PEDIATRIC THEME

Meningococcal disease: is it a latent disease in Mexico?

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Abstract

Infection by *Neisseria meningitidis* occurs first as an asymptomatic carrier before the disease with serious manifestations like meningitis, with or without expressions of fulminating purpura. This disease is caused by different serogroups, A, B, C, Y and W-135 being the most prevalent. Over time they have undergone epidemiological changes in different regions of the world. There is scant information in our country concerning both the carrier and the invading forms; however, it has been proven in some Mexican states that the incidence of carrier status and of invading forms is significant. Accordingly, the possibilities of invading and secondary cases derived from the carrier and through contact with invading forms are feasible. Therefore, increasing the epidemiological surveillance and determining the actual burden of meningococcal disease is required. As far as preventive measures are concerned, prophylaxis of contacts with the index case and vaccination to control outbreaks or in high-risk specific cases is recommended. It would be reasonable as well to establish the indications of the vaccines available in our country.

Key words: *Neisseria meningitidis*, vaccines, epidemiology.

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Received for publication: 8-17-10
Accepted for publication: 8-26-10

Introduction

Meningococcal disease is caused by *Neisseria meningitidis*, an aerobial gram-negative diplococcus, which is a bacterium that lives exclusively in the oropharynx of humans. *N. meningitidis* is surrounded by an outer membrane composed of lipids, outer membrane proteins and lipopolysaccharides. *N. meningitidis* in its capsular polysaccharide wrapping bound to external membrane proteins is considered pathogenic.

N. meningitidis has been differentiated in the laboratory from other species through antibodies that recognize epitopes of the capsule or the outer membrane. Thus, 13 serogroups have been identified: A, B, C, D, X, Y, Z, 29E, W-135, H, I, J, and L.[1] The antigen responsible for the serogroup specificity is the capsular polysaccharide.[2] The 20 serotypes and subtypes are identified based on the differences between the outer membrane polysaccharide (OMP) and the lipopolysaccharide.[1]

N. meningitidis has the capacity to exchange genetic material related to capsule production, providing it with the possibility to change its serogroup, e.g., from B to C and vice versa. The capsule change can be an important virulence mechanism, an essential property that must be taken into account because vaccines provide serogroup-specific protection.[3]

N. meningitidis is a bacterium with broad pathogenic spectrum and can be present as an asymptomatic carrier status or as a mild airway infection. The most serious manifestation is septicemia with multiple organ failure, with or without meningitis. It is the most important cause of bacterial meningitis in the U.S. and in other regions of the world. Estimates indicate that in the U.S. there are from 1400 to 2800 annual cases of invading disease, with a rate of 0.5 to 1/100,000.[4-6] The high disease rates are usually seen in 1-year-old infants (9.2/100,000: 1991-2002); conversely, the incidence in the 11- to 19-year-old population is higher than in the general population (1.2/100,000).[5-7]

Despite the diagnostic, therapeutic, and support therapy advances, mortality rates for meningococcal disease are high (10-14%). Of the survivors, 11-19% suffer sequelae such as palsy, neurological damage, extremity loss, deafness, etc.[7,8] Invading meningococcal disease stems from the *N. meningitidis* carrier status, particularly of virulent strains which, through virulence factors (proteins) that act as adhesins (OPA, OPC), colonize and invade the epithelial cells of the nasopharynx mucosa.[1,2,8] It is worth mentioning that the meningococcal bonding to the epithelial cell occurs through specific receptors (CD46).[9]

Meningococcal transmission mechanism is from one person to another through oropharynx excretion exchange. Carriers are asymptomatic and can remain so for several weeks or months and, on rare occasions, for up to 1 or 2 years. The carrier status has the capacity to induce protective antibodies.[2,8,10]

The carrier status rate in the population is between 5% and 15% and increases in groups living in crowded conditions such as in the military or in prisons where it can vary from 10 to 30% in adolescents and adults and 19-30% in military recruits.[11,12] The colonization rate can usually increase to >50% in schools, boarding schools and military headquarters during the seasons when upper airway viral infections increase, as well as in smokers and crowded spaces such as public bars. During an outbreak, carrier status can increase to 60-80%.[13,14] Many *N. meningitidis* colonizing strains are not pathogenic and the prevalence of asymptomatic carriers in infants is <2%.[14,15]

Carrier status variability is a universal situation and not related to the risk of epidemic outbreaks. However, some studies indicate that if there are >20% in the community, there are >20% of carriers colonized with hypervirulent strains and the risk of an outbreak is higher.

