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Original

Meningococcal meningitis in Spain in the Horizon 2030: A position paper

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ABSTRACT

Meningococcal meningitis (MM) and invasive meningococcal disease remain a major public health problem that generates enormous public alarm. It is caused by *Neisseria meningitidis*, a Gram-negative diplococcus with an enormous capacity for acute and rapidly progressive disease, both episodic and epidemic in nature, with early diagnosis and treatment playing a major role. It occurs at any age, but is most common in children under 5 years of age followed by adolescents. Although most cases occur in healthy people, the incidence is higher in certain risk groups. Despite advances in reducing the incidence, it is estimated that in 2017 there were around 5 million new cases of MM worldwide, causing approximately 290,000 deaths and a cumulative loss of about 20,000,000 years of healthy life. In Spain, in the 2021/22 season, 108 microbiologically confirmed cases of MM were reported, corresponding to an incidence rate of 0.23 cases per 100,000 inhabitants. This is a curable and, above all, vaccine-preventable disease, for which the World Health Organisation has drawn up a roadmap with the aim of reducing mortality and sequelae by 2030. For all these reasons, the Illustrious Official College of Physicians of Madrid (ICOMEM) and the Medical Associations of 8 other provinces of Spain, have prepared this opinion document on the situation of MM in Spain and the resources and preparation for the fight against it in our country. The COVID-19 and Emerging Pathogens Committee of ICOMEM has invited experts in the field to participate in the elaboration of this document.

Keywords: meningitis, meningococcus, meningococcal meningitis, *Neisseria meningitidis*, vaccines, prevention, epidemics, antimicrobial treatment, chemoprophylaxis.

La meningitis meningocócica en España en el Horizonte 2030: Un documento de opinión

RESUMEN

La meningitis meningocócica (MM) y la enfermedad me-

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ningocócica invasiva siguen siendo un importante problema de salud pública que genera una enorme alarma social. Está causada por *Neisseria meningitidis*, un diplococo Gram negativo con una enorme capacidad para producir una enfermedad aguda y de rápida evolución, tanto de carácter episódico como epidémico, en cuya evolución influyen enormemente el diagnóstico y el tratamiento precoces. Se presenta a cualquier edad, pero es más frecuente en niños menores de 5 años seguido de los adolescentes. Aunque el mayor número de casos se da en personas sanas, la incidencia es superior en determinados grupos de riesgo. A pesar de los avances en la reducción de la incidencia, se estima que en 2017 se produjeron alrededor de 5 millones de nuevos casos de MM en todo el mundo causando aproximadamente 290.000 muertes y una pérdida de unos 20.000.000 de años de vida sana acumulada. En España, en la temporada 2021/22, se notificaron 108 casos de MM con confirmación microbiológica, lo que corresponde a una tasa de incidencia de 0,23 casos por 100.000 habitantes. Se trata de una enfermedad curable y, sobre todo, prevenible con vacunas, para la que la Organización Mundial de la Salud ha elaborado una hoja de ruta con el objetivo de reducir su mortalidad y secuelas en 2030. Por todo ello, el Ilustre Colegio Oficial de Médicos de Madrid (ICOMEM) y los Colegios de Médicos de otras 8 provincias de España, han elaborado este documento de opinión sobre la situación del MM en España y los recursos y preparación para la lucha contra el mismo en nuestro país. El Comité de COVID-19 y Patógenos Emergentes del ICOMEM ha invitado a expertos en la materia a participar en la elaboración de este documento.

Palabras clave: Meningitis, meningococo, meningitis meningocócica, *Neisseria meningitidis*, vacunas, prevención, epidemias, tratamiento antimicrobiano, quimioprofilaxis.

INTRODUCTION

Meningococcal meningitis (MM) and invasive meningococcal disease (IMD) continue to be a major public health problem and cause for social alarm, since they can cause death within a few hours, especially in children and young people, who are generally previously healthy, with the appearance of fulminant clinical manifestations, and whose economic impact is high. The reasons for the social alarm it generates are various and can be summarized as follows: the disease has a worldwide distribution with epidemic potential, its lethality is still high, it entails high morbidity with complications during its course and a high percentage of survivors suffer sequelae [1-3].

Early diagnosis and management during the first hour of meningitis with meningococcal sepsis determine the success of treatment and control of its progression. The categorization of the patient and the assessment of his condition, monitoring and therapeutic opportunity, adapting the treatment to the severity of the condition, are fundamental.

Microbiological confirmation with the determination of the meningococcal serogroup is crucial for epidemiological surveillance, post-exposure prophylaxis of contacts and follow-up of possible vaccine failures. Blood and cerebrospinal fluid culture remains the reference method for microbiological diagnosis, but molecular tests are very useful in patients previously treated with antibiotics and results are rapid to obtain. The availability of the strain will make it possible to perform an antibiogram and to follow the evolution of *Neisseria meningitidis* resistance, as well as to carry out other sequencing studies of bacteriological and epidemiological interest [4].

Prevention by vaccination has been carried out since the 1970s with polysaccharide vaccines first, then with vaccines targeting the external membrane and, since 2000, with meningococcal conjugate vaccines. These are the conjugate vaccines against serogroups A, C, W, Y, the monovalent A and C (A marketed for Africa), and the tetravalent vaccine. In 2013, the first vaccine against serogroup B was licensed, which has completed the broad spectrum of global prevention of meningococcal disease by the five most frequent serogroups of the 12 existing ones.

Since 2023, infection by serogroup X, which in recent years has emerged in some countries in the "meningitis belt," is also immunopreventable by a pentavalent vaccine (ACWXY) that has been prequalified by the World Health Organization (WHO) for use in those countries. A second pentavalent vaccine (the first ABCWY), which is a combination of the tetravalent and meningococcal B vaccine, was licensed by the U.S. Food and Drug Administration (FDA) in October 2023 for use from 10 to 25 years of age.

Finally, it should be recalled that in November 2020, the 73rd Session of the WHO World Health Assembly approved the Defeating meningitis by 2030 roadmap for the world [5].

For all these reasons, the Illustrious Official College of Physicians of Madrid (ICOMEM) and 7 other medical colleges in Spain have decided to organize a day of discussion on the situation of meningococcal disease in the world and in Spain and the prospects for compliance with the WHO roadmap. The format consisted of two round tables in which a series of questions on this subject, previously formulated, were answered. The following document is the result of the deliberations of the day.

WHAT IS WHO'S POSITION ON ELIMINATING MENINGOCOCCAL MENINGITIS BY 2030? WHAT ROLE WOULD VACCINES PLAY?

