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Review Article

Latin American Forum on Meningococcal Disease, Latin American Update: Its Prevention

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Abstract

Introduction: The Latin American Society of Pediatric Infectology (SLIPE for its acronym in Spanish) is working hard to strengthen the vaccination recommendations as the most effective method to prevent meningococcal disease, a disease that causes multiple consequences, not only physical, but also social and economic, in children and their families. **Areas covered:** On Friday, May 7th, a Latin American forum of experts on meningococcal disease was held through Zoom platform. Issues such as: Disease burden, epidemiological surveillance programs, meningococcal vaccines, impact of meningococcal vaccination programs, costs of illness, and the role of communication were discussed. **Expert opinion:** Meningococcal disease is an infectious disease event, with a rapid clinical evolution, very serious in some cases and with sequelae that are difficult to quantify in Latin America. Active surveillance through sentinel units is essential to quantify the disease burden and strengthen the available information.

Expert opinion: Article Highlights Box

- Meningococcal disease is an infectious disease event, with a rapid clinical evolution, very serious in some cases and with sequelae that are difficult to quantify in Latin America.
- Active surveillance through sentinel units is essential to quantify the disease burden and strengthen the available information.
- Carriage studies should be part of an epidemiological surveillance program.
- Laboratory and molecular tests are fundamental to analyze the scope of the vaccines applied in the region; the interaction between laboratory, clinical and epidemiology is key.
- Available vaccines are safe and effective and open a horizon for the control of meningococcal disease.

Keywords: Latin America; Meningococcal disease; Meningococcal vaccines; Serogroup

Introduction

Meningococcus is a Gram-negative, intracellular, oxidase-positive, catalase-positive, diplococcus, coccus-type bacterium, first described in 1805 in Geneva, Switzerland. It has certain immunochemical differences in its polysaccharide capsule that allow it to originate different serogroups. Membrane proteins, mainly porins, define serotypes and subserotypes. The immunotype is given by lipo-oligosaccharides, which are associated with septic shock occurring during the clinical course [1]. Six serogroups of *Neisseria menigitidis* (Nm) have been identified with the ability to cause severe disease: A, B, C, X, Y and W; infection by this bacterium can be epidemic or endemic and it is the only bacterium that can cause epidemics of meningitis [2]. Nasopharyngeal colonization is a requisite for invasive disease. It usually occurs as an asymptomatic carriage for a long time, being a dynamic process, whose prevalence can be up to 20%, being higher in adolescents and young adults [3]. According to a study [4] conducted on 2,507 students in their first year of college to determine the prevalence of meningococcal carriage and related risk factors, as well as meningococcal carriage and acquisition; the researchers found that the rates of bacterial carriage increased rapidly in the first week of the trimester, from 6.9% on day 1 to 23.1% on day 4. Independent associations for meningococcal acquisition were: frequency of visits to a residence pub (5-7 visits), current smoking, being male, nightclub visits, and kissing. Invasive Meningococcal Disease (IMD) has multiple clinical presentations, with the most common clinical diagnoses being meningitis (more than 50%) and meningococcemia (17% to 37%) sometimes occurring together (4% to 22%). Clinical presentation generally varies according to the infecting Nm serogroup [5]; this is related to the case fatality rate (10% to 14%) in cases of meningitis, but can improve with early diagnosis and management; while septicaemia has a fatality rate of more than 40%, being fulminant, in some cases within hours. Death occurs in 6% to 10% of cases and sequelae in 4.3% to 11.2%; being a very high rate compared to other pathologies such as diphtheria, pneumococcal pneumonia, Haemophilus influenzae type B meningitis, chickenpox, measles, and others [6,7]. Case fatality rates in Latin American countries range between 10% and 20%, although higher rates have been associated with specific serogroups during outbreaks [8]. The clinical features of classic meningococcal disease appear late in the disease, so recognizing the early symptoms of sepsis could increase the proportion of children identified by primary care physicians and shorten the time to hospital admission. In a study [9] conducted in the United Kingdom, using parental questionnaires and clinical records, the disease course before hospital admission was assessed in 448 children (103 deceased and 345 non-deceased) aged 16 years or younger with IMD. The results showed that most of the children had only nonspecific symptoms in the first 4-6 hours, but were close to death at 24 hours. Only 165 (51%) of the children were referred to hospital after the first consultation. The classic features of hemorrhagic rash, meningismus, and impaired consciousness developed later (13-22 hours); whereas 72% of the children had early symptoms of sepsis that first developed in a median of 8 hours, much earlier than the median time to hospital admission of 19 hours [9].