Molecular biology studies indicate that the invading diseases by meningococcus are limited to a specific number of meningococcal strains

with higher virulence. Conversely, there are meningococcal carriers who never present invading disease, clarifying that meningogocci have several disease-causing virulence factors.[4]

The risk of meningococcal infection in carriers is related to the sensitivity of each host[16] and to the presence or absence of serum antibodies capable of activating the complement, particularly fractions C3, C5 and C9. Absence of these complement factors are a risk component for experiencing invading meningococcal disease.[7,17] Symptomatic carriers are the usual form of transmission. What was found in military recruits is that after the carrier status has begun, some presented invading disease 48 to 72 h after colonization.[8]

Meningococcal disease epidemiological variability

Meningococcal disease has a universal distribution and is endemic in many regions of the world.[18] Distribution of serogroups that cause meningococcal disease are A,B,C,Y, W-135; these serogroups can vary over time and geographic areas.[19] For example, during 1998 and 1991, many cases of meningococcal disease in the U.S. were caused by serogroups B and C, whereas serogroup Y represented 2% of all the cases.[20] More recently, between 1996 and 2000, serogroup Y increased to 39% of the cases reported, followed by serogroup C (31%) and B (23%).[21] Serogroup W-135 is not very frequent and is not a cause of outbreaks in the U.S. However, in the year 2000, meningococcal disease of serogroup W-135 was reported in four subjects[22] after being in contact with a population in Saudi Arabia.[23] Serogroups A and C are still prevalent in Asia and Africa. Serogroup A is the most frequent cause of meningococcal disease in sub-Saharan Africa (the meningitis belt).[22]

It is important to determine the geographic distribution of disease-causing meningococcal serogroups, which result partly from easy access to communication means that facilitate the movement to different regions of the world, generating a potential exposure to different serogroups among regions and the risk of causing an epidemic, even pandemic, outbreak.

Serogroups B, C and Y are responsible for causing almost all meningococcal disease; nevertheless, distribution varies in accordance with age group. Recent data suggest that infants and preschool-age children represent a higher proportion of serogroup B, whereas in 18- to 31-year-olds group C is the most common (48% of cases), and in subjects >65 years of age, group C is the most prevalent (62%).[4]

In Mexico, the Health Ministry reports that meningococcal disease is present in sporadic cases and in small outbreaks, serogroup C being the most frequent as of 2003.[22]

Historic records in Mexico indicate that the last epidemic occurred in 1945 in San Luis Potosí, with ~753 cases affecting all age groups, mainly children, in 45% of the cases.[24]

Immunity mechanisms

At birth, many newborns have bactericidal antibodies for *N. meningitidis* in the serum because of maternal transplacental transfer, with duration of a few months. However, natural acquisition of these antibodies is associated directly with age. For example, infants <2 years old have low antibody levels and, consequently, they are the group at highest risk of acquiring the disease. On the contrary, between 2 and 12 years of age, antibodies increase progressively, leading to a reduction in the incidence of meningococcal disease at these ages.

Adults, regardless of the serogroup, have from 60% to 80% of bactericidal antibodies in the serum.[17]

The natural immunity for *N. meningitidis* is acquired as a result of the nasopharynx colonization of pathogens and non-pathogens or through the colonization of *N. lactamica*, which is related from the antigen point of view to *N.*

meningitidis.[25] At the end of the 1960s, it was stated that the natural acquisition of bactericidal antibodies for serogroup A was related to cross-reactivity of the meningococcus with capsular antibodies estimated by the colonization of *Escherichia coli* or *Bacillus pummilus*, bacteria that express cross-reactivity with the polysaccharide of serogroup A. On the other hand, antibodies of serogroup C are directly related to polysaccharide C.[17,25,26]

As previously explained, risk of meningococcal disease is greater during the first year of life because the specific antibodies decline after some months and develop until the immune system is competent. However, many 1-year-old infants do not develop the disease despite being carriers of virulent strains of *N. meningitidis*.[21,27] The above suggests that there is *innate* immunity that helps to protect the child from meningococcal disease before specific antibodies are developed.