Annually, more than 2.5 million people of all ages and from any country in the world suffer from bacterial meningitis, of which at least 10% may die. Among the survivors, 20% may have at least one or more long-term sequelae, with an enormous family, social, health and economic impact. Despite the strategies currently in place, health systems have not been able to reduce the number of cases in the same way as has occurred with other immunopreventable diseases such as tetanus or measles [5, 6].

WHO therefore developed a roadmap through a series of consultative meetings involving representatives from govern-

Table 1 **Comparative characteristics of meningococcal vaccines according to polysaccharide, conjugate and recombinant platforms based on outer membrane proteins. Adapted from Debbag et al. [10].**

Features	Polysaccharides	Conjugates	MenB recombinant
Effective in infants	✖	✔	✔
Induction of immune memory cells	✖	✔	✔
Hypo-response with booster dose	✔	✖	✖
Prevention in the acquisition of nasopharyngeal carriage of N. meningitidis	✖	✔	✖
Direct / Indirect Protection	✔ / ✖	✔ / ✔	✔ / ✖
Cross protection	✖	✖	✔

✖: absence of the described characteristic; ✔: presence of the described characteristic.
MenB recombinants: recombinant outer membrane protein vaccines against serogroup B

ments, public health agencies, academia, the private sector, and civil society. This roadmap was endorsed by the Strategic and Technical Advisory Group on Infectious Hazards and the Strategic Advisory Group of Experts on Immunization during 2019, and approved at the 73rd World Health Assembly in November 2020 [5, 7]. The work developed aims to establish a plan to address the main causes of acute bacterial meningitis (meningococcus, pneumococcus, *Haemophilus influenzae* and *Streptococcus agalactiae*), focusing on three visionary objectives that include eliminating epidemics of bacterial meningitis; to reduce the number of immunopreventable bacterial meningitis cases by 50% and deaths by 70%; and finally, to reduce disability and improve the quality of life of meningitis survivors, regardless of etiology. In order to achieve this, there are essential activities and milestones, which are summarized in five intertwined pillars: prevention and control of epidemics; disease surveillance; diagnosis and treatment; support and care for people affected by meningitis; and finally, advocacy and commitment to disseminate the importance of this issue globally, bringing together the different actors in a joint effort. [5].

The role that vaccines would play is described primarily in the epidemic prevention and control pillar, and includes increased and improved access to vaccines against meningococcus, pneumococcus and *H. influenzae* type b, increased vaccine coverage in target populations, development of new vaccines against these agents to increase their immunogenicity and spectrum of coverage, including a vaccine against *Streptococcus agalactiae*; improving prevention strategies and ensuring a timely and effective response to meningitis epidemics; all of which should be tailored to regional and local contexts [5].

Currently, several countries have implemented different vaccination strategies, considering the different direct and indirect protective properties of meningococcal vaccines (Table 1), which have proven to be successful in different parts of the world, according to data from their implementation in the real world [8]. At present, polysaccharide conjugate and recombinant vaccines are available in mono- and polyvalent formulations that can confer protection against serogroups A, B, C, W, X and Y . Recently, WHO promulgated its recommendation for the use of pentavalent vaccine against ACWXY serogroups in the meningitis belt in Africa, both at the programmatic and campaign levels, with updated recommendations for other countries worldwide expected by 2025 [9].

WHAT IS THE EXTENT OF MENINGOCOCCAL DISEASE IN THE WORLD?

Meningitis remains a major public health problem. It is endemic worldwide and causes occasional epidemics in different locations, with particular incidence in sub-Saharan Africa.

Although MM affects people of all ages, young children are most at risk, with half of all cases and deaths occurring in children under five years of age. In addition, one in five survivors of bacterial meningitis may have long-term sequelae: hearing loss, impaired vision, speech, language, memory and communication, seizures, paraparesis, scarring deformities and limb amputations. All of these result in a significant burden of disease, disability and reduced life expectancy in good health. Many cases could be prevented by vaccination.

Figures 1 and 2 [11], show the incidence and mortality, respectively, of meningitis per 100,000 inhabitants per year. As can be seen, the rates differ from one country to another.

Meningococcal meningitis epidemics are widespread in Africa in the so-called "meningitis belt" which stretches from Gambia and Senegal in the west to Ethiopia in the east and has a population at risk of approximately 450 million people in 26 countries. Epidemics are cyclical and usually coincide with the onset of the dry season and a strong dry wind called "harmattan: an ill wind that brings disease"[12]. It is the area of the world that bears the greatest burden of disease. In this African belt, serogroup A meningococcus accounted for more than 80% of cases during meningitis epidemics before the introduction of a meningococcal A conjugate vaccine in mass preventive campaigns (since 2010) and routine vaccination programs (since 2016). Three years later the incidence of this meningitis had decreased by 95% in vaccinated areas and has in fact been virtually eliminated in this area [13]. The first WHO prequalified pentavalent conjugate vaccine (MenFive) against

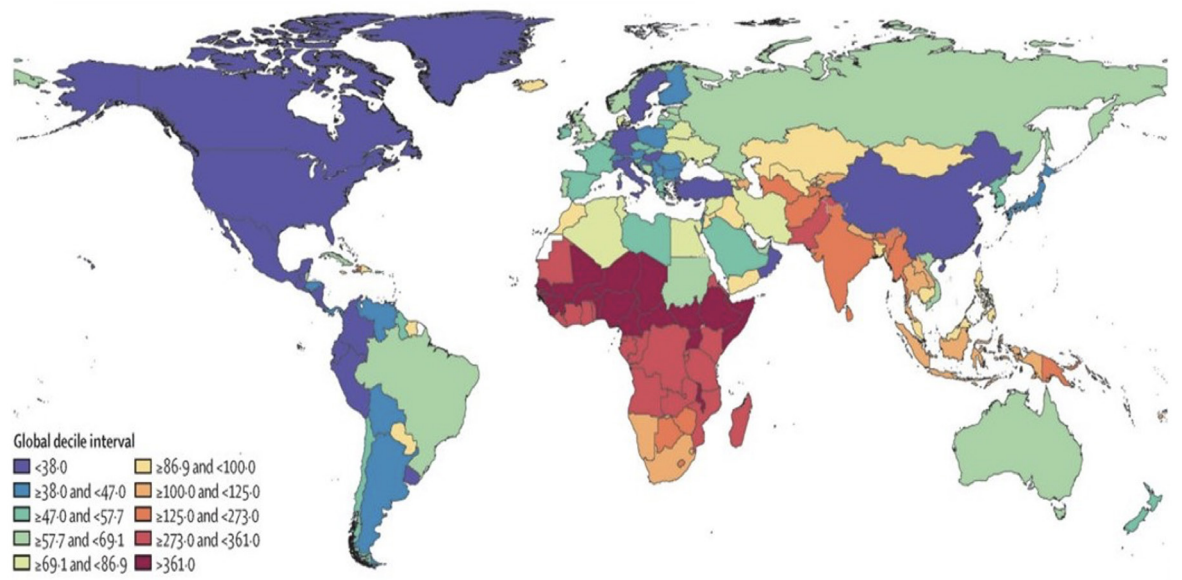

Figure 1 | **Incidence rate of meningitis per 100,000 population and year in children under 5 years of age (2019). Adapted from Global Burden of Disease Study 2019 [11]**

