Epidemiology of meningococcal disease in Latin America: current situation and opportunities for prevention

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Objective: Meningococcal disease continues to be a serious public health concern, being associated with high morbidity and mortality rates in many countries from Latin America. In addition to discussing recent changes in the epidemiology of meningococcal disease in the region, we also analyse the development and potential impact of new vaccines on the prevention of meningococcal disease.

Methods: MEDLINE, SciELO, LILACS and websites of the national Ministries of Health databases were searched using the terms meningococcal disease, meningococcal epidemiology, Neisseria meningitidis, meningococcal vaccines and the name of Latin America countries, from 1998 to 2008, with emphasis on review articles, clinical trials and epidemiological studies.

Results: Epidemiology of meningococcal disease in Latin America is characterized by marked differences from country to country. The overall incidence of meningococcal disease per year varied from less than 0.1 cases per 100,000 inhabitants in countries like Mexico to two cases per 100,000 inhabitants in Brazil. The highest age-specific incidence of meningococcal disease occurred in infants less than 1 year of age. Serogroups B and C were responsible for the majority of cases reported, but the emergence of serogroups W135 and Y was reported in some countries. Serogroup A disease is now rare in Latin America.

Discussion: Although a few countries have established meningitis surveillance programs, the information is not uniform, and the quality of the reported data is poor in the majority of the region. The availability of new effective meningococcal conjugate vaccines and promising protein-based vaccine candidates against meningococcus B highlights the importance of a better understanding of the true burden of meningococcal disease in Latin America and also the need for cost-effectiveness studies before incorporating the new meningococcal vaccines to national immunization programs.

Keywords: Neisseria meningitidis, serogroup, surveillance, epidemiology, meningococcus

Background

Meningococcal disease is a serious public health concern, associated with high case fatality rates (10–20%) and substantial morbidity (up to 20% of survivors of meningococcal disease develop long-term sequelae, including deafness, neurological deficit or limb amputation), despite the continued sensitivity of meningococcus to multiple available antibiotics, including penicillin1,2. Neisseria meningitidis became a leading cause of bacterial meningitis in children and young adults in several Latin American countries, especially after the introduction of Haemophilus influenzae B routine vaccination. Most cases of meningococcal disease are sporadic, with seasonal variations and outbreaks occurring at irregular intervals1,2,3. Although considered as a disease of compulsory notification in most Latin American countries, the incidence of meningococcal disease is probably underestimated because of difficulty in recovering the organism, not only because of the limitations in obtaining adequate samples for culture, but also as a consequence of previous antibiotic use. This results in the inclusion of many of these infections in the group of undetermined meningitis and highlights the need for additional surveillance studies to better estimate the real burden of meningococcal disease in Latin American countries.

In this article, we present an up-to-date summary of the available epidemiological data of meningococcal disease in Latin America, review how to manage the disease in our setting and discuss the appropriateness of the introduction of new meningococcal vaccines in the region.

Meningococcal biology

The causative agent of meningococcal disease, N. meningitidis, is a Gram-negative, aerobic, non-motile diplococcus belonging to the Neisseriaceae family.
Based on phenotypic characteristics, meningococci can be classified into 13 different serogroups according to the antigenic composition of the polysaccharide capsule: A, B, C, D, H, I, K, L, W135, X, Y, Z and 29E\(^6\). Serogroups A, B, C, Y and W135 are responsible for virtually all cases of the disease, only infecting humans. Meningococci can be further classified into serotypes, serosubtypes and immunotypes, according to the antigenic composition of their outer membrane proteins: PorB, PorA and lipooligosaccharide, respectively\(^6,7\). An example of this serological typing is B:4:P1.4, indicating serogroup B, serotype 4 and subtype P1.4.

Although phenotypic characterization is of great importance for the development of vaccination strategies, genomic techniques such as multilocus sequence typing and others are now a standard for genomic typing and identification of virulent clone complexes, offering a better insight into the epidemiology and clonal expansion of disease-causing \textit{N. meningitidis}.

Meningococcal virulence can be estimated by the number of cases of disease that occurs in a population after acquisition and is related to capsule expression (e.g. serogroups A, B, C, Y, W135, etc.), other surface structures and virulent associated genotypes (e.g. ST-11, ST-5, ST-103, etc.)\(^6\).

Complete genome sequences have been determined for a serogroup A strain (Z2491), a serogroup B strain (MC58) and a serogroup C strain (FAM18). Recombination of multiple repeat units results in gene conversions that characterize the antigenic variations of meningococci. Meningococci have been shown to have the potential capacity to exchange the genetic material responsible for capsule production and switch serogroups from C to B or vice versa. Antigenic variations of capsular and of surface proteins resulting from these genetic mechanisms enhance the ability of meningococci to evade immune responses\(^8\). Since the protection afforded by vaccines is specific to the serogroup, this exchange has also important implications for the development of vaccines.