Meningococcal Disease Epidemiology

Regarding the epidemiology of IMD compared to other invasive pathogens, adolescents and young adults have the highest rates of nasopharyngeal carriage and transmission, so they may be spreaders among themselves and to younger or older age groups, depending on risk factors or predisposing conditions. Compared with immunization strategies restricted to young children, an adolescent-focused strategy may have deeper and longer-lasting indirect impacts and may be more cost-effective [10]. In a study conducted in different continents [11], a systematic bibliographic review was performed in six databases to identify studies (published between the years 2010 and 2017) on meningococcal serogroups data for the years 2010 to 2016. With the results obtained, independent random effects meta-analyses were performed for serogroups A, B, C, W, X, Y, and others; including 173 studies from 59 countries. The results demonstrated that the distribution of meningococcal serogroups differed markedly between countries and regions, an example of these being serogroups MenC and MenW which accounted for much of the IMD in most of Africa and Latin America; for its part, serogroup B was the predominant cause of IMD in many places in Europe, America, and the Western Pacific; finally, serogroup Y also caused many cases of MS in these regions, especially in the Nordic countries. In Latin America, according to information posted on the Pan American Health Organization (PAHO) website, with data from 2010 to 2018, from the SIREVA II program [12], serogroups C, B, and W are the most prevalent, with South America being the region with the highest number of serogroup C. In another study [13], which sought to see the proportion of Nm serogroups globally and regionally (Africa, America, Europe, Western Pacific, and Eastern Mediterranean) 102 studies were included; which, on analysis, the results demonstrated that the highest and lowest proportion of serogroups in IMD was serogroup B with 48.5% and X with 0.7%, respectively. Reports from WHO programmatic regions report serogroup W with 57.5% in the Mediterranean, and Z (of little epidemiological interest) with 0.1% in the Americas. Among the age groups 1 to 4 years, serogroup C had a higher proportion of 9.7%, as did serogroup B in children under 1 year of age with 9.5%. Globally, serogroup B represented in this study the highest proportion of Nm serogroups in the IMD.

Epidemiological Surveillance Systems

Regarding epidemiological surveillance, there are two types: active and passive; the former, originates in emergency departments, and therefore offers more clinical and epidemiological information, is more robust and more costly. The second, originates in laboratories, is less costly compared to active surveillance, but offers less clinical and epidemiological information, requiring a greater number of strains and hospitals to obtain information. Passive surveillance generates an under-reporting of cases that must be considered when conducting analyses or making decisions. Active surveillance offers a more specific analysis of statistical and epidemiological data; it also allows to describe the clinical features of the cases and thus, clinical cases of atypical presentation are easier to identify if there is active surveillance, with trained health personnel and laboratory personnel collaborating with microbiological and molecular diagnostics; variables such as: case fatality rates and their associated factors, sequelae (types, degrees), related serogroups, as well as annual incidence rates distributed by different variables and denominators can also be evaluated. This type of surveillance also allows carrying out studies and analyses on disease burdens, climatological associations [14], detecting potential migratory impact of populations and with real (not estimated) costs, being able to carry out pharmacoeconomic studies, such as cost-effectiveness of vaccination, and even being able to choose an immunization scheme more “adapted” to each region. Since 1993, the importance of bacterial pneumonias and meningitis prompted PAHO to implement a regional surveillance program based on a network of hospitals and sentinel laboratories, SIREVA and later SIREVA II, to provide prospective information on serotype distribution data and susceptibility of *S. pneumoniae*, *H. influenzae* and *N. meningitidis* to antibiotics, as well as epidemiological information for estimating the burden of these diseases and the formulation of increasingly efficient vaccines [15]. The SIREVA II network had several objectives, including: to generate reliable data on the burden of MS in Latin America and the Caribbean; to generate information on the phenotypic and genetic characteristics of the strains causing MS circulating in the region; and to create a representative database for the region, with annual publications so that physicians, epidemiologists and the scientific community in general would have access to the information for making decisions on treatment, vaccination or public health. SIREVA II is an important program that offers member countries technical cooperation in one or more of the following areas: promoting the integration of different partners in the surveillance system and strengthening active surveillance of bacterial meningitis in the country; consolidating the basic capabilities of the International Health Regulations and event management; promoting the design of specialized studies on the burden, clinical variations, virulence, social and environmental determinants of IMD in a representative population sample; and finally, offering a Regional Monitoring Platform for IMD.