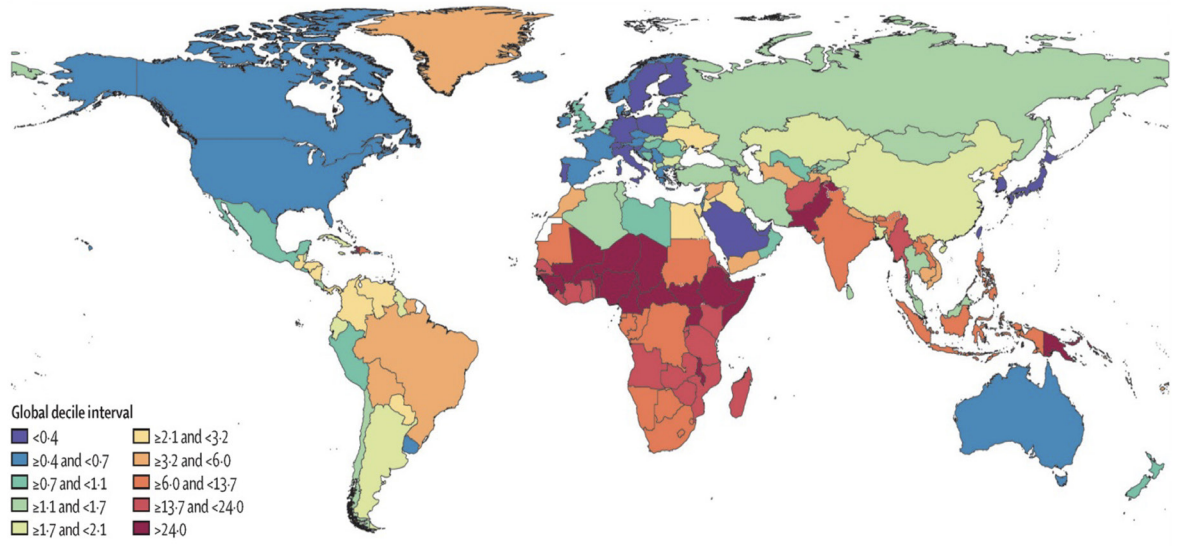

Figure 2 | **Meningitis mortality rate per 100,000 population and year in children under 5 years of age (2019). Adapted from Global Burden of Disease Study 2019 [11]**

the five predominant serogroups in Africa (A, C, W, Y and X) is currently planned for use [14].

As mentioned above, WHO launched the global roadmap "End Meningitis by 2030", which was adopted in 2020 [5] and has called for the establishment of a Global Meningitis Genome Partnership linking resources for: *N. meningitidis*, *S. pneumoniae*, *H. influenzae*, and *S. agalactiae* to improve global coordination in strain identification and tracking by optimizing resources.

Vaccination recommendations are established in two main groups: 1) for countries with high (>10 cases/100,000 inhab/year) or intermediate (2-10 cases/100. 000 inhab/year) and/or frequent epidemics of invasive meningococcal disease, the

recommendation is to establish large-scale meningococcal vaccination programs, and 2) for countries with low endemic rates (< 2 cases/100,000 inhab/year) the recommendation is meningococcal vaccination for defined risk groups.

WHAT ARE THE FIGURES FOR INVASIVE MENINGOCOCCAL DISEASE IN SPAIN AND ITS EVOLUTION IN RECENT YEARS?

Meningococcal disease has been notifiable in Spain since 1901. Currently, data are collected by the National Epidemiological Surveillance Network (RENAVE) managed by the National Epidemiology Center (CNE) integrated in the Carlos III Health Institute. The last RENAVE report that collects cumulative data on invasive meningococcal disease is from the 2021/22 season was published in the first quarter of 2023 in the Weekly Epidemiological Bulletin (BES) [15]. However, provisional data disaggregated by Autonomous Community (CCAA) are collected every week and published in the BES.

In Spain, 108 cases of meningococcal meningitis with microbiological confirmation were reported in the 2021/22 season. The incidence rate corresponds to 0.23 cases per 100,000 inhabitants with a slightly higher incidence in males (54.6%), with the youngest age group being the most affected (incidence rate of 5.16 in children under 1 year of age and 1.08 in the 1-4 year age group). Among the serogroups described, serogroup B was the most common, causing 48.1% (n=45, incidence 0.11) of the cases. This serogroup was followed by 6 cases of W, 5 of Y and 3 of C. Of note, 34.3% (n=37) of the cases were associated with nontypable or unknown serogroups. In the 2021/2022 season, the MM incidence rate dropped dramatically (0.14/100,000 population), with COVID-19 pandemic confinement being the most likely cause. The 2021/22 data are up to 72.6% lower than pre-pandemic (2018/19). In 2021/22 cases followed a typical seasonal pattern with the highest number of cases documented in the month of January.

By Autonomous Communities (AC) the highest number of cases per 100,000 inhabitants in 2021/22 occurred in the Basque Country (incidence 0.60), Cantabria (0.34), Castilla la Mancha (0.34), Andalusia (0.33) and Asturias (0.30) and the autonomous city of Ceuta (1.22) and there were ACs that did not report any cases (Aragon, Extremadura, La Rioja and the autonomous city of Melilla).

Preliminary data for 2022/23 indicate a clear upward trend, with 226 cases (incidence of 0.47)[16]. As in 2021/2022, the majority was serogroup B (105 cases, 46.5%, incidence 0.22) followed by W (25 cases, 11.1%, incidence 0.05), Y (18 cases, 8.0%, incidence 0.04) and C (3 cases, 1.3%, incidence 0.01).

WHAT ARE THE CHARACTERISTICS OF *N. MENINGITIDIS* IN SPAIN AND WHAT IS ITS RELATIONSHIP WITH THE EPIDEMIOLOGY OF MENINGOCOCCAL DISEASE?

