

Review

The current situation of meningococcal disease in Latin America and updated Global Meningococcal Initiative (GMI) recommendations



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ABSTRACT

The Global Meningococcal Initiative (GMI) was established in 2009 and comprises an international team of scientists, clinicians, and public health officials with expertise in meningococcal disease (MD). Its primary goal is to promote global prevention of MD through education, research, international cooperation, and developing recommendations that include decreasing the burden of severe disease. The group held its first roundtable meeting with experts from Latin American countries in 2011, and subsequently proposed several recommendations to reduce the regional burden of MD. A second roundtable meeting was convened with Latin American representatives in June 2013 to reassess MD epidemiology, vaccination strategies, and unmet needs in the region, as well as to update the earlier recommendations. Special emphasis was placed on the emergence and spread of serogroup W disease in Argentina and Chile, and the control measures put in place in Chile were a particular focus of discussions. The impact of routine meningococcal vaccination programs, notably in Brazil, was also evaluated. There have been considerable improvements in MD surveillance systems and diagnostic techniques in some countries (e.g., Brazil and Chile), but the lack of adequate infrastructure, trained personnel, and equipment/reagents remains a major barrier to progress in resource-poor countries. The Pan American Health Organization’s Revolving Fund is likely to play an important role in improving access to meningococcal vaccines in Latin America. Additional innovative approaches are needed to redress the imbalance in expertise and resources between countries, and thereby improve the control of MD. In Latin America, the GMI recommends establishment of a detailed and comprehensive national/regional surveillance system, standardization of laboratory procedures, adoption of a uniform MD case definition, maintaining laboratory-based surveillance, replacement of polysaccharide vaccines with conjugate formulations (wherever possible), monitoring and evaluating implemented vaccination strategies, conducting cost-effectiveness studies, and developing specific recommendations for vaccination of high-risk groups.

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Abbreviations: ANLIS, Administración Nacional de Laboratorios e Institutos de Salud (Argentina); CFR, case fatality rate; GMI, Global Meningococcal Initiative; MCC, meningococcal C conjugate; MD, meningococcal disease; MoH, Ministry of Health; NIP, National Immunization Program; PAHO, Pan American Health Organization; PCR, polymerase chain reaction; RT-PCR, real-time polymerase chain reaction; SIREVA, Sistema Regional de Vacunas; SIREVA II, Sistema de Redes de Vigilancia de Agentes Bacterianos Causantes de Meningitis y Neumonías.

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1. Introduction

Neisseria meningitidis remains a major cause of invasive bacterial disease worldwide and is associated with substantial morbidity and overall case fatality rates (CFRs) of around 10% (overall CFRs as high as 20% have been reported in some countries [1–4]). Disease caused by serogroup W alone has been associated with CFRs of >30% [5]. In Latin America, incidence rates and serogroup distribution of meningococcal disease (MD) are highly variable (from <0.1 to almost 2 cases per 100,000 inhabitants), with the highest burden of disease reported in Brazil and the Southern Cone countries (Argentina, Chile, and Uruguay); very limited data are available from the Andean region, Mexico, and Central America [6].

The Global Meningococcal Initiative (GMI), established in 2009, is a multidisciplinary group with expertise in areas such as public health, epidemiology/seroepidemiology, pediatrics, infectious disease, microbiology, immunology, and vaccinology. It aims to help prevent MD worldwide through education, research, international cooperation, and to develop recommendations that include decreasing the burden of severe disease [7] through promotion of prevention strategies, early diagnosis and treatment, and disease awareness.

At the first GMI regional Latin American roundtable meeting in 2011, the epidemiology of MD in the region was reviewed and several recommendations were proposed to reduce the burden of MD (Table 1) [6]. It was concluded that MD burden in Latin America is largely underestimated, and it was stressed that control efforts should focus on educating physicians and regulators on the importance of the disease, its diagnosis, improving meningococcal surveillance in the region, and the need for uniform, good-quality data. To improve surveillance in the region and facilitate data comparisons, a uniform case definition was proposed that supplemented Pan American Health Organization (PAHO) criteria with confirmation by polymerase chain reaction (PCR; where available) [6]. It was felt that end-point PCR and real-time PCR (RT-PCR) could make a difference in the region in terms of recognition of the disease (especially given the increasing early use of antibiotics, which leads to culture-negative results) [6]. While countries should use

whichever PCR method is available to them, it is well accepted that RT-PCR is more sensitive and precise than end-point PCR, and is less time consuming [8]. RT-PCR uses a fluorescent dye system that provides a higher sensitivity and specificity than end-point PCR, which uses ethidium bromide and UV light to visualize bands in the agarose gel medium.