During this phase, the innate system of the complement contributes to antibody-independent protection against meningococcal disease, even though the complement system is a trigger of specific antibodies through the classical route. This route is also activated efficiently by proteins that represent the innate immune response in absence of specific antibodies. Two routes in the innate immune system are capable of activating complement: the first one is through interaction of factor B, factor D, and properdin, and the second one would be the activation of the innate complement system that occurs through the manose route—linked to lectins.[28-30]

Preventive measures

Safe and efficacious preventive measures started at the end of the 1960s when Gotschilch et al. worked in the development and purification of the meningococcal polysaccharide that could be used for the immunization of humans.[17]

Meningococcal vaccines

Polysaccharide vaccines

There are monovalent polysaccharide vaccines for serotypes A and C, bivalent for serotypes A-C, and tetravalent (MPSV4) with serogroups A, C, W-135, and Y.

Monovalent vaccines are efficacious and safe and have been used since 1969-1970 in subjects at risk of acquiring the disease (particularly in military recruits), showing 83% efficacy in adults. In children 2 to 9 years of age, the efficacy is lower—after its application, titration of bactericidal antibodies last 2 to 3 years. However, the protection is considered to persist for up to 10 years.[31] Thus, efficacy is directly related to age. This vaccine has been applied routinely in the U.S. Army since 1972, providing good results in disease control.[32]

Concerning the polysaccharide vaccine A, its efficacy has shown differences with the other polysaccharide vaccines such as that of serotype C, because the efficacy is acceptable in children <2 years of age. However, applying two doses in infants <18 months of age is recommended. The bivalent vaccine A-C is used for the protection of serogroup A and C in children <2 years old.

The tetravalent vaccine (MPSV4) for serogroups A, C, W-135, and Y has been applied in the U.S. since 1981. It is safe and immunogenic, with efficacy in older children and adults for serogroups A and C estimated at 85% and 100%, respectively.[33-35] Serogroups Y and W-135 are immunogenic in older children and adults, but there are no efficacy data available.[34]

The tetravalent vaccine is approved to be applied in children >2 years of age and is recommended to control meningococcal disease outbreaks and to protect groups at risk, for example, people who travel to hyperendemic regions, patients who have undergone splenectomy (surgically or functional, such as those subjects with falciform cell anemia), or with deficiency of the complement terminal route.[17]

Polysaccharide vaccines have limitations because they are thyme-independent antigens that stimulate mature B lymphocytes but not T lymphocytes, which produce a memory response. Therefore, they cannot be applied in children <2 years of age.[33,36] Another limitation is that even in children >2 years of age and in adults, they do not provide long-term immunity. In addition, when multiple doses are applied, they can produce a low immune response.[32,37] Another limitation is that these polysaccharide vaccines do not reduce the nasopharynx carrier status of *N. meningitidis*; therefore, they are not efficacious to disrupt horizontal transmission. For this reason, they do not provide herd immunity.[38,39]

Conjugated meningococcal vaccines

These are conjugated polysaccharide vaccines with a carrying protein that changes the immune response of the bacterial polysaccharide, from being T-independent to T-dependent, thus granting a better immune response in children <2 years of age and a strong immune memory response.[32]

In the United Kingdom, three conjugated vaccines of serogroup C are marketed: Meningtec (Wyeth pharmaceutical company), Menjugate (Chirion Pharmaceutical Company), and Neis Vac (Baxter Pharmaceutical Company). Two of the vaccines (Meningtec and Menjugate) contain a short polysaccharide chain (O-acetylated), which is derived from the capsular polysaccharide of serogroup C and is conjugated with CRM197 (non-toxic mutating diphtheria toxin). The vaccine Neis Vac has a polysaccharide of serogroup C (O-acetylated) conjugated with tetanus toxoid.[40,41]

The tetravalent conjugated antimeningococcal vaccine (Menactra MCV4) has a capsular polysaccharide of *N. meningitidis* of serogroups A, C, Y and W-135, conjugated with diphtheria toxoid. It was approved by the U.S. Centers for Disease Control and Prevention (CDC) in January 2000 to be routinely applied in individuals between 11 and 12 years old at risk for acquiring meningococcal disease. Vaccine approval was based on the safety and immunogenicity studies and, similar to the conjugated vaccines of serogroup C, no efficacy studies were performed.[42,43]

The similarity of these vaccines to other conjugated vaccines such as the *Haemophilus influenzae* type B and *Streptococcus pneumoniae* vaccines generates the same success expectations concerning direct and indirect effects of vaccination against *N. meningitidis* with the conjugated tetravalent vaccine.[44-46]

In 1999, the universal launch took place in the United Kingdom of the serogroup C conjugated vaccine for subjects from 12 months to 17 years of age.[46] The monovalent C conjugated vaccine was tested in several studies since 1990 showing its efficacy and safety in infants and young children,[47,48] but no efficacy data are available.[42]