The epidemiology of MM, both in Spain and globally, has always been unpredictable due to the changing nature of the causal microorganism, *N. meningitidis*, which causes epidemic waves and inter-epidemic periods generally associated with the circulation of certain hypervirulent strains [17]. This classical image of IMD has been greatly altered by the use of vaccines that in some cases provide not only individual protection but also herd immunity with enormous public health impact. This ability to produce herd immunity is only associated with polysaccharide conjugate vaccines (A, C, Y and W) but is not achieved with the use of protein formulation vaccines (B). In this context, and until 2019, the situation in Spain was one of a slow but sustained increase of serogroups W and Y, which in that year together reached 45% of the total number of confirmed cases received in the Reference Laboratory, with cases of serogroup B (historically the majority in Spain), 44.2%, with an overall rate of IMD collected by the RENAVE of 0.83 cases per 100,000 inhabitants, which confirmed a growing trend observed in the previous 4 years. It should be noted that the high percentage of non-typeable isolates or isolates with unknown serogroups mentioned in the previous question are probably an artifice, since the data were not included at the time of reporting, so that the distribution by serogroups is probably better reflected by taking the data from the ISCIII meningococcal reference laboratory as a source.

With the arrival of the COVID-19 pandemic in 2020, and associated with the containment measures to reduce the transmission of the SARS-COV-2 virus, in Spain, as in other countries around the world, there was a marked decrease in the incidence not only of IMD but also of *S. pneumoniae or H. influenzae* as reflected in the data of the International Consortium "Invasive Respiratory Infection Surveillance (IRIS)" in which the Reference Laboratory of Spain actively collaborates. This decrease can be observed especially in the year 2021, with an incidence rate of only 0.14 X 10^5 in the year 2021, with such a small number of cases that it is impossible to draw conclusions with statistical significance. As the containment measures related to the pandemic have been relaxed, the number of cases has been slowly increasing so that in 2023, the number of cases is slightly higher than that observed in 2020, and the distribution of serogroups again shows similar values. There are other factors that could have had an impact on the overall decrease in cases of IMD, which are probably more difficult to evaluate, such as the use in private pediatrics of a serogroup B vaccine with a protein formulation in children outside the vaccination schedule (not funded) until 2022, the introduction of this vaccine in the schedule (funded) from 2023, without forgetting a saturation of the surveillance services due to the pandemic that could be responsible for a limited and difficult to quantify loss of registered cases.

No significant differences were observed in the circulating clonal complexes before and after the pandemic, nor in the distribution of antigens included in the available vaccines against serogroup B in the strains isolated from invasive processes.

Table 2 **Microbiological techniques used in the diagnosis of meningococcal meningitis and invasive meningococcal disease.**

Techniques	Comments
Conventional diagnosis	
Gram stain	Rapid result, operator-dependent sensitivity and bacterial load.
Latex agglutination	In disuse due to its low sensitivity.
Culture	Variable sensitivity depending on bacterial load. Necessary for further sensitivity and typing studies (serogroup).
Susceptibility study	Difficulties in culture medium.
Isolates typing	Seroagglutination against polysaccharide capsule antigens. Indispensable for vaccine design and monitoring of possible vaccine escapes
Molecular diagnostics	
Syndromic panels	Versatile (detection of various pathogens), low handling. Rapidity.
Whole genome sequencing (WGS)	Analysis of protein variable regios (PorA, PorB, FetA), coreMLST (cMLST), core gene SNVs (cgSNVs) Knowledge of the resistome

WHAT IS THE ROLE OF NEW TOOLS IN THE DIAGNOSIS OF INVASIVE MENINGOCOCCAL DISEASE? ARE THEY INFLUENCING REGISTRATION?

The microbiological diagnosis of IMD has changed radically in recent years with the introduction of the so-called molecular techniques based on the amplification of nucleic acids, thus gaining greater sensitivity [18] (Table 2). Previously, this diagnosis was based exclusively on direct sample staining, essentially Gram staining, and microbiological culture of cerebrospinal fluid, blood cultures or some tissues with a highly variable sensitivity depending on the microorganism and bacterial load (10-95%). Rapid immunological techniques based on agglutination with latex particles or immunochromatography were also used, also with a very variable sensitivity [19].

Currently, the most effective methods in the diagnosis of IMD are the so-called syndromic panels that amplify several targets covering different pathogens, including bacteria, fungi and viruses and even resistance markers. They also have the advantage over culture in obtaining results in a short time (less than 90 minutes). The most widespread are based on real-time PCR (RT-PCR) or isothermal amplification (LAMP). Despite their sensitivity and high negative predictive value, they are not free of false-positive results, although they do not usually occur with N. meningitidis [19, 20].

The introduction of these molecular techniques has improved microbiological diagnosis, transforming probable and suspected cases into confirmed cases (with microbiological diagnosis). However, microbiological culture continues to be the reference in the diagnosis of IMD as it allows strain recovery and subsequent sensitivity study.

Serogroup typing is traditionally performed by slide agglutination test with sera containing antibodies against the different capsular antigens. In Spain, serogroup typing is performed by the microbiology laboratory itself or by the National Reference Laboratory for Meningococci of the Instituto de Salud Carlos III.

The notification of the microbiological results to the Public Health authorities takes place almost in real time through the computer systems of the laboratories and Microbiology Services. Given the importance of IMD, this speed in the transmission of results must be preceded by the availability of microbiology laboratories with continuous attention (also called 24/7) that ensure microbiological diagnosis with both culture and molecular techniques [21].

Currently, other typing techniques are also being added to serogroup knowledge, including the amplification of specific sequences of variable regions (PorA, PorB, FetA) in conjunction with MLST (multilocus sequence typing) schemes [22]. The introduction of whole genome sequencing (WGS) techniques, including from direct samples, will provide a better understanding of the epidemiology of *N. meningitidis* and its spread [23]. A recent study analyzed nearly 70,000 sequences of *N. meningitidis* deposited in open access databases, demonstrating the usefulness of these studies in the knowledge of the global epidemiology of this pathogen, the identification of epidemic clones and their temporal dispersion, as well as possible evolutionary trajectories [24].

IS IT POSSIBLE TO SUMMARIZE THE FACTORS THAT INCREASE THE RISK OF MENINGOCOCCAL MENINGITIS?

