is largely preventable through vaccination, but progress in the fight against this unpredictable disease is behind other vaccine-preventable diseases. Invasive meningococcal disease (IMD), caused by the bacterium *Neisseria meningitidis* (*N. meningitidis*), is a major cause of meningitis and septicaemia. More than one million cases of IMD are reported annually, with an overall case fatality rate estimated to be between 4.1–20.0%. Meningococcal meningitis can develop in anyone, at any age, anywhere, at any time, and outbreaks are unpredictable, occurring even in settings where disease incidence is low. In most cases, there are no identifiable environmental, setting, or host risk factors for meningococcal meningitis, and it is not possible to predict whether an individual will develop meningitis or the severity

of the disease course. Meningococcal meningitis onset is characteristically sudden, with various non-specific symptoms that delay diagnosis. In addition, the disease course is unpredictable, and once the disease is clearly identified, it is often too late to make specific recommendations. Hence, vaccination programmes against IMD are critical to optimise immunisation rates and support the prevention of meningitis. For this article, EMJ conducted an interview in July 2024 with key opinion leader Federico Martinón-Torres, from Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain, to raise awareness of the unpredictability of meningitis, and explore the challenges associated with prevention, diagnosis, treatment, and management of this disease. Martinón-Torres, who has a wealth of experience and expertise in the clinical management of meningitis, provided valuable insights into topics such as the unpredictability of meningococcal meningitis in terms of variable epidemiology, lack of identifiable risk factors, and non-specific symptoms, as well as potential host genetic risk factors for this infectious disease. Also discussed were prevention of meningococcal meningitis through vaccination, including conjugated vaccines against A, C, W, X, and Y serogroups, and protein-based vaccines against serogroup B, the development of pentavalent vaccines, and the importance of disease surveillance. Finally, Martinón-Torres discussed the World Health Organization (WHO) goal to eliminate meningitis by 2030 and outlined what the future of meningitis prevention might look like.

INTRODUCTION

Meningitis is a rare[1] and unpredictable[1,2] disease globally, with a high case fatality rate,[3] causing an estimated 250,000 deaths in 2019.[4] One in 10 patients with IMD die, with the majority being children and young people,[5,6] and one in five have devastating long-term sequelae,[1,4,7] including limb weakness, limb amputations, hearing loss, seizures, and difficulties with vision, speech, language, and memory.[8] In addition, meningitis has a considerable emotional, social, and financial impact on individuals, families, and communities, with meningitis epidemics also presenting a substantial challenge for healthcare systems, economies, and society.[4] Therefore, meningitis prevention is critical.

Meningitis is largely preventable through vaccination, but progress in the fight against this unpredictable disease[2] is behind other vaccine-preventable diseases.[4] The WHO, in collaboration with global partners and experts, has developed a roadmap with goals to eliminate bacterial meningitis epidemics, reduce cases of vaccine-preventable bacterial meningitis by 50% and deaths by 70%, and decrease disability and improve quality of life after meningitis of any cause by 2030.[4]

BACTERIAL MENINGITIS

There are four main causes of acute bacterial meningitis: *N. meningitidis* (meningococcus), *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae*, and *Streptococcus agalactiae* (group B streptococcus).[8] These bacteria cause more than half the deaths from meningitis globally.[8] IMD, caused by *N. meningitidis*, is a major cause of meningitis and septicaemia,[1,9] and is a serious public health concern.[3,10] More than one million cases of IMD are reported annually, with average fatality rates ranging from 4.1–20.0%,[10] depending on clinical presentation and geographical location.[11] The incidence of IMD is highest in infants and toddlers, with a resurgence of cases in adolescents and adults over 50 years of age.[1] Despite well-developed healthcare settings, an epidemiological study in Europe conducted before the first introduction of routine vaccination against meningococcal serogroup B (MenB) (see Figure 2 in the publication by Martinón-Torres et al.[12]) found that *N. meningitidis* was the most frequently identified microorganism in children with life-threatening infectious diseases.[13] Martinón-Torres commented: "The results of this study give us an idea of how important meningococci might be...

and are a thermometer of what is actually happening (regarding the prevalence of *N. meningitidis*) in Europe." Martinón-Torres proposed that targeting meningococcal infections is a critical component of the drive to eliminate meningitis by 2030.

THE UNPREDICTABILITY OF MENINGOCOCCAL MENINGITIS

Martinón-Torres explained that meningococcal meningitis can develop in anyone, at any age, anywhere, at any time, and outbreaks are unpredictable, occurring even in settings where disease incidence is low. Meningococcal serogroups A, B, C, W, X, and Y cause nearly all IMD;[14-17] however, the relative predominance of serogroups varies between and within regions and countries.[18] Martinón-Torres acknowledged that the sporadic and unpredictable nature of meningococcal meningitis complexifies the development of a preventive strategy.