In June 2013, a second GMI Latin American meeting was held to provide an update on the epidemiology of MD, with an emphasis on the recent emergence of serogroup W disease in Argentina and Chile. The experience with recent meningococcal vaccination programs implemented in the region (i.e., routine meningococcal C conjugate [MCC] vaccination for infants and toddlers in Brazil and reactive quadrivalent [serogroups A, C, W, and Y] meningococcal conjugate vaccination in Chile) was discussed. In addition, recommendations for the control and prevention of MD in Latin America were updated. This article summarizes the discussions that took place at the meeting.

2. Epidemiology of meningococcal disease in Latin America

Informed decisions about appropriate vaccination strategies to control MD depend upon a thorough understanding of the epidemiology of the disease in the various countries. The reported annual incidence of MD in Latin America varies widely, ranging from <0.1 cases per 100,000 inhabitants in countries such as Bolivia, Cuba, Mexico, Paraguay, and Peru to nearly two cases per 100,000 inhabitants in Brazil [6,7,9]. The reporting of MD is mandatory in Latin America, but surveillance systems and reporting are not standardized across countries [9,10]. In addition, there is limited access to hospital care in some countries, as well as differences in the diagnostic methods/conditions and MD case definitions [6,10]. These differences may contribute to the variability in disease incidence; caution should therefore be exercised when interpreting epidemiologic data from the region.

Despite MD being a mandatory notifiable disease in all Latin American countries, reports are likely to represent underestimates of the true disease burden [7]. In Latin America, laboratory-based diagnosis of suspected cases of MD is based principally on culture methods, and inadequate microbiologic services and previous antibiotic use (risk factors for culture negativity) may contribute to disease underreporting [11]. Restrictive case definitions of MD in some countries, such as Mexico, may also contribute to low reporting rates [6]. The highest rates of MD in Latin America are reported for Argentina, Brazil, Chile, and Uruguay, but this is probably because these countries have more advanced surveillance systems and laboratory services than some others [6]. Indeed, the introduction of multiplex RT-PCR testing for *N. meningitidis* in hospitals in São Paulo, Brazil, increased the diagnostic yield for MD by 85% over culture-based methods [11]. In addition to this, in 2013 and 2014 in Chile, after the implementation of PCR by the Instituto de Salud Pública, approximately 15% of the cases reported were identified by this methodology [12].

A Latin American, laboratory-based surveillance network (Sistema Regional de Vacunas [SIREVA]) was introduced in 1993 by the PAHO, to collect laboratory and epidemiologic data on specific bacterial diseases [12]. SIREVA II (Sistema de Redes de Vigilancia de Agentes Bacterianos Causantes de Meningitis y Neumonías) currently performs a systematic analysis of *N. meningitidis* isolates recovered by the epidemiologic survey network from countries in Latin America and the Caribbean, and 20 countries/areas in Latin America are participating in the surveillance program (Table 2) [6,12,13]. Strengthening surveillance systems for MD and establishing a closer link between epidemiology, laboratory testing, and clinical aspects of the disease are challenges and key goals of the Latin America and Caribbean network.

Table 1
Global Meningococcal Initiative recommendations for reducing the global burden of meningococcal disease in Latin America (as described in Sáfadi et al. [6]).