Additional benefits could be achieved by sequencing the meningococcal genome. Using reverse vaccinology, Pizza and colleagues\(^9\) were able to identify proteins that could be antigenic candidates to develop a promising vaccine against serogroup B. After identifying open reading frames (potential proteins) in the bacterial DNA, these potential proteins were analysed for their suitability as vaccine candidates and expressed in \textit{Escherichia coli}. The proteins were selected based on the capacity to induce high bactericidal activity against different meningococcal strains and whether they were surface-exposed proteins and proved to have highly conserved genes.

Meningococci are transmitted from person to person by aerosolization of or contact with respiratory secretions or saliva. Acquisition of meningococci can be transient, lead to colonization (carriage) or result in invasive disease. A majority of individuals will harbor \textit{N. meningitidis} in the throat asymptptomatically throughout their lives\(^10\). Carriage rates for \textit{N. meningitidis} among healthy individuals are estimated to be as high as 40% in certain age groups, increasing with age, mostly with little or no pathogenic potential. When invasive disease develops, it usually occurs within 1–14 days of acquisition. In households in which a case of meningococcal disease has occurred, the risk for invasive disease in family members is increased by a factor of 500–800\(^7\).

**Meningococcal epidemiology**

Invasive infections by \textit{N. meningitidis} result in a wide clinical spectrum that includes meningitis, meningococcalemia or both, with meningitis being the most common clinical presentation\(^7\). Against this background, the term ‘meningococcal disease’ is appropriate and has been adopted internationally. The distribution of patients by sex reveals a slight predominance of the disease among male patients. The disease also exhibits seasonality, with a larger number of cases during the winter\(^11\).

Meningococcal disease affects individuals of all age groups, but the highest incidence is in children under 5 years old and especially among children under 2 years of age\(^12\). During epidemics, a shift in the age distribution of meningococcal disease is observed, with increased numbers of cases among adolescents and young adults\(^13\). A second peak in incidence can be observed, in some populations, among adolescents and young adults, probably as a result of increased risk of transmission, particularly observed in college students living in dormitories\(^12\).

Meningococcal disease occurs all over the world, although there are marked geographical differences in incidence and in the distribution of the different serogroups that cause disease. Historically, serogroup A is associated with epidemic disease in developing countries, especially in Sub-Saharan Africa, which is known as the meningitis belt. The annual incidence of disease during these epidemics can reach levels up to 1200 cases per 100,000 inhabitants. Outbreaks of meningococcal disease caused by the W135 serogroup have been reported among nomadic Muslims in Saudi Arabia and also in countries in the African belt\(^14\).

In developed countries, such as the USA and in Europe, the disease is mostly endemic. In Europe, before the introduction of meningococcal C conjugate vaccines in the routine immunization programs of several countries, more than 95% of cases were attributed to serogroups B and C\(^14\). In the USA, incidence rates of meningococcal disease have remained steady over recent years (approximately one case per 100,000 inhabitants), with serogroup B being the primary cause of endemic disease and serogroup C related to outbreaks among adolescents and young adults. Increases in the proportion of cases due to serogroup Y have been observed during the last decade, mainly among adults and the elderly\(^14\).

**Epidemiology updates on meningococcal disease from individual countries in Latin America**

Meningococcal disease is of compulsory notification in Latin America. Although many countries have a
surveillance system with regular and detailed reported data regarding the epidemiology of meningococcal disease, this is not the case in others, and this information is usually neither published nor easily accessible.

In 1993, the Pan American Health Organization and World Health Organization implemented a Latin American surveillance network program, named SIREVA, initially for cases of invasive Streptococcus pneumoniae infection. This network was extended in 1999 to cases of H. influenzae and in 2000 to cases of N. meningitidis. It performs a systematic analysis of all isolates recovered by the epidemiological survey network from 20 countries in the region. The Instituto de Salud Carlos III, in Spain, is the international reference center, and the Adolfo Lutz Institute in São Paulo, is the regional reference laboratory responsible for N. meningitidis characterization and other tests. From 2000 to 2006, almost 9000 isolates, recovered mainly from cerebrospinal fluid, were sent to the Adolfo Lutz Institute from these countries in Latin America15,16 (Figure 1).