Vaccine effectiveness, after being applied, was from 88% to 98% in different age groups[49,50] and showed impact on carrier status of 66% of adolescents 15- to 17-years of age[40] and herd immunity of 67% in nonvaccinated children from 1 to 17 years of age, and 35% in subjects >25 years of age.[41] So far, there is no evidence of the vaccine protection duration. Three doses at 2, 3 and 4 months of age are recommended as a significant antibody reduction is achieved. Therefore, a booster dose is proposed to increase protection when the child is >1 year old.[49]

The Advisory Committee on Immunization Practice (ACIP) recently recommended that the MCV4 vaccine (Menactra of Sanofi Pasteur) can be administered in children 2 to 10 years old, changing the previous recommendation that stated that it should be applied between 11 and 55 years of age. This change is due to the increase of meningococcal disease risk in this age group.[51] It is based on the fact that the immunogenicity and safety in children of this age group showed, in a double-blind randomized controlled trial in healthy children from 2 to 10 years old in the U.S. comparing MCV4 and MPSV4, were both sig-

nificantly higher in both age groups after 28 days and 6 months after the vaccination with MCV4. In the same trial, the undesirable effects of both vaccines were similar.[52]

Safety and efficacy studies of anti-meningococcal vaccine

When the immunogenicity of MCV4 was compared with that of MPSV4 (nonconjugated meningococcal tetravalent vaccine), it was seen that the antibody titration showed a considerable increment in both vaccines, but for a short period of time in all the serogroups. Later on, a trial was performed to assess the antibody duration in a 3-year period, showing that the antibody titration was substantially higher in MCV4 than in MPSV4. Another study where both vaccines were applied in different groups and were given a booster dose 3 years later, the antibody response was higher with MCV4 than with MPSV4.[4]

Adverse events have been studied in both vaccines and were more frequent in those who received MCV4 when compared with those who were administered MPSV4. Those who received MCV4 had pain and motion limitation in the extremity where it was applied in 11-13% of cases, and those who were given MPSV4 showed the same results only in 3% of cases. Systemic adverse events such as fever >37.7°C amounted to 3% for MCV4 vs. 2 to 15% for MPSV4.[4] However, in the studies by Pichichero et al. the undesirable effects were similar for both vaccines.[52]

MCV4 safety studies, when applied at the same time with other vaccines (DPT) in persons aged 11 to 17 years, the frequency of local adverse effects reported was higher when MCV4 was administered with DPT. When it was administered alone, the effects were similar to those of the vaccine MPSV4.[53-61] There were no discrepancies either in systemic adverse events when the MCV4 vaccine was applied concomitantly with DPT and compared with placebo (54.1%).

When the MCV4 vaccine was applied simultaneously with the typhoid vaccine and after 28 days, no differences were present in subjects 18 to 55 years of age. The serious events after a 6-month follow-up occurred in 1.3% of cases both for MCV4 and for MPSV4 from a total of 5453 individuals 11 to 55 years old.[17]

In October 2005, a possible association between Guillain–Barre syndrome (GBS) was found in some of the subjects who received the MCV4 vaccine.[56] Seventeen cases were confirmed, but the GBS epidemiological data showed a slight risk increase, not higher than expected in a non-vaccinated population for GBS. Therefore, the CDC continues recommending the routine application of the MCV4 vaccine in adolescents and high school students in dormitories because the risk of meningococcal disease is high.[4,57]

The MCV4 vaccine is recommended routinely by the CDC and the Advisory Committee on Immunization Practice (ACIP) in adolescents between 11 and 12 years of age[17] and in adolescents of ~15 years of age who are about to start school and who have not received the vaccine.[4,56]

Another absolute vaccine application recommendation is for persons who are frequently exposed to the bacteria, for example, bacteriologists, military recruits, travelers, or persons who live in endemic and hyperendemic areas.[4,56] It is also recommended for persons with immune deficiencies such as defects of the complement terminal route or anatomic and/or functional asplenia as well as HIV patients, but there is still no evidence of the efficacy of the vaccine in these patients.[14,57]