1.	The supplementation of culture with standardized nucleic acid amplification techniques for disease confirmation and implementation of molecular genotype characterization techniques as a routine in national and regional reference laboratories
2.	The introduction of quality controls so that data from different laboratories can be harmonized
3.	Consistent and universal use of standardized diagnostic protocols, such as those set out by SIREVA II or PAHO
4.	The forging of partnerships between resource-rich and resource-constrained regions to improve laboratory capacity (and the quality and quantity of the epidemiologic data available)
5.	The implementation of active population- and laboratory-based surveillance for invasive MD at selected sites to assist in early outbreak detection and estimation of age-specific incidence rates and serogroup distribution
6.	Replacement of polysaccharide vaccines with conjugate formulations—wherever possible
7.	Proposed vaccination policies against MD should be country-specific and based on local disease dynamics and health priorities
8.	Novel financing arrangements should be considered, such as: <ul style="list-style-type: none"> • Technology transfer agreements • The PAHO Revolving Fund • Advanced market commitments

MD, meningococcal disease; PAHO, Pan American Health Organization; SIREVA II, Sistema de Redes de Vigilancia de Agentes Bacterianos Causantes de Meningitis y Neumonías.

Table 2
Number of *Neisseria meningitidis* isolates, from invasive MD cases, reported by SIREVA II during 2006–2012 [13].

Country	Number	Country	Number
Argentina	935	Guatemala	0
Bolivia	3	Honduras	5
Brazil	4416	Mexico	66
CAREC	8	Nicaragua	6
Chile	507	Panama	73
Colombia	189	Paraguay	61
Costa Rica	41	Peru	4
Cuba	41	Dominican Republic	57
Ecuador	29	Uruguay	209
El Salvador	29	Venezuela	167
		Total	6846

CAREC, the Caribbean Epidemiology Center/Pan American Health Organization (Barrabados, and Trinidad and Tobago); SIREVA II, Sistema de Redes de Vigilancia de Agentes Bacterianos Causantes de Meningitis y Neumonías.

The GMI has proposed a number of recommendations to help improve and standardize reporting of MD in Latin America. These recommendations include a clear definition of a suspected case, the use of molecular diagnostic techniques (e.g., PCR/RT-PCR) in routine surveillance, expanding the use of culture methods, establishing well-equipped sentinel and reference laboratories with highly trained staff, and adopting a single case definition for use in all Latin American countries (Table 3) [6,14]. This definition includes molecular diagnostic techniques (where available and for countries that have resolved the issue of prompt sample collection and testing, which is the first step toward improving diagnosis capacity). RT-PCR has high sensitivity and specificity for *N. meningitidis* versus culture methods, and even when bacteria are nonviable after antibiotic treatment, PCR is able to detect *N. meningitidis* deoxyribonucleic acid [11]. The GMI recommends an integrated surveillance approach of laboratory and clinical notifications, as conducted in Chile, where the Department of Epidemiology of the Ministry of Health manages all of the country's MD information and the Public Health Institute coordinates the activities of a network of centers trained in RT-PCR. Nevertheless, the GMI recognizes that some countries have resource and financial constraints, which prevent them from taking up all recommendations, and it therefore encourages alliances to be formed with other supportive organizations [6].

As elsewhere, the highest incidence of sporadic MD in Latin America occurs in infants and young children [7,9], but data on

Table 3
Case definition for meningococcal disease (MD) proposed by the Global Meningococcal Initiative for use in Latin America (PAHO case definition plus confirmatory diagnosis by PCR) [6], copyright© 2013, Informa Healthcare. Reproduced with permission of Informa Healthcare.

Suspected MD (clinical case definition) [14]

An illness with sudden onset of fever (>38.5 °C rectal or >38.0 °C axillary) and one or more of the following:

- Neck stiffness
- Altered consciousness
- Other meningeal sign or petechial or purpuric rash

In patients <1 year old, MD should be suspected when fever is accompanied by bulging fontanel

Confirmed (suspected MD plus at least one of the following laboratory criteria):

- Detection of bacterial antigen(s) in CSF
 - Positive bacterial culture in normally sterile body site (such as CSF and/or blood and/or skin lesion)
 - Detection of bacterial DNA by PCR or RT-PCR in normally sterile body site (such as CSF and/or blood and/or skin lesion)

CSF, cerebrospinal fluid; DNA, deoxyribonucleic acid; PAHO, Pan American Health Organization; PCR, polymerase chain reaction; RT-PCR, real-time PCR.

outbreaks have shown an increased number of cases in adolescents and young adults [15,16]. This peak among adolescents and young adults during outbreaks may be related to behavioral risk factors (e.g., kissing, smoking, or frequenting nightclubs) [17,18] and the introduction of new clones [19].