Brazil, Argentina, Uruguay and Chile

Meningococcal disease is endemic in Brazil, with periodic occurrence of outbreaks in several cities. In 2006, 28,100 cases of meningitis were reported, with 3142 cases of meningococcal disease5. The incidence rates are stable in the recent years, with approximately two cases per 100,000 inhabitants (Table 1).

During the 1970s, Brazil suffered its largest recorded epidemic of meningococcal disease, with its epicenter in São Paulo and characterized by two overlapping epidemic waves, the first provoked by serogroup C meningococcus, starting in April 1971, and the second by serogroup A meningococcus, beginning in April 1974, without the incidence of cases related to serogroup C meningococcus returning to endemic values by then. The incidence rate reached a peak of 179 cases per 100,000 inhabitants in 1974. This epidemic provided the first major experience in the world with polysaccharide A and C vaccines on a large scale, resulting in control of the epidemic from 197518.

During the 1980s, there was a period of reduced disease incidence (1 case /100,000 inhabitants), with serogroup B becoming more prevalent than C and practically no cases of serogroup A were reported. From 1987 onwards, there was an increase in the number of cases, with epidemics attributed to serogroup B in several locations around the country. This growth reached its peak in 1996, with 7104 cases recorded (4.5 cases/100,000 inhabitants), to a great extent resulting from outbreaks in large cities such as São Paulo and Rio de Janeiro18. Phenotype B:4,7:P1.19,15, responsible for an epidemic emerging in 1988 in São Paulo, still represented the predominant B phenotype by 2000–2001. The other prevailing phenotypes recently identified were B:4,7:P1.7,1 and the ‘Norwegian’ epidemic phenotype B:15:P1.7,16 (almost confined to the southern states of the country). These three prevalent serosubtypes belong to the same electrophoretic type, ET-524.

PorA variable antigenic regions VR1, VR2 and VR3 of N. meningitidis serogroups B and C isolated in Brazil recently were analysed, and a high genetic diversity was found among the PorA regions VR1 and VR2 isolates from patients with meningococcal disease and healthy carriers in Brazil, contrasting with the stability found in the PorA VR3 of these isolates. The presence of VR3 epitope variant 35 or 36 on the surfaces of 87% of the strains analysed suggests that these antigens should be considered for inclusion in new formulations of vaccines against serogroup B meningococci in Brazil29.

Nevertheless, from 2002 onwards, a significant increase in the proportion of cases attributed to serogroup C was observed in some regions of the country, such as the states of Pernambuco, Minas Gerais and São Paulo, and today, serogroup C is the most frequent serogroup causing meningococcal disease in Brazil (in 2006, serogroup C was responsible for 55.2% of cases identified, serogroup B for 38.2%, serogroup W135 for 5% and serogroup Y for 1.6%)5,16 (Figure 2). A comprehensive study analysing a collection of 1059 serogroup C isolates recovered from 1976 to 2005 in São Paulo was recently published, showing that three major clone complexes, sequence types 11, 8 and 103, were identified, with two major antigenic replacements: from 2a:P1.(5,2) to 2b:P1.3 and subsequently to 23:P1.14-626. The case fatality rates in Brazil are still very high, reaching 18–20% in recent years5,18,27.

An increase in the identification of serogroup W135 was recently reported in different regions of the country. In the State of Rio de Janeiro, from 1998...
to 2002, the proportion of cases due to W135 and Y was 0.3 and 0.1% of all isolates, respectively, and in the period from 2003 to 2005, the proportion of cases due to W135 increased to 11%, with serogroup Y remaining at 0.1%28. Also in the state of Rio Grande do Sul, a significant increase in the prevalence of serogroup W135 was observed in the period of 2003–2005 (17.8%), compared to the period of 1995–2002 (3.2%)29.

Several outbreaks of meningococcal disease (defined as an occurrence of at least three confirmed or probable cases of the same serogroup, except secondary or coprimary cases, in a period of <3 months, within a limited geographic area, with an attack rate equal or higher than ten cases for 100,000 inhabitants) caused by serogroup C, were registered in Brazil in recent years, affecting different cities, like Itapeva in 2004, Estrela D’Oeste and Sucupira county in 2006, Heliopolis county in 2007 and Guaruja and São José do Rio Preto in 2008 in the State of São Paulo, Muriaé in 2006 and Sete Lagoas in 2007 in the State of Minas Gerais, Paraty in 2004 and Buzios in 2008 in the State of Rio de Janeiro17.

As a strategy to control these outbreaks, besides chemoprophylaxis to contacts, vaccination was recommended to the population age groups exposed to higher risk. In these programs, meningococcal C conjugate vaccines were used to children under 2 years of age, and meningococcal A/C polysaccharide vaccines were used for those older than 2 years of age17.