The highest incidence occurs in children under 5 years of age (especially under one year of age), with a second peak among adolescents and young adults, who are also the main carriers and transmitters of the disease. Meningococcus has a

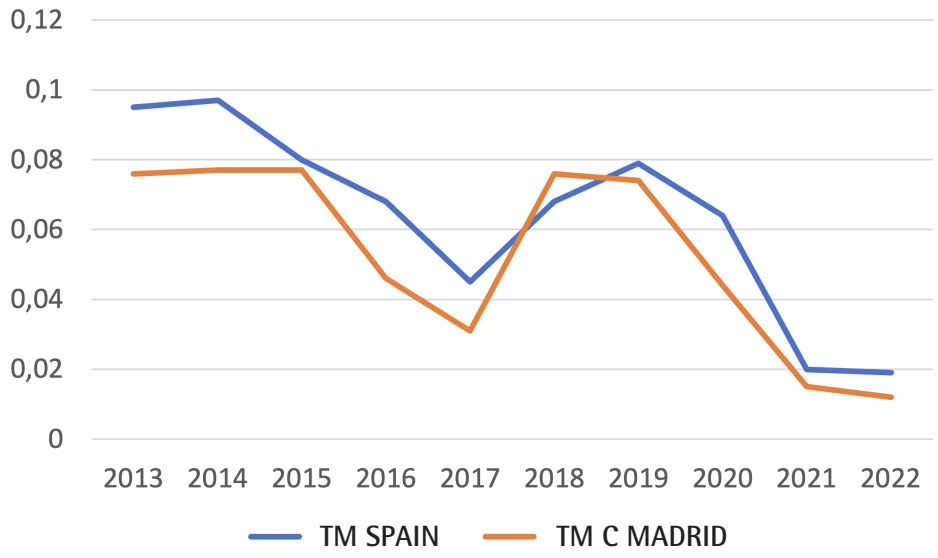

Figure 3 Rate of deaths per 100,000 inhabitants caused by Invasive Meningococcal Disease in Spain and the Community of Madrid. Prepared by the General Directorate of Public Health of the Community of Madrid

TM, Total Mortality and TMC , Total Mortality Community of Madrid

special predilection for the extreme ages of life, with people over 64 years of age being the next most important age group.

Predisposing diseases include: anatomical or functional asplenia, complement factor deficiency, treatment with eculizumab or ravulizumab, hematopoietic stem cell transplant recipients, patients with HIV infection, patients with previous episodes of IMD by any serogroup, and contacts of an index case of IMD by serogroup A, B, C, W or Y [25].

Another risk factor is travel to countries with a high incidence, especially sub-Saharan African countries or the pilgrimage to Mecca.

WHAT IS THE MORTALITY RATE OF MENINGOCOCCAL MENINGITIS AND ITS SEQUELAE IN OUR ENVIRONMENT?

Analyzing the period 2019-2023, the incidence of IMD in the Community of Madrid (CM) has presented a notable decrease, similar to the rest of Spain, partially explained by the application of SARS-CoV-2 containment measures (from March 2020), which resulted in a decrease in the incidence of respiratory-transmitted infectious diseases, in addition to, by the inclusion in the vaccination schedule of the Men ACWY vaccine in adolescents.

The mortality rate (number of deaths per hundred thousand inhabitants) for this heading is low, both in the Community of Madrid and in Spain as a whole (Figure 3).

In this disease, given its severity, it is important to analyze the lethality data (deaths due to meningococcal disease/EMI cases), which in the last five-year period (2019-2023) ranges between 8-15% in the Community of Madrid. The overall case fatality rate can be seen in Table 3.

Table 3 Meningococcal disease fatality rate in Spain. Seasons 2012-13 to 2022-23.

Year	Spain (%)
2012-13	10.5
2013-14	10.2
2014-15	10.6
2015-16	10.1
2016-17	10.7
2017-18	12.1
2018-19	10.1
2019-20	12.0
2020-21	6.1
2021-22	7.0
2022-23*	6.0

Prepared by the authors based on the weekly epidemiological bulletin ISCIII [15]
*Provisional data.

Of the total number of reported cases of MM in the 2022-2023 season, 6 deaths were reported, 3 caused by serogroup B, 1 by other serogroups, 1 by unknown serogroup and 1 non-typeable.

During the 2109-20 and 2020-2021 seasons, the age group with the highest case-fatality rate was the over 84 years old (26.7% and 28.57%, respectively) and the group with the lowest case-fatality was the 1-4 years old (5.56%). During the 2021-22 season, the age group with the highest case fatality rate was 45-64 years (20%). In the age groups under 1 year, 1-4 years, and 10-14 years, the case fatality rate was 0%.

In the five-year period 2019-2023 in the Community of Madrid, the evolution of most of the cases has been favorable, although 10% of the cases presented sequelae in the five years of follow-up of the study. The sequelae in these cases were as follows: 43% (6 cases) of the cases had hypoacusia, 4 cases in patients over 65 years of age; 28% (4 cases) had partial amputations of lower limbs (2 cases), total amputation of a foot (1 case), amputation of distal fingers (1 case), hydrocephalus (1 case), renal failure (2 cases) and subacute myopathy (1 case).

COULD AGE BE A DETERMINANT IN PRODUCING A DELAY IN DIAGNOSIS?

During the five-year period 2019-2023 there has been no significant delay in diagnosis in any age group. All cases reported to the Community of Madrid have required admission to a hospital. To assess the delay, the difference between the reported date of symptom onset and the date of hospital admission was analyzed. The mean was 1.6 days and the median 1 day.

However, atypical presentation of IMD in adults older than 55 years is described, often linked to a comorbid condition, including myocarditis/endocarditis and arthritis. Initially in these cases, IMD was not suspected and *N. meningitidis* was detected once the patients were admitted to the hospital [26].

Atypical presentation of IMD may result in diagnostic delay. The comprehensive review by Guedes et al. [26], found evidence that IMD in older adults is caused mainly by serogroups that are not generally predominant circulating strains (W and Y), and have a higher case fatality rate as well as a higher likelihood of atypical symptoms.

WHAT ARE THE MOST IMPORTANT FEATURES OF ANTIMICROBIAL TREATMENT OF MENINGOCOCCAL MENINGITIS? IS ANTIMICROBIAL RESISTANCE A PROBLEM?

It is well known that delay in diagnosis and initiation of antibiotic treatment is directly related to increased mortality in MM [27]**.** Therefore, its administration should not be delayed and should be started as soon as possible after the extraction of samples for microbiology, even before performing a cranial CT scan and lumbar puncture if these will delay the start of the antibiotic.