Monitoring phenotypic and genotypic characteristics of circulating *N. meningitidis* strains is of fundamental importance in understanding MD in each country. Six serogroups (A, B, C, W, X, and Y) cause nearly all cases of MD globally [20]. Most cases of MD in Latin America are sporadic and caused by serogroups B and C, with emergence of serogroup W in Southern Cone countries, particularly Argentina and Chile (Fig. 1) [7,13,21]. In contrast, serogroup A has virtually disappeared from Latin America [6,13]. Molecular typing is also of importance given that control and management of MD are predicated upon understanding current epidemiology (see [Supplementary Material](#)).

Information about the carriage of *N. meningitidis* is essential in understanding the transmission dynamics of meningococcal infection [22], and for assessing the extent and potential that exists for vaccination strategies to induce herd protection [10]. Although there are limited published data on carriage of *N. meningitidis* in Latin America [10,23], four carriage studies (Brazil, Argentina, Colombia, and Paraguay) are ongoing or have been completed recently. A study among adolescents ($n = 1208$, age 11–19 years) in Campinas, Brazil, showed an overall carriage rate of 9.9%, with dominance of serogroup C (1.3%) and the highest prevalence (12%) in older adolescents (age 17–19 years). In addition, a study of healthy Chilean university students, using only culture, found an overall carriage rate of 4% [25].