In Argentina, meningococcal disease is of compulsory notification since 1960. A decrease in the incidence rates of meningococcal disease was observed in the last years (from 2-4 cases per 100,000 inhabitants in 1994 to 0-7 cases per 100,000 inhabitants in 2007), without any specific vaccination intervention, except control of outbreaks30. During this recent period, case fatality rates were stable, between 8 and 10%16,30.

In terms of serogroup distribution, serogroup B was prevalent until 1995, when an increase in the proportion of cases due to serogroup C was observed, making it prevalent until 2000, when a new change was identified in the epidemiology of the disease and serogroup B became prevalent with a decrease in the proportion of cases due to serogroup C and also a slight increase in the proportion of cases due to serogroups W135 and Y30. In 2007, serogroup B was responsible for 68.8% of all cases identified, serogroup C for 11.4%, serogroups W135 for 13% and serogroup Y for 6.8%31 (Figure 3). From 2000 to 2005, the prevalent Men B serosubtypes isolated were B:15:P1.7,16, B:4:P1.14 and B:4:P1.15. Men C phenotypes C:2b:NT and C:2b:P1.15 were the prevalent C serosubtypes identified in the same period32.

A recent report describing the Por A types of N. meningitidis serogroup B isolates collected in Argentina showed a substantial number of distinct VR types and a new VR2 from the P1.16 family, anticipating the difficulty in designing a useful outer-membrane vaccine applicable in this region32.

Uruguay registered a peak in the incidence of meningococcal disease in some regions of the country in 2001, when the incidence rates reached 30 cases per 100,000 inhabitants. A shift in the age distribution of the disease was observed with detection of disease in older age groups and a predominance of one strain (B:4,7:P1.15,19) over a combination of other N. meningitidis group B strains19. At that time, health authorities decided to start a massive campaign with the Cuban-produced outer membrane vesicle vaccine, including all children and adolescents from 4 to 19 years old. It was estimated that at least 70% of the target population were vaccinated, and a decrease in the incidence rates was observed. In the following years, from 2002 to 2007, meningococcal disease incidence rates remained stable in the country, around 1-6 cases per 100,000 inhabitants, with almost 95% of all cases identified in 2006 caused by serogroup B16, higher incidence rates in children younger than 5 years of age and case fatality rates of 15%.

From 1994 to 2001, Chile was characterized by stable incidence rates of meningococcal disease, around three cases per 100,000 inhabitants. A decreasing trend in the incidence rates is being registered in the last years with 128 cases reported in 2006 and 109 cases in 2007 (incidence rates of 0.8 and 0.7 cases per 100,000 inhabitants, respectively) and a case fatality rate of 11% in 200720 (Table I). A clear predominance of serogroup B was observed in this recent period, and in 2006, 78% of the isolates characterized were serogroup B, 12% serogroup C and 6% serogroup W135 and Y. Phenotype B:15:1-3 was the prevalent serosubtype identified in the last years5,20.

**Peru, Paraguay and Bolivia**

These countries reported a very small number of cases each year. In Peru, ten cases were confirmed in...
2005 and four cases were confirmed in 2006. Paraguay reported ten cases in 2005 and nine cases in 2006. In both countries, serogroup B is the prevalent serogroup. Bolivia reported only four cases between 2004 and 2005 and no cases in 2006.

Colombia, Venezuela and Ecuador

Since 1994, the Instituto Nacional de Salud runs a surveillance network for acute bacterial meningitis in Colombia. Until 2005, serogroup B was the most frequently isolated serogroup causing meningococcal disease in Colombia. In 2003, an unexpected increase in serogroup Y was identified, and by 2006, this serogroup became prevalent, representing almost 50% of the isolates identified in Colombia. Among serogroup Y isolates, 75-0% were serotype 14 with three different subtypes: Y:14:NST, Y:14:P1.5.2 and Y:14:P1.10; 9-8% were non-typeable with two subtypes (non-typeable, P1.5.2 and non-typeable, NST), and 14-6% belonged to five other serotypes.

The age distribution of cases of meningococcal disease during the period from 1994 to 2005 showed that 64% of cases occurred in children younger than 9 years of age, 17-9% in adolescents of 10–19 years, 10-4% in adults of 20–39 years and 6-6% in adults over 40 years.

Venezuela also reported an increase in the proportion of cases due to serogroup Y in 2006, when it represented 50% of all cases identified, serogroup B represented 36% and serogroup C represented 14% of cases.

In Ecuador, from 2000 to 2006, 69% of the isolates characterized were from serogroup C, 16% serogroup B and 15% serogroup Y and W135.