MCV4 and MSPV4 vaccines are recommended in outbreaks of meningococcal disease by serogroups included in the vaccines. MCV4 and MSPV4 vaccines are both administered in one dose (0.5 ml). MCV4 is administered by IM route, whereas MSPV4, it administered subcutaneously. For the people who have been vaccinated already with MSPV4 and who are at

constant contagion risk, the recommendation for it is to be applied every 5 years, preferably with MCV4. When the vaccination occurs before 4 years of age, a booster is recommended every 2 or 3 years. So far, evidence shows that there is no need of it when the MCV4 vaccine has been applied.[4,55]

After the MCV4 vaccine was authorized, it showed efficacy with protective antibody duration of 5 to 10 years after a single dose. It can be applied concomitantly with other vaccines, like cellular DPT. One of the epidemiological impact indirect effects is that it provides herd immunity by reducing the carrier status of the serogroups included in the vaccine.[4,55]

The tetravalent conjugated vaccine MCV4, through the administration of three doses at 2, 4, and 6 months of age, has shown good immune response and adequate safety. It also generates a good anamnesic response at 15-18 months of age when a booster is applied.[57]

At present, the MCV4 vaccine is administered to children between 2 and 10 years of age. Its safety is similar to MPSV4, but the immune response is better in all the serogroups included in the vaccine than when MPSV4 is applied.[52]

In regard to serogroup B, it is clear that the capsular polysaccharide has poor immune response in humans. Vaccines developed for the meningococcal serogroup are based on a common protein, present in the outer membrane protein (OMP) of specific endemic strains. This vaccine efficacy has been proven in older children and adults, but not in infants and preschool-age children where the disease risk is higher due to the OMP variability in the endemic meningococcus B strains.[59] This vaccine can have application limitations in the U.S. and in other countries for its inadequate response.[60,61] Other alternatives are searched for. One is the modification of the serogroup B polysaccharide because the meningococcal serogroup B genome is already known, representing some potential for the vaccine.[60-69]

Recently, two new quadrivalent meningococcal conjugate vaccines would be available in the market. One of them is the conjugate with tetanus toxoid (Men ACWY-TT GSK Biological, Risenxart, Belgium). After 3 years of follow-up, the vaccine is well tolerated and with adequate immunogenicity. Men ACWY-CRM has been recently licensed by FDA.

Studies are being developed that compare safety and immunogenicity with Men ACWY-D,[70] another quadrivalent glycoconjugate semi-synthetic vaccine, and Men ACWY-CRM (Menveo, Novartis Vaccines, Siena Italy). Men ACWY-CRM consist of two components: 1) 10 μg of lyophilized meningococcal serogroup A capsular polysaccharide conjugates to CRM_{197} (MenA) and 2) 5 μg each of capsular polysaccharide of serogroup C, Y, and W-135 conjugated to CRM_{197} in 0.5 mL of phosphate buffered saline, which was used to reconstitute the lyophilized MenA component before injection. It has two presentations, one with adjuvant aluminum phosphate and the other without adjuvant. The immunization schedule is to 2, 3 and 4 months (accelerated scheme) and 2, 4 and 6 months in a routine immunization. The immune response is protective for the four serogroups but serotype A showed a minor response compared with other serogroups. With adjuvant conjugate vaccine the immune response was more robust; nevertheless, serotype A showed a similar response.[71]

Available information shows that the administration of the first dose at 6 months of age and the second dose at 1 year provided a good level of protection for all serotypes including serotype A.[72]

When the vaccine has been administered after the second year of age, two doses are recommended. With an 8-month interval between the first and the second dose an effect of booster is observed. It is very important and necessary for children of this age to be administered the second dose in order to be protected against invasive meningococcal infections.[73]

Regarding the conjugate meningococcal vaccines, the quadrivalent formulations MenACWY are safe and immunogenic against invasive meningococcal diseases caused by the four most common serotypes worldwide. There are robust data for recommending MCV4 (Menactra, Sanofi Pasteur) and available information for MenACWY-CRM (Menveo, Novartis). Available information of the impact of immunization programs in the U.S. with MCV4 (Menactra) showed a high reduction in the incidence; nevertheless, more information in other countries is necessary.

Actually, there are different immunization programs with quadrivalent vaccines alone and quadrivalent vaccines simultaneous with monovalent conjugate meningococcal C vaccine in the United Kingdom and Canada.

An ideal recommendation for every country would be to consider epidemiological information as incidence, burden of disease, as well as predominant and circulating serogroups.