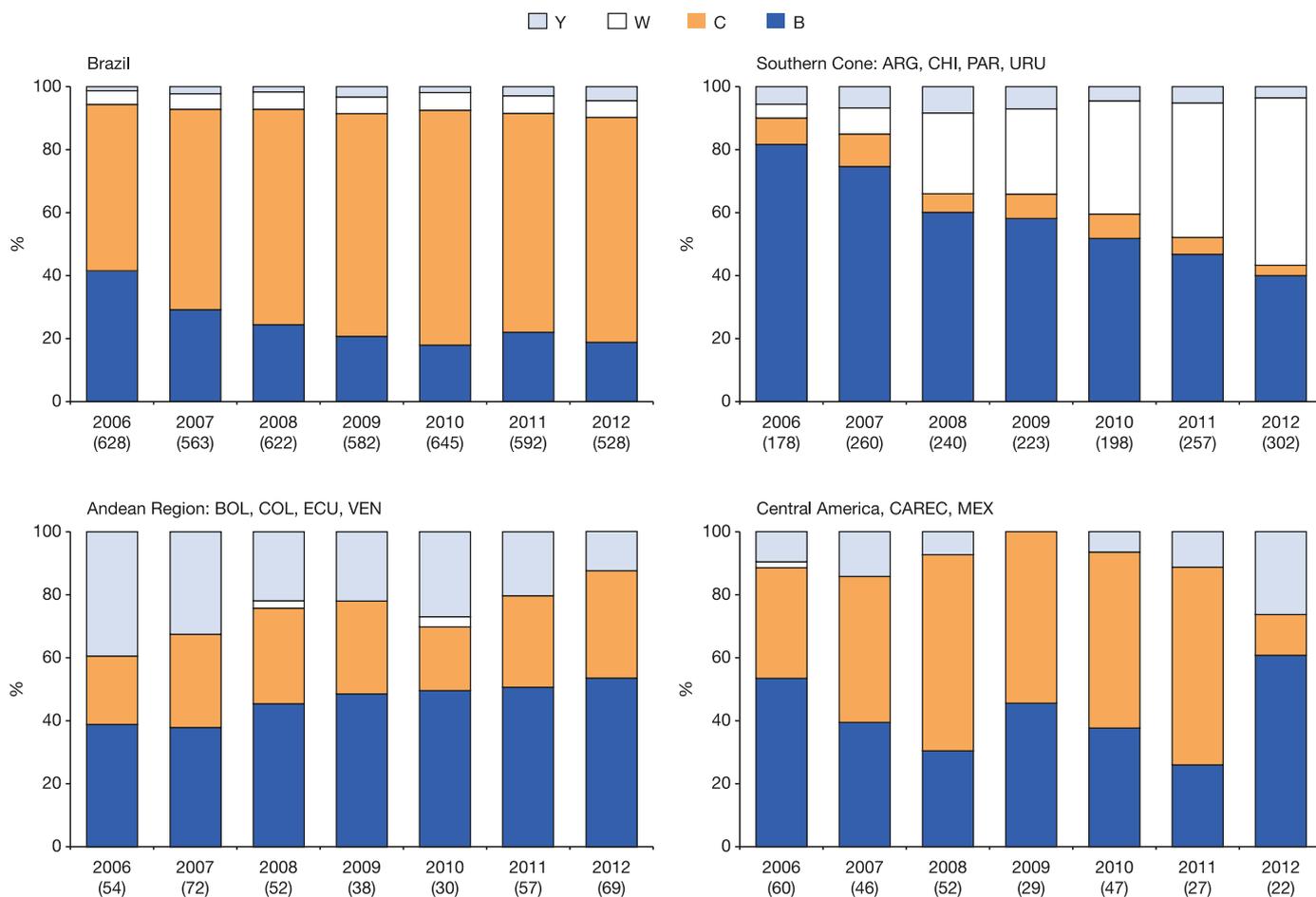
3. Importance of serogroup W

3.1. The spread and rise of serogroup W

Outbreaks due to serogroup W (formerly W-135) were first reported in pilgrims attending the Hajj in Mecca, Saudi Arabia. Following this, W outbreaks (many travel-related) were detected in countries and regions across the globe (including the United States, Turkey, Europe, and sub-Saharan Africa; see [Supplementary Material](#)).

3.2. The emergence of serogroup W in Latin America

Currently in Latin America, serogroups B and C are dominant, but increases in the proportion of MD cases attributable to serogroup W, and W outbreaks, have been reported in several countries [12,26]. Since 1990, cases of W:2a:P1.5.2:ST-11 complex MD were detected in the region [27]. One recent study analyzed laboratory data for 4735 isolates collected by the national reference laboratories in 19 Latin American countries and the Caribbean Epidemiology Center from 2006 to 2010 [12]. In Brazil and the Andean region, a small percent of isolates were serogroup W (5.2% and 1.2%, respectively), while none were isolated in Venezuela. Similarly, in Mexico, Central America, and the Caribbean region, a very small percent (0.4%) of isolates were serogroup W, while a considerably larger percent (19.6%) of isolates in the Southern Cone region belonged to serogroup W (this percent will be higher currently, given the marked increase in W in the region). The largest increase in prevalence of serogroup W in the region was observed in Argentina, where in 2006 it represented 6.3% of the isolates, increasing to 52% by 2012. Moreover, in 2006, there were only four invasive serogroup W isolates detected in Argentina, which dramatically increased to 96 isolates in 2012 [28,29]. SIREVA II data also revealed that specific age groups were affected disproportionately by serogroup W and changed over



Data: SIREVA II; Instituto Adolfo Lutz.

ARG, Argentina; BOL, Bolivia; CAREC, Caribbean Epidemiology Center; CHI, Chile; COL, Colombia; ECU, Ecuador; MEX, Mexico; PAR, Paraguay; SIREVA, Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonías y Meningitis Bacterianas; URU, Uruguay; VEN, Venezuela.

Fig. 1. Meningococcal serogroup distribution in selected countries in Latin America (2006–2012), for all age groups [13,21].

time. In 2006, serogroup W affected older individuals primarily, but from 2008 onward, younger individuals were impacted more often—a situation similar to that observed in the sub-Saharan region [30]. Other research shows that during the past 6 years in Brazil, MD caused by serogroup W has mainly been connected to local strains from the ST-11 clonal complex, as has been reported in other countries [31]. Whole genomic sequencing analysis recently demonstrated that the MenW:cc11 strain, which is currently endemic in Brazil and Argentina is distinct from the Hajj outbreak strain [32].

3.3. The Chilean experience

The Chilean experience provides a unique opportunity to learn more about serogroup W disease due to the in-depth data that have been amassed to date. Indeed, we now understand that serogroup W is a hypervirulent strain often belonging to sequence type 11 clonal complex, and has been associated with very high CFR. We also have enhanced knowledge regarding its dynamics, and how it acts on carriers at different ages, as cases are rare in adolescents compared with infants, young children, and the elderly. The events can also be used to evaluate the effectiveness of surveillance and the implementation of a reactive quadrivalent (serogroups A, C, W, and Y) meningococcal conjugate vaccination against serogroup W disease.