Mexico, Central America and the Caribbean

Low incidence rates of meningococcal disease are consistently reported in Mexico (Table 1). Several isolates submitted to characterization in these countries, the following serogroup distribution was reported by SIREVA:

In Costa Rica, from 2000 to 2005, 48% of the isolates were from serogroup B, 27% serogroup Y, 15% serogroup C and the remaining 10% serogroup W135 and X. In 2006, serogroup B remained prevalent, identified in 85% of cases submitted to identification, with serogroups C and Y responsible for the remaining 15% cases. In Mexico, from 2000 to 2005, 71% of the isolates characterized were serogroup C, 12% serogroup B and 8% serogroup Y, and in 2006, all cases identified were from serogroup C. In Dominican Republic, 44% of isolates were serogroup B, 35% serogroup C and 10% serogroup Y.

Jamaica, Barbados, Saint Vincent and Trinidad and Tobago reported a very low number of cases, and virtually all isolates from Cuba, Nicaragua and Panama were from serogroup B.

Management

Infection with N. meningitidis can present with a wide spectrum of manifestations, ranging from asymptomatic carriage, the most common form of infection, to death within hours with fulminant meningococcemia. Bacteremia without sepsis, meningococcemia, meningitis or both are the most frequent clinical manifestations of meningococcal disease. Less common manifestations include pneumonia, endocarditis, pericarditis, endophthalmitis, urethritis, osteomyelitis, cellulitis, sinusitis, conjunctivitis and otitis media. Chronic meningococcemia, with intermittent symptoms, occurs rarely.

Despite the increasing availability of intensive care units and improvement in health care assistance, case fatality rates of meningococcal disease are still high in many Latin American countries. Early diagnosis and initiation of antibiotic treatment, transfer to a hospital with an intensive care unit and aggressive management of shock are critical to reduce the case fatality rates associated with meningococcal disease.

There are several acceptable antibiotic options for the treatment of meningococcal disease, including penicillin G (Pfizerpen®, Pfizer, New York, USA) at a dose 250,000–400,000 U/kg/day divided q4–6 hours i.v., or third generation cephalosporins like cefotaxime (Claforan®, Sanofi-Aventis, Frankfurt, Germany) 200 mg/kg/day i.v. or ceftriaxone (Rocephin®, F. Hoffmann-La Roche, Basel, Switzerland) 100 mg/kg/day i.v. Chloramphenicol (Chloromycetin®, Parke-Davis, Karlsruhe, Germany) 75–100 mg/kg/day divided q6 hours i.v. can also be used. However, because of its potential bone marrow toxicity (dose-related bone marrow depression and also aplastic anemia, a severe reaction not related to dose or duration of treatment), chloramphenicol is no longer used as first-line therapy in the USA and in most European countries, but continues to be frequently used for treatment of bacterial meningitis in many Latin American countries.

In Brazil, due to the current level of resistance to penicillin observed in invasive strains of S. pneumoniae, ceftriaxone alone is the drug of choice for empirical treatment of bacterial meningitis, and penicillin remains the drug of choice when susceptible strains of N. meningitidis are isolated. For patients allergic to β-lactam antibiotics, chloramphenicol is the recommended antibiotic treatment. Although isolates of N. meningitidis with relative resistance to penicillin (minimal inhibitory concentration of penicillin of 0.1–1.0 μg/ml) have been reported in Brazil and other Latin American countries, this degree of penicillin resistance (attributed to a genetic mutation that causes alteration in penicillin-binding protein 2) does not appear to impact response to therapy. Guidelines recommend 5–7 days of treatment, but usually, patients are treated for at least 7 days.

Optimal supportive care is critical. In children with shock, lumbar puncture should not be attempted. After airway, breathing and circulation assessment and oxygen administration, vascular access and aggressive fluid treatment with intravenous infusion of 20 ml/kg of colloids or crystalloids in boluses, to increase the circulating blood volume and prevent organ dysfunction, should be started immediately. Depending on the response, additional infusion of 20 ml/kg is administered. If the patient still presents signs of shock after 40–60 ml/kg of fluid resuscitation, then elective endotracheal intubation and...
mechanical ventilation are indicated. Vasoactive drugs such as dopamine, dobutamine, adrenalin and noradrenalin are usually needed, and the patient should be transferred to an intensive care unit. Dialysis is usually required in patients with meningococcal septicemia. Children presenting signs of increased intracranial pressure (decreasing or fluctuating level of consciousness, hypertension and relative bradycardia, asymmetric, dilated or poorly reacting pupils, focal neurological signs, seizures and/or papilledema) should be treated emergently with endotracheal intubation and hyperventilation (to control PCO₂). Mannitol (Pearlitol®, Roquette Freres, Lestrem, France) 0-25 g/kg, followed by furosemide (Lasix®, Sanofi-Aventis, Frankfurt, Germany) 1 mg/kg, should also be given to reduce intracranial pressure. Patients with meningitis without signs of raised intracranial pressure or inappropriate secretion of antidiuretic hormone should receive the normal daily requirement of fluid intravenously\textsuperscript{10}.