Meningococcal Vaccination Programs and Challenges

Due to advances in vaccine development, vaccines are now available for five of the six serogroups that cause meningococcal disease (A,B,C,W and Y). Depending on the molecular vaccine structure, 3 types of vaccines are available: the first are polysaccharide vaccines, which are the actual capsular polysaccharide of Nm; the second are conjugate vaccines, which have a highly immunogenic protein in addition to the capsular polysaccharide; and the third are outer membrane vesicle vaccines (OMV), which have a protein and non-capsular target. Due to the emergence of non-vaccine serogroups, recommendations have gradually changed, in many countries, from monovalent conjugate vaccines to tetravalent MenACWY conjugate vaccines to provide broader protection. Despite significant improvements, meningococcal disease remains a global public health problem [16]. Effective vaccines provide direct protection to immunized individuals, but may also provide benefits to unvaccinated people by reducing transmission and thereby decreasing the infection risk [17]. Adolescents have the highest rates of meningococcal carriage and transmission; reducing carriage and transmission within them and to other age groups could help control meningococcal disease [10], in particular if conjugate vaccines are used, which have shown an effect in reducing and preventing meningococcal acquisition by generating an immune response such that it can prevent the vaccine from being colonized by meningococcus. The best experiences in immunization against Nm come from the Netherlands and the United Kingdom. In the United Kingdom, the immunization focus on adolescents was crucial to maximize the indirect effects, since most meningococcal transmission occurs in this age group, which was demonstrated after the introduction of MenC conjugate vaccines, with reductions in disease attack rates in non-immunized individuals and significantly lower serogroup C carriage [18]. The Netherlands, meanwhile, in 2002 similarly introduced a MenC conjugate vaccine, with Tetanus Toxoid as carrier protein, as a single dose at 14 months of age; a catch-up campaign was conducted targeting all individuals between 14 months and 18 years old, resulting in improved protection in adolescents, but in children a single-dose schedule was shown not to provide sufficient long-term protection and, therefore, they recommended considering a booster dose in early adolescence [19]. Regarding the Latin American experience, the effect of vaccination against meningococcus in Chile has been a significant decrease in IMD by serogroup W in the age group of vaccinated children, with no impact at other ages and a stable number of cases of IMD per year; in addition to a high incidence in children under 1 year of age, with a predominance of serogroup W. Brazil incorporated the Men C conjugate vaccine for children under 2 years of age (the age group with the highest incidence rates) in the national immunization plan. Following the vaccination program, a dramatic early impact on MenC disease and mortality rates could be observed, with significant reductions in disease incidence rates in all age groups, including individuals who were old enough to have been vaccinated, indicating the presence of herd protection [20].

Expert Opinion

In general, and throughout the region, children under 1 year old have a high incidence of IMD, while adolescents play a very important role in carriage and transmission. The identification of Nm serogroups varies according to each country and although mortality due to IMD has decreased in the last decade, lethality is still very high, so one measure that should be considered is to increase and promote campaigns to expand knowledge of the disease among health personnel and decision-makers in ministerial and governmental bodies, and thus integrate collaborative management of IMD; This should go together with further improvement of vaccination accessibility programs for high-risk groups, as well as adequate access in cases of outbreaks. Knowledge of the IMD dynamics in each country of the region is crucial and, in addition to knowledge of the epidemiological trends of the disease, will allow appropriate definition of the control and prevention measures to be taken and, especially, the time at which they should be applied. Epidemiological surveillance data, on its part, will make it possible in the future to measure the impact of vaccination in relation to IMD, just as continuous laboratory surveillance over time will make it possible to detect changes in the meningococcal population that affect the coverage predicted by the vaccine in each country. To achieve the objectives mentioned before, baseline data must be available to measure the effectiveness of vaccines, and these can only be obtained in an adequate manner with active surveillance, which offers an extraordinary quantity and quality information compared to passive surveillance, but requires a greater collaboration of the different centers, sentinel hospitals, laboratories, and a more complex logistics, but at the same time, it is much more useful. In order to achieve a more expeditious active surveillance, the option of having reference laboratories distributed by geographical area in different regions of Latin America should be considered. During the COVID-19 pandemic, a drastic reduction in the incidence rates of IMD was observed in the countries for which recent information is available; however, this should not be a reason to lower epidemiological surveillance, since IMD is unpredictable and incidence rates can rebound as the health and social measures taken because of the pandemic decrease; and regardless of this, vaccines are the most effective way to prevent IMD. For this reason, PAHO platforms (such as SIREVA II) and the platforms of the member countries, together with the support and expertise of SLIPE, should promote active disease surveillance in the different countries of the region.

From a regional point of view, studies on pharyngeal carriage of Nm should be integrated into epidemiological surveillance, as well as molecular diagnosis of clonal types, in order to have robust epidemiological information in the region and avoid under-reporting as a result of passive and voluntary epidemiological surveillance. There are very few pharmacoeconomic studies of meningococcal disease published in the region, so local and regional research should be encouraged. It is also necessary to continue researching the impact of this disease on both the health system and the community, and efforts should be made to improve registration systems, adapting pharmacoeconomic research designs to the possibilities of the region to contribute to the health decision-making process based on the highest and best possible quality of evidence. Several safe and immunogenic meningococcal vaccines are currently available in the region, with schedules varying according to epidemiological contexts. Conjugate vaccines are immunogenic, effective and safe, and a drastic reduction in disease incidence rates has been demonstrated after immunization programs with these vaccines; rMenB vaccines, for their part, are a current reality with growing information, offering direct protection, with no indirect community protection effect, and there is discussion about the cross-protection they can provide. It is important to follow up and pay attention to the ABCWY and ACWYX vaccines in development; these are new multivalent conjugate vaccines against meningococcus, which anticipate the possibility of broader protection. Finally, indirect protection, achieved through catch-up programs in adolescents and young adults, has been crucial for the success of meningococcal conjugate vaccine programs. In countries with consistently collected data, the incidence of IMD has tended to decline and recent global efficacy and impact data support the use of Men-ACWY and MenB vaccines within immunization schedules; it is important to emphasize that vaccine efficacy declines rapidly, especially in young children, underscoring the need for booster doses to keep vaccinated subjects protected.

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