Serogroup W emerged in Argentina and Brazil around 2001, and the number of W cases has since increased (three invasive isolates were recorded in 2001 rising to 96 in 2012 in Argentina, and 17 invasive isolates were detected in Brazil in 2001 rising to 28 in 2012) [13,28,29,33]. Likewise, cases due to serogroup W belonging to the clonal complex ST-11 were identified in Chile in 2001, and in 2010 and 2011 most of the serogroup W strains that were characterized were shown to belong to clonal complex ST-11 (6/6 in 2010 and 19/23 in 2011) [34,35]. In 2010, 9% of the isolates in Chile were serogroup W [12]. By 2012, this serogroup accounted for 58% of all cases, surpassing serogroup B (37%) for the first time [26]. Meanwhile, the overall incidence rate of invasive MD was 0.7 per 100,000 population, and almost 50% of cases occurred in children <5 years old [26]. As expected, the incidence rate was highest (19 per 100,000) in very young infants (3–4 months old). A peak was also observed in persons >60 years old, whereas the number of cases in adolescents was very low [26]. In 2013, more serogroup W cases were identified versus 2012 [36]. In 2012, the CFR for MD caused by serogroup W was high (31.7%), probably due to the high rates of meningococemia observed [5]. A high CFR was also observed in 2013. Most cases in 2012 and 2013 were reported in the Santiago Metropolitan Region [37], the likely reason for this being its higher population density versus other regions of the country. A study is ongoing to identify factors that increase the risk for serogroup W infection.

3.4. Control measures to manage serogroup W outbreaks

In response to the increase in CFR associated with serogroup W in Chile, the Ministry of Health (MoH) implemented a serogroup W action plan [26]. This plan required the MoH and public health centers to work together to improve surveillance, and included integrated epidemiologic surveillance; antimicrobial chemoprophylaxis of close contacts; a communicative media plan; an immunization plan; partnerships with the Ministry of Education; proposals for epidemiologic studies; and the involvement of the Immunization Advisory Committee and the scientific societies.

In Chile, it is now mandatory to report all suspected clinical cases of MD. Patients and results are referred locally, and at the same time the information is sent to the health ministry and regional ministerial center.

Previously, routine vaccination was not used for prevention of meningococcal disease, and local vaccination was conducted during outbreaks due to *N. meningitidis* serogroup C in some places to prevent further infection. All close contacts of infected patients were treated with chemoprophylaxis within 24 h of notification of index cases. In response to the increased number of serogroup W cases and the associated CFR observed, strategic vaccination of children aged 9 months to 5 years was initiated in October 2012 using the tetravalent conjugate vaccine. This approach has been successful in this age group, as no further cases due to serogroup W have been identified in this vaccinated cohort.

Several articles on the Chilean experience have been, or are in the process of being, published [26,35,38]. In addition, the Web pages of the Public Health Institute and the Department of Epidemiology of the MoH include weekly updates so that the effectiveness of the Chilean strategies can be evaluated [37]. Currently, there is a need to strengthen integrated surveillance (epidemiologic, laboratory, and clinical) to assess the effectiveness of vaccination in the short term and to evaluate the epidemiologic behavior of the disease and the risk groups periodically. The impact of the interventions used in Chile is of great importance globally, as lessons learned here could be applied in other countries. It is also of interest to determine if the interventions will affect other age groups, although this has not been observed to date. New potential strategies, including immunization of young infants and a catch-up campaign targeting adolescents and young adults, are being discussed to optimize the impact of the vaccination program in Chile.

In summary, much has been learned from the Chilean experience, such as the importance of an integrated surveillance system, a rapid response, and transparent dissemination of data to the public. Chile has a legal and organizational structure in place to control and manage MD, as well as technical resources. As serogroup W disease is appearing/rising in other countries, what has been learned in Chile will be of great importance not only regionally, but also globally.