The use of steroids in children with shock caused by \textit{N. meningitidis} is controversial since no pediatric studies have documented its benefit. Pediatric intensive care specialists use steroids in children with meningococcal disease who have refractory shock and inadequate adrenal gland function\textsuperscript{10}. There is available evidence to support the use of dexamethasone therapy given before antibiotics to reduce morbidity in children with Hib meningitis\textsuperscript{7}. However, routine use of dexamethasone cannot be recommended for treatment of meningococcal meningitis based on current data.

New promising therapies like anticoagulant agents (recombinant activated protein C and recombinant factor VIIa) alters the nature of the response. When B cells recognize the polysaccharide, they process the conjugated carrier protein and present it to helper T cells. This antigenic peptide epitope to T CD4\textsuperscript{+} cells.

### Prevention

**Chemoprophylaxis**

Although the risk of contracting meningococcal disease among contacts of infected individuals is low, the attack rate for household contacts is 500 times the rate for the general population. Chemoprophylaxis is indicated for all close contacts of an index case, whether sporadic or in situations of outbreaks and epidemics. Since the majority of secondary cases occur within 5 days after a case, the recommendation of the Ministry of Health in Brazil\textsuperscript{17} is to start chemoprophylaxis for the contacts, ideally, in the first 24 hours after the patient admission. Chemoprophylaxis should be offered to all household contacts, people living and/or sleeping in the same household, childcare and nursery school contacts (same room and period and also the staff members responsible to feed the children) and people who have been directly exposed to a patient’s oral secretions through close contact, such as kissing or sharing of toothbrushes and others, during the 10 days before onset of symptoms of disease in the index case. Routine prophylaxis is not recommended for health care professionals, except in cases when mouth to mouth resuscitation, endotracheal intubation, or aspiration of secretions were made without respiratory precautions\textsuperscript{17,27}.

The index case should also receive chemoprophylaxis before hospital discharge, unless ceftriaxone or cefotaxime are the antimicrobial agents used for treatment of meningococcal disease, to eradicate nasopharyngeal carriage of \textit{N. meningitidis}.

Rifampin (Rifadin®, Sanofi-Aventis, Bridgewater, NJ, USA) is the drug of choice for chemoprophylaxis of children and adults in our setting. Based on our experience of treating tuberculosis in pregnant women with rifampin, we do not contraindicate this drug for pregnant women\textsuperscript{27}. Ceftriaxone given in a single intramuscular and ciprofloxacin (Cipro®, Bayer AG, Leverkusen, Germany) in a single oral dose proved to be effective options to eradicate pharyngeal carriage of meningococci. Ciprofloxacin should only be used for people older than 18 years of age (Table 2).

**Vaccines**

Vaccination is considered the best control strategy for prevention of meningococcal disease. Plain polysaccharide vaccines for serogroups A, C, W135 and Y meningococcal disease have been available since the 1970s. These vaccines proved to be safe and effective in controlling outbreaks and epidemics. However, in common with other unconjugated polysaccharide vaccines, they do not generate adequate immune response in children under 2 years of age because of the lack of response to T-independent antigens at this age. Another important characteristic of these vaccines is that, even in patients over 2 years of age, the protection offered is of limited duration; they are unable to induce immune memory. Furthermore, they are capable of inducing hyporesponsiveness after subsequent doses. For these reasons, these polysaccharide vaccines are not used as a routine, but are indicated only for high risk groups or during outbreaks or epidemics\textsuperscript{6,8,12,18,35}.

The conjugation of polysaccharides to protein carriers [non-toxic diptheria mutant toxin (CRM197) or tetanus toxoid] alters the nature of the antipolysaccharide response to a T-dependent response. When B cells recognize the polysaccharide, they process the conjugated carrier protein and present peptide epitopes to T CD4\textsuperscript{+} cells. This antigenic complex induces the production of elevated antibody