In this regard, it should be borne in mind that only 40% of MM cases present with the classic triad of fever, headache and neck stiffness, which can make it difficult to diagnose patients and delay the initiation of antibiotic treatment [27]. A review of the literature showed that the association between delay in antimicrobial administration and patient prognosis depended primarily on the clinical presentation, such that this relationship was lost when the patient did not present altered consciousness or the classic clinical triad [28]. The accentuation of headache with exploratory maneuvers is considered positive if the headache is exacerbated by turning the head horizontally two or three times per second. The maneuver is intended to rule out meningitis without the need for lumbar puncture [29].

The choice of antibiotic treatment for invasive infection by *N. meningitidis* is based, as for any serious disease, on the choice of a potent antimicrobial, with high bactericidal capacity, with a low rate of resistance in the community for this microorganism, pending the antibiogram, and on its ability to spread to the infectious focus.

In relation to sensitivity, resistance to antibiotics used in the treatment and prophylaxis of meningococcal disease is relatively rare in Spain. The antibiotic with the highest percentage of resistance is penicillin, around 10%. Resistance to third generation cephalosporins is rarely reported. However, in about 1% of cases, strains with reduced sensitivity to both cefotaxime and ceftriaxone have been observed [30, 31]. Finally, it should be noted that resistance to rifampicin has been reported among meningococci, mainly after prophylaxis, and resistance to ciprofloxacin, although this is rare [32].

In relation to diffusion to the focus, in the case of meningitis it is necessary to take into account the difficulty of some antibiotics to cross the blood-brain barrier (BBB) and reach sufficient concentrations in the cerebrospinal fluid (CSF). The penetration of the antibiotic will depend on its molecular size (the lower the molecular mass, the greater the ease of diffusion), liposolubility (which favors diffusion), binding to plasma proteins (the lower the binding, the more free drug to reach the CSF) and its affinity for BBB transporter proteins, which expel the antibiotic as efflux pumps. However, MM is an inflammatory disease that favors antibiotic penetration through BBB due to effacement of the intercellular sealing of the endothelium, moderate reduction of CSF production and reabsorption, and decreased activity of transporter proteins, which are inhibited by the presence of inflammatory cytokines [33].

Beta-lactams are molecules of low molecular mass, with variable binding to plasma proteins, low liposolubility and variable affinity for efflux pumps. In the absence of meningeal inflammation their penetration is relatively low, 10-20%, but the concentration they reach in CSF in a situation of meningeal inflammation is sufficient to exceed the MIC of sensitive pathogens. In addition, ß-lactams have a relatively low toxicity, so that the dose administered can be increased to ensure high concentrations in CSF without assuming a high risk of adverse effects [33]. Based on the above, the antibiotic treatment of choice for meningococcal meningitis is the administration of third-generation cephalosporins (ceftriaxone 2g/12h or cefotaxime 2-4 g/4-6h intravenous in adult). The alternative in patients allergic to cephalosporins would be aztreonam 2g/6h intravenous. Quinolones are small molecules, moderately li-

Table 4 Chemoprophylaxis of contacts of patients with meningococcal meningitis.

Rifampin[a]	Adult: 600 mg every 12 h orally, for 2 days Children 1 month to 12 years: 10 mg/kg/12 h orally, for 2 days Children < 1 month: 5 mg/kg/12 h orally, for 2 days
Ciprofloxacin[b]	Adult: 1 dose of 500 mg orally
Ceftriaxone[c]	Adult: 1 dose of 250 mg intramuscularly Children < 12 years: 1 dose of 125 mg intramuscularly

[a]Not recommended in pregnancy and lactation. Contraindicated in severe hepatic insufficiency. Decreases the efficacy of oral contraceptives.
[b]Ciprofloxacin is contraindicated in pregnant, lactating and < 18 years old.
[c]Useful in pregnancy and lactation.

posoluble and with low binding to plasma proteins. Concentrations in CSF can reach 40% for ciprofloxacin and 80% for levofloxacin and moxifloxacin [33]. *N. meningitidis* is very sensitive to ciprofloxacin and levofloxacin and these drugs are an alternative in patients allergic to beta-lactams.

MM may be accompanied by sepsis requiring specific management [34, 35]. In these cases, patients must be monitored, ensure adequate oxygenation, sometimes requiring intubation, administer fluid therapy or vasoactive drugs to maintain adequate tissue perfusion and treat any complications that may arise, such as hypoglycemia, ionic alterations, coma or intracranial hypertension.

Finally, it should be noted that the administration of dexamethasone decreases the rate of complications, and even mortality, in patients with meningitis due to *H. influenzae,* pneumococcus or tuberculosis when it is administered before the first dose of antibiotic or no later than one hour after its administration. However, it has not shown any benefit in MM [31].

WHAT SHOULD BE THE ANTIMICROBIAL PROPHYLAXIS OF THE COHABITANTS AND ASSISTANTS OF PATIENTS WITH MENINGOCOCCAL MENINGITIS?

The aim of meningococcal chemoprophylaxis is to eliminate the possible nasopharyngeal carrier status of the contact and break the chain of transmission, as well as to protect the individual from developing the disease. It is estimated to reduce the risk of transmitted meningococcal disease by 90% [36].

It should be performed in children and adults who have lived with the index case during the 7 days prior to the onset of symptoms and up to 24 hours after initiation of appropriate antibiotic treatment. It should be administered as soon as possible and as long as 10 days or more have not elapsed since contact.

Only cohabitants or close contacts should receive chemoprophylaxis, considering these to be those who have had prolonged contact (more than 8 hours) with the patient, close (less than 3 meters) or who have been directly exposed to the patient's oral secretions [31,36,37]. In the case of healthcare personnel, brief, non-intimate transient contacts are excluded, unless they have participated in cardiopulmonary resuscitation maneuvers, endotracheal intubation or aspiration of respiratory secretions.

Chemoprophylaxis is summarized in Table 4. The antibiotic of choice is rifampicin in all age groups, which reduces the carrier rate by up to 96%. An alternative in adults is ciprofloxacin, but it is not recommended during pregnancy, lactation or in growing children and adolescents. The advantage over rifampicin is that it is administered in a single oral dose. For this reason, it can be used as a first choice in groups of adults where difficulties in administration or follow-up are foreseeable. Finally, ceftriaxone is another alternative, especially in case of pregnancy and lactation, if it has been decided to administer chemoprophylaxis.

WHAT VACCINES ARE AVAILABLE AGAINST INVASIVE MENINGOCOCCAL DISEASE? WHO SHOULD RECEIVE THEM? WITH WHAT GUIDELINES?