Adolescents and young adults have the highest rate of nasopharyngeal carriage of *N. meningitidis*.[19,20] Although carriage is typically transient, some adolescents and young adults may have persistent carriage and are likely to be an important group in the transmission of meningococci.[21] Martinón-Torres remarked that it is not possible to predict whether a carrier will remain asymptomatic or develop IMD.

There was a drop in the number of IMD cases globally during the COVID-19 pandemic, most likely because of reduced exposure to *N. meningitidis* and a decrease in seasonal respiratory infections that might collaborate on *N. meningitidis* spread, due to the implementation of COVID-19-related mitigation measures.[22] Now, there appear to be rebound IMD cases without clear patterns.[23] Martinón-Torres suggested that this may simply be a return to the known unpredictability of *N. meningitidis* infections, and it is difficult to predict when these rebound cases will decline.

Martinón-Torres specified that, in most cases, there are no identifiable environmental, setting, or host risk factors for meningococcal meningitis, and it is not possible to predict whether an individual will develop meningitis or the severity of the disease course. He stated that only a minority of patients with meningococcal meningitis have identified known risk factors, including congenital deficiencies in terminal complement components,[24] which are associated with increased risk of IMD up to 10,000 times higher than that in healthy subjects.[24,25] HIV infection, functional and anatomic asplenia, and certain medications, including complement inhibitors, also increase the risk of IMD.[26]

Although meningococcal meningitis can occur at any age, young children are most at risk,[6] followed by adolescents and young adults.[8] The highest burden of bacterial meningitis disease is in the African meningitis belt, a region of sub-Saharan Africa.[8,27] Higher risk is observed in densely populated areas,[8] in socially deprived populations,[28] and at mass gatherings, such as pilgrimages.[29] Martinón-Torres commented that, apart from examples such as these, there are no obvious personal or environmental factors that predict the higher risk of meningococcal meningitis. However, Martinón-Torres noted that up to 10% of individuals with meningococcal meningitis have a family history of the disease, which implies an inherited susceptibility and indicates the importance of host factors.[13]

Meningococcal meningitis onset is characteristically sudden, with various non-specific symptoms, including fever, headache, neck stiffness, rash, nausea, and/or vomiting,[11] which are often difficult to distinguish from other illnesses.[11,30] Martinón-Torres disclosed that this leads to delayed diagnosis, particularly in areas of low incidence and outside high-risk groups, when clinicians may be less likely to be suspicious of meningitis. In addition, Martinón-Torres emphasised that the disease course is unpredictable, and once the disease is clearly identified, it is often too late to make specific recommendations as progression to severe or fatal disease can be within 24 hours of the onset of illness.[11] Martinón-Torres emphasised: "Despite the great advances in detection, diagnosis, and treatment, the number of

cases of meningococcal meningitis, and rates of morbidity and mortality, are stable across the world…We have reached a ceiling of what we can achieve in developed countries. Hence, measures to protect against IMD are critical to support the prevention of meningitis."

INVESTIGATING RISK FACTORS FOR MENINGOCOCCAL MENINGITIS

According to Martinón-Torres, exploring the unpredictability of meningococcal meningitis requires research beyond environmental and pathogen-related factors to focus on host susceptibility. There is considerable research interest in potential host genetic risk factors for meningococcal meningitis.[31-34]

N. meningitidis evades complement-mediated killing by the binding of host complement factor H (CFH) to the meningococcal factor H-binding protein.[31] Research by Davila et al.[31] showed that host genetic variation in these regulators of complement activation plays a role in determining the occurrence of invasive disease versus asymptomatic colonisation by this pathogen.[31]

Protective (more resistant) gene polymorphisms are more common in populations in East Asia (approximately 50%), where the incidence of meningococcal meningitis disease is lower, versus populations in Africa (approximately 4%) in which there is high disease incidence.[34] According to Martinón-Torres, this observation supports the role of these gene polymorphisms in susceptibility to IMD.

Martinón-Torres commented that research is ongoing into the mechanism of intragenic regulation of CFH levels, with the aim to identify those at particular risk of meningococcal meningitis and provide more personalised prevention and treatment strategies.

PREVENTION OF MENINGOCOCCAL MENINGITIS THROUGH VACCINATION

Conjugated vaccines against *N. meningitidis* A, C, W, and Y serogroups can provide direct protection to the vaccinated cohort and reduce carriage, thereby providing indirect protection to unvaccinated cohorts.[16] Martinón-Torres highlighted that vaccination of adolescents, one of the main carriers,[12,19] prevents colonisation and spread of *N. meningitidis*, and helps control disease in all age groups. In contrast, the protein-based vaccines against serogroup B can provide direct protection to recipients but do not reduce carriage;[16] therefore, a different implementation strategy is required as vaccinating a single cohort does not lead to herd immunity.[35]

According to Martinón-Torres, from a prevention perspective, meningococcal meningitis should be regarded as a single disease caused by different serogroups,[36] with vaccines available for most invasive and epidemiologically important serogroups (A, C, W, X, Y, and B). It is well understood that vaccination against meningococcal serogroups A, C, W, and Y does not guarantee protection against serogroup B, hence the need to include B vaccines in immunisation programmes. Martinón-Torres indicated: "Any new case of meningococcal meningitis globally could be considered a public health failure because this disease is vaccine-preventable; however, widespread implementation of available vaccines is lacking."