### Table 2 Chemoprophylaxis for contacts of people with meningococcal disease

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<thead>
<tr>
<th>Drug of choice</th>
<th>Age group</th>
<th>Dosage and duration</th>
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<tbody>
<tr>
<td>Rifampin</td>
<td>&lt;1 month</td>
<td>5 mg/kg orally every 12 hours for 2 days</td>
</tr>
<tr>
<td></td>
<td>≥1 month</td>
<td>10 mg/kg (maximum 600 mg) orally every 12 hours for 2 days</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>&lt;15 years</td>
<td>125 mg intramuscularly single dose</td>
</tr>
<tr>
<td></td>
<td>≥15 years</td>
<td>250 mg intramuscularly single dose</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;18 years</td>
<td>500 mg orally single dose</td>
</tr>
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levels, including in young infants, higher antibody avidity and increases serum bactericidal activity. They also induce the formation of long-lasting memory B lymphocyte populations, providing an excellent anamnestic response (booster effect) on re-exposure.6,8,12,18,35

Conjugated meningococcal vaccines were developed from meningococcal serogroup C isolates containing the polysaccharide capsule conjugated to the mutant diphtheria toxoid (MCC-CRM197, Menjugate; Novartis Vaccines and Diagnostics, Siena, Italy; Meningitec®, Wyeth-Lederle Vaccines and Pediatrics, Pearl River, NY, USA) or to the tetanus toxoid (MCC-TT-Neisvac-C; Baxter Vaccines, Beltsville, MD, USA; MCC-TT-Hib, Menitorix®, GSK, Rixensart, Belgium). After licensure, serogroup C meningococcal conjugate vaccines have been successfully introduced in the UK, Spain and other European countries, Australia and Canada.36-46 All these countries observed a significant reduction in the incidence of meningococcal disease, even in age groups that were not vaccinated, apparently demonstrating that conjugate vaccines protect not only individuals who are vaccinated but also the rest of the population, as a result of the reduced number of people carrying bacteria in their nasopharynx (‘herd immunity’).38,42,43 In the UK and Spain, routine immunization of infants consisted of three doses of the vaccine in 2, 3 and 4 months and 2, 4 and 6 months, respectively. In both countries, waning efficacy was reported among these children immunized during their first year of life leading to changes in the immunization schedule, in order to confer longer lasting protection, to two doses after 2 months of age, followed by a booster dose administered at 12 months of age.44 An alternative strategy that has been shown to be more cost-effective was adopted in The Netherlands, where, in 2002, a successful routine immunization program was implemented with a single dose of the meningococcal C-tetanus toxoid conjugate vaccine at 14 months of age. In addition, a catch-up campaign was conducted targeting nearly all children and adolescents aged 1–18 years with the same vaccine. The first results, published in 2006, demonstrated a dramatic reduction in the incidence of meningococcal disease, both in vaccinated as well as in unvaccinated age groups, with the highest reduction (99%) observed in the age groups that were vaccinated. To date, there have been no reports of meningococcal disease in previously vaccinated children in The Netherlands.

In Latin America, meningococcal C conjugate vaccines are licensed since 2002 and used mainly in the private sector of few countries. Brazil is the only country in the region that has already decided to add meningococcal C conjugate vaccine to the routine childhood immunization schedule, anticipating that, from October 2010 on, the vaccine will be available for all children under two years of age, without catch-up campaigns in older age groups.

Combination conjugate vaccines, containing more than one meningococcal polysaccharide, have been developed to broaden protection against the disease. A tetravalent meningococcal A, C, Y and W-135 conjugate vaccine (Menactra®, Sanofi-Pasteur, Swiftwater, PA, USA) is licensed only in the USA and Canada for use in 2–55-year-old children, adolescents and adults.3,46 Other tetravalent meningococcal A, C, Y and W135 vaccine conjugated to CRM-197 (developed by Novartis, Siena, Italy) is being evaluated in phase III trials and, based on recent published results, is expected to be licensed for all age groups, including infants.47

The major challenge in meningococcal disease prevention continues to be the development of vaccines that are immunogenic against serogroup B. The capsular polysaccharide of meningococcus B has an antigenic structure (acetylation neuraminic acid) similar to that found in embryonic neural tissues. This peculiar characteristic, in addition to making it impossible for polysaccharide vaccines containing serogroup B to be immunogenic, also results in a risk of autoimmune reactions to the use of these vaccines. As a result, no polysaccharide conjugate vaccines have been developed for meningococcus B that could be shown to be immunogenic and risk free. One attempt to overcome this problem was to develop vaccines that used non-capsular antigenic components of meningococcus B, such as outer membrane vesicles, lipooligosaccharide, transferring-binding protein B and cross-reacting antigens of Neisseria lactamica. Vaccines based on outer membrane vesicles were used with success to control outbreaks; however, the immunoresponsiveness to these vaccines is specific to the serosubtypes of meningococcus B included in the vaccine, preventing the protection offered from covering other meningococcus B serosubtypes.6,18,35 The identification of conserved novel surface proteins, through genome sequencing of the bacteria, which could be antigenic candidates and the discovery of novel group B capsule specific antigens,48 are very promising alternative strategies to find a broadly protective meningococcal B vaccine. Based on reverse vaccinology, a meningococcal B vaccine consisting of multiple antigens with the New Zealand outer membrane vesicle in the vaccine formulation was developed. Results from phase I trials have demonstrated satisfactory safety and immunogenicity in adults. This recombinant vaccine also proved to be well tolerated and immunogenic in infants, according to recent results from phase II trials.49