Eight meningococcal vaccines are currently available in Spain. Six of them are polysaccharide conjugates and the other two against serogroup B are prepared from subcapsular proteins [38-40] (Table 5). In the conjugates, the oligo- or capsular polysaccharide of the different serogroups binds to a carrier protein that can be tetanus toxoid or a mutant of diphtheria toxoid (CRM197). Among them, there are three that are monovalent against serogroup C (MenC): Menjugate, Meningitec and NeisVac-C and three tetravalent against serogroups A, C, W and Y (MenACWY): MenQuadfi, Menveo and Nimenrix. The "C" component of these tetravalent vaccines generates immunity similar to that of monovalent vaccines against that serogroup and can replace them in the vaccination regimens in which they are used. Both Meningitec and Menjugate are currently out of use in our country, in favor of NeisVac-C, the only vaccine against MenC that allows the administration of a single dose during the first year of life. There are two vaccines authorized against meningococcal B, one from 2 months of age (Bexsero) and the other from 10 years of age (Trumenba) (Table 5).

Table 5 **Authorized vaccines in Spain against meningococcus.**

Brand name	Serogrups	Active principle	Transporter protein	Adyuvant	Minimum age of use
Menjugate (GSK)	C	10 µg capsular oligosacáride, group C	12,5-25 µg CRM197	0,3 a 0,4 mg aluminum hydroxide	2 months
Meningitec (Nuron Biotech)	C	10 µg capsular oligosaccharide, group C	15 µg CRM197	0,125 mg de aluminum phosphate	2 months
NeisVac-C (Pfizer)	C	10 µg capsular polysaccharide (de-O-acetylated) of group-C	10-20 µg tetanus toxoid	0,5 mg de hydrated aluminum hydroxide	2 months
MenQuadfi (Sanofi Pasteur)	A, C, W, Y	10 µg capsular polysaccharide of groups A, C, W and Y	55 µg tetanus toxoid	-	12 months
Menveo (GSK)	A, C, W, Y	10 µg capsular oligosaccharide of group A and 5 µg oligosaccharide of group C, W and Y	16,7-33 µg CRM197 (A) 7,1-12,5 µg CRM197 (C) 3,3-8,3 µg CRM197 (W) 5,6-10 µg CRM197 (Y)	-	2 years
Nimenrix (Pfizer)	A, C, W, Y	5 µg capsular polysaccharide of groups A, C, W and Y	44 µg tetanus toxoid	-	6 weeks
Bexsero (GSK)	B	50 µg recombinant fusion protein NHBA\50 µg recombinant protein NadA\50 µg recombinant fusion protein fHbp\25 µg OMV Neisseria meningitidis B (PorA P1.4)	-	0,5 mg aluminum hydroxide	2 months
Trumenba (Pfizer)	B	60 µg fHbp lipidated subfamily A (A05) of Neisseria meningitidis B\60 µg fHbp lipidated subfamily B (B01) of Neisseria meningitidis B	-	0,25 mg aluminum phosphate	10 years

The posology, indications and ages of use of these vaccines may undergo imminent changes depending on studies currently underway and reviews of the EPAR by the European Medicines Agency. The first pentavalent meningococcal vaccine, ABCWY (Pfizer), has recently been approved by the American FDA but is not yet available in our country. This vaccine is authorized only for persons aged 10 to 25 years.

The Spanish Interterritorial Council includes in its current meningococcal vaccination recommendation systematic vaccination against meningococcal C in infants at 4 and 12 months, against meningococcal ACWY at 12 years of age, and against meningococcal B in infants at 2, 4 and 12 months of age. Outside these ages, vaccination would only be indicated in specific risk groups, which we listed above, specifically B and ACWY in asplenia, complement deficiencies and treatment with eculizumab, hematopoietic progenitor transplantation, personal history of invasive meningococcal disease and laboratory personnel exposed to meningococcus, and ACWY in HIV.

WHAT WOULD BE THE IDEAL VACCINATION SCHEDULE?

It is not easy to establish the ideal meningococcal vaccination schedule, and only in Europe is there a wide variety, and the differences cannot be explained by epidemiological or logical criteria. In the opinion of some of the authors of this manuscript, the best is the most complete, and should cover both serogroup B and ACWY, and include at least both infants and adolescents (Figure 4). Vaccination of adolescents against ACWY is known to work in the medium term, based on the class effects of conjugate vaccines on carriers, and also the positive objective results of this strategy in the UK. However, with current coverages, it is not possible to count on indirect protection of unvaccinated subjects, except for serogroup C. Once indirect protection is achieved in the community through high and maintained coverage in the ACWY adolescent cohort, infant doses could be omitted. In the case of meningococcus B, since there is no impact on carriers, protection would always be direct. There are no objective data to confirm that a booster dose of meningococcus B is necessary in older children or adolescents correctly vaccinated as infants, nor that a single dose at this age is sufficient to maintain protection or to obtain the potential benefits of cross-protection described in the literature for this age group. Nevertheless, vaccination of adolescents against meningococcal B is important because of their protection as the second group with the highest incidence of meningococcal disease, and it is also possible that through the cross-protection that these protein vaccines can generate, a certain degree of clinical protection against gonorrhea, a disease that is on the rise and for which there are no specific vaccines.

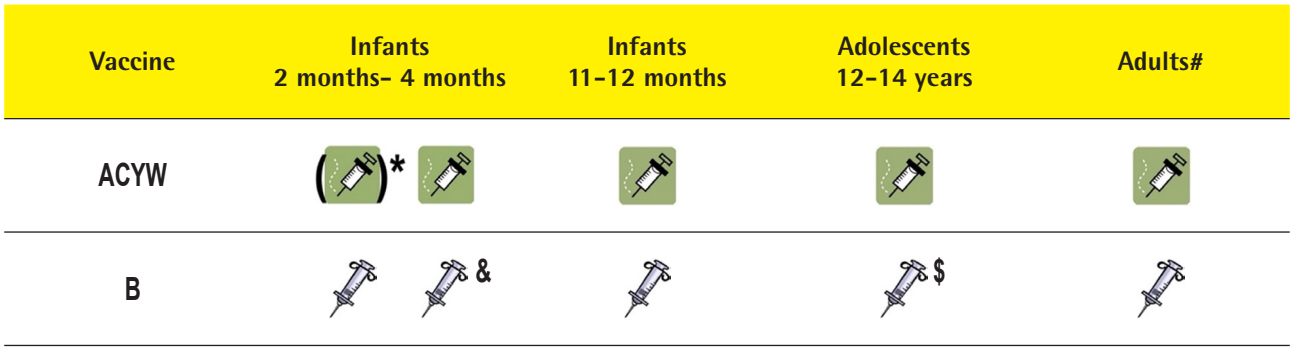

Figure 4 | **Most complete meningococcal vaccination schedule according to the vaccines currently available. The application of this schedule is subject to the technical data sheets of the vaccines according to the age at which they are administered, as well as to the epidemiological context. Adapted from Martinón-Torres et al. [41,42]**