Vaccination experience in Mexico

In Mexico, the meningococcal vaccine is applied only in special situations, particularly for outbreak control. So far, we are not aware of the meningococcal disease burden. However, a study conducted by our group[74] has shown that *N. meningitidis* is in carrier status in children in daycare centers and in adolescents in ~1.6%.[69] Also, the latest data obtained by Chacón et al.[75] report that in the last 27 months a total of 14 confirmed cases of invading meningococcal disease was described in the Civil Hospital of Tijuana, Baja California with predominance of serogroup C and similar incidence to the U.S. and much higher than the domestic reports.

Data concerning carrier status and invading disease reported in our country must be taken into account because these studies have shown that the most frequent serotypes of *Neisseria meningitidis*, both in carrier status and in invading forms, are found when they are looked for intentionally. This suggests that more information must be offered to health care workers concerning the overall knowledge of the problem and consider that the carrier status is key for invading meningococcal disease.[1,10] Ongoing epidemiological surveillance should be carried out to determine the reality of meningococcal disease and implement the most adequate recommendations in terms of preventive measures.

Vaccination recommendations in travelers

As a result of the increase in international travel, there is potential risk of dissemination of meningococcal disease. Evidence of this incidence in international travelers is lower than other vaccine-preventable diseases; however, the impact can be significant because morbidity and mortality rates are high.[64]

The risk of meningococcal disease in travelers and during international flights has been estimated to be 4 cases/1,000,000 travelers on a monthly basis.[65] Transmission risk in airplanes is very low, and we generally find only anecdotal reports. One of the first cases was during the year 2000 in a flight from Africa to Singapore, and the meningococcal serogroup responsible was W-135.[66]

There are other reports of contagion in international travel with serogroup B.[67,68] Protection strategies can be different in each country; for example, in the U.S. where MCV4 is available and licensed for its application as well as the conjugated serogroup C and the polysaccharide MPSV4 vaccines. Any of these could be applied based on the circumstances, unlike other countries where they are not available and where they use the tetravalent polysaccharide vaccine MPSV4 or the conjugated serogroup C vaccine.[69]

A requirement to visit Saudi Arabia is to have the meningococcal vaccine, which has to be evidenced through the tetravalent meningococcal vaccine application card along with the visa for

any of the countries found within the meningitis belt, particularly during the months of December to June. This recommendation is also valid for the following countries: Burundi, Rwanda, Republic of Tanzania, Congo, Angola, and Somalia, where outbreaks have occurred. The vaccine is recommended for long stays in those countries where there will be permanent contact with the population.[68]

Recommended vaccines in case of travelling to high-risk areas are MCV4 and MPSV4 instead of the vaccine C and A because serogroups W-135 and Y are emerging. Individuals who receive serogroup C vaccine in their country of origin must remember that they are protected only for serogroup C. Therefore, conjugated and tetravalent polysaccharide vaccines would be required.[76,77]

Other preventive measures

Another way to prevent secondary cases is through the administration of chemoprophylaxis with antimicrobials, particularly to the contacts of patients with invading meningococcal disease. Close contacts include family members who live with the patient, children in daycare centers where a case is reported, or any individual who has been in contact with the secretions of the patient by kissing, with mouth-to-mouth resuscitation maneuvers, or through endotracheal intubation, passengers who travel by plane and who have been in contact with secretions of the index case (who travels on a plane) and all passengers when the length of the flight is >8 h.[55,78]

When a case occurs at home and there is contact with other family members, the risk is of 4 cases/1000 for the persons exposed, meaning that the risk is 500 to 800 times higher than in the general population.[79] Healthcare workers who are exposed to patients with meningococcal disease have a 25-fold risk.[80]

When the contacts of the index case have high disease risk and when they meet the requirements previously mentioned, antimicrobial prophylaxis must be initiated immediately (efforts should be made so that it is within 24 h after the contact with the index patient). If chemoprophylaxis is initiated 14 days after the contact, it is highly likely that no effect is achieved. Taking a nasopharynx or pharynx exudate culture is not recommended for the subjects who were exposed to the index case to confirm the presence of *N. meningitidis* because no benefit has been shown and chemoprophylaxis could be delayed.

Indicated antimicrobials are rifampicin, ciprofloxacin and ceftriaxone because their efficacy in reducing or eradicating *N. meningitidis* is 90-95% and they are the agents accepted as the gold standards of preventive measures in those cases of risk for contagion with patients with meningococcal disease.[81,82] Studies show that a single dose of azithromycin (500 mg) given orally is effective to eradicate nasopharynx carriers of *N. meningitidis*.[82] It can be given to adults and children because it comes in tablets and suspension.

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