Martinón-Torres highlighted that surveillance is essential to identify changes in meningitis epidemiology, and to measure the effect of preventive measures; however, this identification may not be early enough or sufficiently clear to shift serogroup recommendations.

Martinón-Torres emphasised that the development of first-generation pentavalent vaccines that combine existing vaccines has been an important step forward in meningococcal meningitis prevention.

WORLD HEALTH ORGANIZATION GOAL TO ELIMINATE MENINGITIS BY 2030

Martinón-Torres acknowledged: "The WHO goal to defeat meningitis by 2030 is an ambitious plan as immunisation strategies are not well established worldwide." According to Martinón-Torres, in countries where infants are routinely offered meningococcal meningitis vaccine, vaccinating adolescents is a reasonable next step,[36] and expanding programmes to include adults could be considered. However, he noted that such developments depend on public health resources and priorities, and require political, academic, healthcare, and public commitment to achieving the WHO goal. Widespread implementation of meningococcal meningitis vaccination covering all epidemiologically important serogroups is needed to prevent meningococcal meningitis disease as a whole. Supranational organisations have an important role in sharing information about vaccination strategies and may enable countries with low coverage rates to learn from those with successful programmes in place. Martinón-Torres emphasised: "Some countries may not eliminate meningitis by 2030, but if all countries take at least one step towards more comprehensive vaccination programmes for meningitis, this can be considered a success."

FUTURE OF MENINGITIS PREVENTION AND CONCLUSIONS

Martinón-Torres recommended that healthcare professionals should be continuously proactive and committed to existing meningococcal meningitis immunisation programmes in their countries to achieve optimal vaccine uptake while expanding these programmes to include more at-risk age groups. He emphasised that healthcare teams need to be particularly vigilant to ensure that patients at known high risk of meningococcal meningitis are vaccinated. Furthermore, healthcare professionals should be continuously mindful of the possibility of meningitis and have a high level of suspicion for this aggressive disease when assessing their patients. Finally, Martinón-Torres would like to see improved surveillance in countries where it is not established, the possibility for personalised immunisation based on host genetic and other risk factors, and stronger public health infrastructure to ensure that meningitis is eliminated globally.

References

1. Taha MK et al. Changing patterns of invasive meningococcal disease and future immunization strategies. Hum Vaccin Immunother. 2023;19(1):2186111.
2. Martinón-Torres F, Trilla A. Meningococcal disease: can we predict the unpredictable? Med Clin (Barc). 2020;154(1):20-2.
3. Wang B et al. Case fatality rates of invasive meningococcal disease by serogroup and age: a systematic review and meta-analysis. Vaccine. 2019;37(21):2768-82.
4. World Health Organization (WHO). Defeating meningitis by 2030. Available at: https://www.who.int/initiatives/defeating-meningitis-by-2030. Last accessed: 19 July 2024.
5. Gordon SM et al. Neonatal meningitis: overcoming challenges in diagnosis, prognosis, and treatment with omics. Front Pediatr. 2017;5:139.
6. World Health Organization (WHO). WHO and partners call for urgent action on meningitis. Available at: https://www.who.int/news/item/28-09-2021-who-and-partners-call-for-urgent-action-on-meningitis. Last accessed: 21 July 2024.
7. Centers for Disease Control and Prevention (CDC). Meningococcal disease symptoms and complications. Available at: https://www.cdc.gov/meningococcal/symptoms/index.html. Last accessed: 26 July 2024.
8. World Health Organization (WHO). Meningitis. Available at: https://www.who.int/news-room/fact-sheets/detail/meningitis. Last accessed: 19 July 2024.
9. European Centre for Disease Prevention and Control (ECDC). Factsheet about meningococcal disease. Available at: https://www.ecdc.europa.eu/en/meningococcal-disease/factsheet. Last accessed: 19 July 2024.
10. Wang B et al. The inpatient costs and hospital service use associated with invasive meningococcal disease in South Australian children. Vaccine. 2014;32(37):4791-8.
11. Martinón-Torres F. Deciphering the burden of meningococcal disease: conventional and under-recognized elements. J Adolesc Health. 2016;59(2 Suppl):S12-20.
12. Martinón-Torres F et al. Evolving strategies for meningococcal vaccination in Europe: overview and key determinants for current and future considerations. Pathog Glob Health. 2022;116(2):85-98.
13. Martinón-Torres F et al.; EUCLIDS Consortium. Life-threatening infections in children in Europe (the EUCLIDS Project): a prospective cohort study. Lancet Child Adolesc Health. 2018;2(6):404-14.
14. Marshall HS et al. First statewide meningococcal B vaccine program in infants, children and adolescents:

evidence for implementation in South Australia. Med J Aust. 2020;212(2):89-93.