4. Impact of routine meningococcal vaccination programs in Latin America

4.1. Brazil: experience of routine immunization against MD

In late 2010, Brazil became the first Latin American country to introduce MCC vaccination into the routine National Immunization Program (NIP) [39,40]. The decision by the Brazilian MoH was based on the epidemiologic situation and the serogroup C outbreaks reported across the country. During the period immediately before the introduction of the MCC vaccination program, annual incidence rates of MD were stable, with approximately 1.6 cases per 100,000 inhabitants, varying in 2010 from <1 case per 100,000 in the northern region to 3.5 cases per 100,000 in São Paulo—the state

with the most well-established meningitis surveillance system [40]. The highest age-specific incidence of MD occurred in children <5 years old [12]. However, during outbreaks and epidemics, increased numbers of cases were often observed in adolescents and young adults [10]. The overall CFR was consistently high in the past decade (around 20%). From 2002 onward, a significant increase in the proportion of cases attributed to serogroup C (ST-103 complex) was observed [10], and by 2010, serogroup C was responsible for approximately 80% of identified MD cases [12,40].

The MCC vaccine was introduced into the routine immunization schedule of infants (two doses, at 3 and 5 months, and a booster dose at 12 months) [10]. Toddlers aged 12–23 months received one vaccine dose, with no catch-up campaign for older age groups [9,10]. Coverage for the two primary doses was ~85% in late 2011, rising to 90–95% in 2012 [41]. The introduction of the MCC vaccine into the NIP provided an immediate reduction in incidence rates of MD in children aged <2 years, the age group targeted for vaccination (Table 4) [41]. However, no early impact was observed in unvaccinated age groups (Table 4), probably reflecting the lack of a catch-up program targeting adolescents and young adults—the age groups primarily responsible for carriage and transmission [22]. Interestingly, Brazil is the first country in the world to provide experience with MCC vaccines against non-ST-11 *N. meningitidis* [42].

5. Achievements and unmet needs in Latin America in recent years

5.1. Achievements

5.1.1. Surveillance of meningococcal disease

As discussed, although notification of MD is compulsory in Latin America, surveillance is inconsistent. Recent improvements have included implementation of more reliable population-based surveillance systems and inclusion of accurate detection techniques (e.g., standardized culture techniques and PCR applied to blood, cerebrospinal, and other sterile fluids) [12]. These improvements, however, have been implemented to varying degrees.

Although tremendous efforts have been made in Latin America to improve surveillance systems and the diagnostic methodology for MD, the only countries where there is evidence of routine use of PCR are Brazil and Chile; only a limited level of PCR use occurs in Argentina, Mexico, and Paraguay. In Chile, since 2009, RT-PCR has been incorporated into the final confirmation process for samples received and processed in the Institute of Public Health. Similarly, in Brazil, all suspected cases of MD occurring in the public and private healthcare systems are reported to a national case-based information system for notifiable diseases (Sistema de Informação de Agravos de Notificação) [43]. This system, managed by the Brazilian MoH, was implemented in 1994 and has undergone a number of improvements over the years, the most recent occurring in 2007 when an Internet-based data transfer system was implemented [43,44]. In Mexico, PCR confirmation has been implemented in a limited number of hospitals since 2011, and this might lead to increases in disease detection rates and the reliability of disease burden information [45]. In Argentina, since 1960, it has been compulsory for provincial public hospitals to report cases of MD to the Argentinian National Surveillance System [9]. In recent years, some improvements have been made and laboratory-based surveillance of invasive MD has been carried out by a national surveillance network, comprising 74 laboratories covering 23 provinces, and the National Reference Laboratory (Administración Nacional de Laboratorios e Institutos de Salud [ANLIS]) [46]. ANLIS is part of the SIREVA II surveillance network. Paraguay (also part of SIREVA II) has a surveillance system that includes molecular techniques. Most of the molecular techniques are performed at a central public health

Table 4
Incidence rates of meningococcal disease before and after meningococcal C conjugate vaccination in Brazil, 2008–2012 [41], copyright© 2014 Oxford University Press, reproduced by permission of Oxford University Press on behalf of the Pediatric Infectious Diseases Society.