Conclusions

Although the quality and availability of published data for meningococcal disease in Latin America are not uniform across the countries, certain findings were consistent. N. meningitidis became a leading cause of bacterial meningitis in children and young adults in many countries of Latin America, especially after the introduction of Hib routine vaccination. The overall incidence of meningococcal disease varied widely, from <0.1 cases per 100,000 inhabitants in countries like Mexico to almost two cases per 100,000 inhabitants per year in Brazil, and the highest age-specific incidence of meningococcal disease was consistently observed in infants <1 year of age. The exceedingly low rates of meningococcal disease reported by some countries and the high proportion of meningitis without a determined bacterial etiology probably underestimate the real burden of
meningococcal disease in the region and highlight the difficulty in recovering the organism, not only by limitations in obtaining adequate samples for culture, but also in consequence of the common practice of previous antibiotic use.

Regarding serogroup distribution, we could confirm that serogroups B and C are responsible for the majority of cases reported. Emergence of serogroups W135 and Y was reported in some countries, and serogroup A disease is now rare in Latin America. A significant rise in the proportion of cases due to serogroup C was registered in the last years in countries like Brazil, Ecuador and Mexico, while in Argentina, Chile, Uruguay and in most countries from Central America and the Caribbean, the majority of cases are due to serogroup B. Serogroup Y emerged in Colombia and Venezuela, where it became the prevalent disease-causing serogroup in 2006.

The high morbidity and mortality associated to meningococcal disease in some countries in Latin America, even in the face of early therapeutic intervention, emphasize that a better understanding of the true burden of meningococcal disease in the region is urgently needed to help the promotion and introduction of new effective vaccines in national immunization programs.

The development of conjugate vaccines (capsular polysaccharides conjugated to protein antigens) represented an enormous progress in the possibility of controlling meningococcal disease caused by vaccine serogroups and offers hope for a more effective prevention strategy against meningococcal disease in Latin America. Effectiveness data are only currently available for meningococcal C vaccines. These conjugate vaccines have shown themselves to be immunogenic in infants, to induce immunological memory, to decrease carriage such that non-vaccinees were protected (herd immunity) and highly effective, with a dramatic and immediate reduction in the incidence of meningococcal disease caused by serogroup C in countries that have introduced them in their national immunization programs. The recent licensure of a quadrivalent meningococcal conjugate vaccine for serogroups A, C, W135 and Y and the late stage development of new multivalent meningococcal conjugate vaccines at last offers the real possibility of also reducing the incidence of meningococcal disease epidemiations caused by serogroups A, W135 and Y.

N. meningitidis group B remains a major cause of meningococcal disease in Latin America, associated with a high diversity of serotype causing disease. To date, attempts to obtain an effective and broad-spectrum vaccine for meningococcus B have failed. While outer membrane vesicle vaccines have proven themselves effective for the control of outbreaks caused by strains homologous with the vaccine, they do not offer protection that covers the remaining meningococci B serosubtypes, in addition to only offering modest immunogenicity in children under 4 years old. Early studies using reverse vaccinology have produced promising results for the development of a vaccine that offers wide-ranging protection from serogroup B.

Global analyses of the cost effectiveness of vaccination against meningococcal disease have found different results, which can be explained by different epidemiological conditions from country to country, as well as different analytical approaches (inclusion of only direct or direct and indirect costs, inclusion or exclusion of the costs of the sequelae) and also the type of immunization strategy (inclusion of infants in the routine immunization schedule and targeted age groups of catch-up). These cost-effectiveness studies together with the analysis of the burden of disease in terms of incidence, prevalence, morbidity and mortality in a determined country are the key factors influencing the decision for introducing new vaccines in the National Immunization Programs in the region.

Given the availability of new highly effective vaccines, better epidemiological information and characterization of N. meningitidis isolates are critical to understand the epidemiology of meningococcal disease in Latin American countries and to anticipate the appropriateness of the multivalent conjugate vaccines and the new protein-based meningococcal B vaccines in this region.

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