* According to current data sheets, vaccination of infants under 6 months of age requires at least two doses of primary vaccination. Replacing the current 4-month monovalent C dose with ACWY would be sufficient for protection against serogroup C. The results of a clinical trial evaluating the 1+1 schedule with ACWY-TT (Nimenrix) at 3 and 12 months of age have recently been reported, showing its safety and immunogenicity. It could be considered to progressively dispense with the infant doses against ACWY, once indirect protection in the community has been achieved through high and maintained coverage in the cohort of adolescents with ACWY, as was done in the past with the monovalent vaccine doses against C in infants.

& The second dose of meningococcal B could be administered as early as 3 months of age in the 3-dose primary vaccination schedule. In the 2-dose regimens, the minimum interval between doses is 8 weeks according to the technical data sheet.

$ This dose could be administered at 12 or 14 years of age, taking advantage of other vaccination visits. We do not yet have data to justify the need for a booster dose of meningococcal B in children who have been correctly primed, nor that a dose at this age is sufficient to maintain adequate levels of protection or to obtain the potential benefits of cross-protection described in the literature for this age group.

Information on meningococcal vaccination in adults is limited and restricted to its use in specific risk groups. We do not know the persistence of the protection of childhood primovaccination in adults. More data are needed to justify routine adult vaccination as part of a vaccination schedule.

Older adults face the highest mortality rates associated with invasive meningococcal disease, which could be attributed to multiple factors, including the presence of comorbidities and the manifestation of atypical clinical symptoms that complicate early diagnosis and treatment. Although incidence rates are lower than in childhood, the increase in invasive meningococcal disease in older adults is objective and particularly worrisome due to the progressive increase in the elderly population worldwide, so more research is needed to determine the most effective and efficient vaccination strategies and to provide a solid basis for health authorities to decide on the expansion of national immunization programs to protect this age group. In any case, although there is limited information on the long-term protection of the available meningococcal vaccines, it is important to note that the following information is not yet available [26, 41]. Adult meningococcal vaccination should be considered as part of a meningococcal disease eradication program [42-44].

MM is only one, but it is caused by different serogroups, and today there are safe and effective vaccines that cover practically all the cases that occur in our country. In the opinion of some of the authors of this work, if we really want to control meningococcal disease and work decisively towards a world free of meningitis by 2030, the official calendar should move in the direction of this broader proposal, providing coverage against all possible serogroups and protecting both infants and adolescents. At the present time, the meningococcal vaccination schedule closest to the "ideal" in Spain, in the opinion of some of the authors of this study, is that of the autonomous community of Galicia, which includes vaccination against ACWY at 4 months, 12 months and 12 years, against B at 2, 4 and 12 months, and should only include vaccination against meningococcal B in adolescents to complete it (not a unanimous opinion) [2] (Figure 4).

CAN PROTECTION AGAINST OTHER PATHOGENS BE EXPECTED FROM VACCINATION AGAINST MENINGOCOCCUS?

As mentioned above, the polysaccharide A, C, Y and W conjugate vaccines provide not only individual protection, but also indirect protection [45] which has an enormous impact on public health. Herd immunity is not achieved with the use of protein-formulation vaccines, such as those directed against meningococcal B [46]. However, the subcapsular antigens contained in the 4CMenB vaccine are present to a greater or lesser extent in other serogroups of Neisseria meningitidis, so it is possible that the vaccine could offer some degree of protection against IMD due to serogroups other than B [47].

On the other hand, the 4CMenB vaccine could offer a certain degree of cross-protection against gonococcus based on the fact that *N. meningitidis* and *N. gonorrhoeae* are very

similar in genetic and antigenic terms, with 80-90 % nucleotide identity in the genome. Of the 22 major proteins of the outer membrane vesicles (OMVs) of meningococcus, 20 have homologues in gonococcus. In addition, the meningococcal NHBA antigen has a surface-exposed and highly conserved homologue in gonocococcal strains, with 67 % identity. Several studies [48-50] have shown some protection against gonorrhea from meningococcal vaccines with OMV in their composition. The results of these studies support ongoing randomized controlled trials [51, 52] on the efficacy of 4CMenB against gonorrhea.

WHAT IS THE ROLE OF PATIENT ASSOCIATIONS IN SPAIN?

The Spanish Association Against Meningitis (AEM) is the only one in Spain that fights against Meningitis as its main mission. The role of the AEM is aligned with the WHO's global plan to work to reduce the disease by 2030. In fact, as members of CoMO (Confederation of Meningitis Organizations) the AEM was invited in 2018 to draft in London, the main pillars to achieve that end.

The scientific committee of the AEM is coordinated by Dr. Federico Martin Torres, and its messages reach the general population with truthful and science-based information on the signs and symptoms of this disease and on the benefits of vaccination to prevent it.

There is also a network of volunteers that includes affected families who lead the representation of the AEM in their region or community, as well as a team of mental health professionals such as psychiatrists, psychologists, therapists, and occupational therapists who offer free support to affected families, both individually and collectively.

It is important to highlight the diversity of funding received by the AEM, since thanks to the solidarity events and the support of companies from different sectors, both public and private, can reach families in need with grants that for example in 2023 reached 20,000 €.

The AEM is, therefore, a non-profit organization whose mission is to support research and families affected by this disease. It will soon be eight years old with a large presence in media and social networks reaching thousands of people. Being the only patient association that spreads the benefits of prevention through vaccines places the AEM in a very high first level, which does not prevent us from being aware of the responsibility of this situation.

The AEM also fulfills a fundamental and very new role in patient associations: "Advocacy" or institutional relations. Until now, the ability to reach politicians and health authorities was limited, but thanks to a great deal of training and help from its English counterparts, the AEM has managed to understand the language, the moment, and the way to present petitions to politicians. Proof of this is the photo of the steps of the Parliament of Catalonia in November 2022, where they managed to make the Minister understand the seriousness of the consequences of this disease and decided a few months later to vaccinate infants born in Catalonia against one of the most common serogroups of meningococcus.

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CONFLICTS OF INTEREST

The author declares no conflicts of interest

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