15. Abio A et al. An epidemiological review of changes in meningococcal biology during the last 100 years. Pathog Glob Health. 2013;107(7):373-80.
16. Clark SA, Borrow R. Herd protection against meningococcal disease through vaccination. Microorganisms. 2020;8(11):1675.
17. Di Pietro GM et al. Meningococcal disease in pediatric age: a focus on epidemiology and prevention. Int J Environ Res Public Health. 2022;19(7):4035.
18. Peterson ME et al. Meningococcal serogroups and surveillance: a systematic review and survey. J Glob Health. 2019;9(1):010409.
19. Christensen H et al. Meningococcal carriage by age: a systematic review and meta-analysis. Lancet Infect Dis. 2010;10(12):853-61. Erratum in: Lancet Infect Dis. 2011;11(8):584.
20. Gabutti G et al. Epidemiology of Neisseria meningitidis infections: case distribution by age and relevance of carriage. J Prev Med Hyg. 2015;56(3):E116-20.
21. McMillan M et al. Longitudinal study of meningococcal carriage in adolescents and young adults in South Australia 2017-2020. J Infect. 2024;88(2):149-57.
22. Bloom DE et al. Meningococcal disease in the post-COVID-19 era: a time to prepare. Infect Dis Ther. 2023;12(12):2649-63.
23. Santé Publique France. Invasive meningococcal infections in France in 2023. Available at: https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-a-prevention-vaccinale/infections-invasives-a-meningocoque/documents/bulletin-national2/infections-invasives-a-meningocoque-en-france-en-2023. Last accessed: 22 July 2024.
24. Shears A et al. Clinical outcome and underlying genetic cause of functional terminal complement pathway deficiencies in a multicenter UK cohort. J Clin Immunol. 2022;42(3):665-71.
25. Ladhani SN et al. Invasive meningococcal disease in patients with complement deficiencies: a case series (2008-2017). BMC Infect Dis. 2019;19(1):522.
26. Centers for Disease Control and Prevention (CDC). Risk factors for meningococcal disease. Available at: https://www.cdc.gov/meningococcal/risk-factors/index.html. Last accessed: 23 July 2024.
27. Barichello T et al. Bacterial meningitis in Africa. Front Neurol. 2023;14:822575.
28. Taha MK et al. Equity in vaccination policies to overcome social deprivation as a risk factor for invasive meningococcal disease. Expert Rev Vaccines. 2022;21(5):659-74.
29. Yezli S et al. Meningococcal disease during the Hajj and Umrah mass gatherings. Int J Infect Dis. 2016;47:60-4.
30. National Institute for Health and Care Excellence (NICE), Evidence review for risk factors associated with meningococcal disease: meningitis (bacterial) and meningococcal disease: recognition, diagnosis and management [Internet] (2024) NICE Guideline. Available at: https://www.ncbi.nlm.nih.gov/books/NBK604178/. Last accessed: 5 September 2024.
31. Davila S et al.; International Meningococcal Genetics Consortium; ESIGEM network; European Society for Paediatric Infectious Diseases (ESPID) meningococcal consortium – UK; EUCLIDS consortium members. Genome-wide association study identifies variants in the CFH region associated with host susceptibility to meningococcal disease. Nat Genet. 2010;42(9):772-6.
32. Kumar V et al. Variation in CFHR3 determines susceptibility to meningococcal disease by controlling factor H concentrations. Am J Hum Genet. 2022;109(9):1680-91.
33. Borghini L et al.; EUCLIDS consortium. Identification of regulatory variants associated with genetic susceptibility to meningococcal disease. Sci Rep. 2019;9(1):6966.
34. Martinón-Torres F et al.; ESIGEM network; European Society for Paediatric Infectious Diseases (ESPID) meningococcal consortium – UK; EUCLIDS consortium members. Natural resistance to meningococcal disease related to CFH loci: meta-analysis of genome-wide association studies. Sci Rep. 2016;6:35842.
35. Kesanopoulos K et al. Characterization of meningococcal carriage isolates from Greece by whole genome sequencing: implications for 4CMenB vaccine implementation. PLoS One. 2018;13(12):e0209919.
36. Martinón-Torres F. Do we really want to end meningococcal disease (and current inequity)? An Pediatr (Engl Ed). 2024;100(5):e28-30.

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