Age groups (years)	Incidence rates (cases/100,000 population)				
	2008–2010	2011	Reduction (95% CI)	2012	Reduction (95% CI)
<1	13.5	10.8	20% (14–27)	7.9	42% (34–49)
1	7.2	4.2	42% (31–51)	2.9	60% (48–71)
2	5.8	5.1	12% (2–21)	2.5	57% (44–69)
3	5.5	5.6	–	4.0	27% (17–38)
4	4.2	5.1	–	4.5	–
5–9	2.7	2.9	–	2.7	–
10–14	1.9	1.8	–	1.8	–
15–19	1.4	1.7	–	1.6	–
20–29	0.8	0.9	–	0.8	–
30–39	0.6	0.6	–	0.7	–
40–49	0.6	0.7	–	0.8	–
50–59	0.5	0.7	–	0.6	–
≥60	0.4	0.6	–	0.5	–
Total	1.52	1.47	–	1.3	15% (12–17)

CI, confidence interval.

laboratory where all samples are sent for typing, however, PCR is currently performed in three centers.

5.1.2. Vaccine introduction and financing

The introduction of meningococcal vaccines into NIPs across Latin America in the past few years can be seen as an important achievement in the control of MD. However, there remain significant challenges in ensuring that the best strategies, both in terms of public health impact and cost-effectiveness, are being implemented. For most countries, the high cost of novel vaccines, including meningococcal vaccines, significantly increases the cost of the NIPs. In some countries, such as Chile, meningococcal vaccines cost more than all the other vaccines in the NIPs altogether, which is why appropriate justifications for inclusion of meningococcal vaccines have become mandatory. However, cost-effectiveness studies are uncommon in the decision-making process in the majority of Latin American countries. Currently, inclusion of meningococcal vaccines in NIPs in countries with relatively good surveillance, such as Brazil and Chile, is providing good-quality information from which other similar countries may be able to extrapolate and learn. For example, it is becoming quite clear that the control of meningococcal serogroup C in Brazil will require implementation of catch-up vaccination strategies in the adolescent population (specific age groups will need to be defined and vaccinated, and the impact well monitored). Also in Brazil, all outbreak-reactive vaccinations against serogroup C disease occurring are being carried out with conjugate formulations rather than polysaccharides for all targeted age groups [47], and depending on the outcome, this may become the recommendation for the whole region. In Chile, the control of serogroup W will require additional strategies aimed at decreasing the number of cases in young infants and the elderly, as the strategy of vaccinating 1–5-year-olds has had a marked impact in this age group only [39,41]. Several new challenges are arising that will require evidence-based approaches generated through progressively improved surveillance systems, which will be key for improved policy decision-making processes.

Another key issue for improved vaccine use in Latin America is vaccine affordability, and consequently, access. The PAHO Revolving Fund is a strategic mechanism [48–50] that has played an important role in improving access to available vaccines at lower prices in Latin American (and Caribbean) countries. It works by allowing several countries with the same vaccine needs to apply for vaccine supplies together, increasing the overall order and resulting in a decreased vaccine cost. Indeed, in July 2013, during the XXI Meeting of PAHO's Technical Advisory Group on Vaccine-Preventable Diseases, several important recommendations were

made (see http://www.who.int/immunization/sage/meetings/2013/november/3_PAHO_TAG2013_FINAL-report.pdf) [51]. Based on these recommendations, it is likely that the PAHO Revolving Fund will now assist with increasing the implementation of meningococcal vaccination. Other novel financing arrangements allowing more affordable vaccines have also been implemented in some Latin American countries; in Argentina, for example, a national company has entered into joint ventures with foreign vaccine manufacturers able to provide technical expertise, so that vaccines can be produced at a lower cost.

5.2. Partially met and unmet needs

Although surveillance systems are in place in Latin America, a marked imbalance exists in the infrastructures and available resources. This imbalance continues to be a major barrier to adoption of the best preventative strategies, especially in the region's resource-deprived countries. The lack of sharing of surveillance data between local and national health authorities also remains an unmet need in many countries, such that it should be implemented in the areas where it is lacking and strengthened where already in place. Further improvements to the surveillance systems include the development of infrastructures that involve both clinical case detection as well as laboratory capacity to confirm and characterize *N. meningitidis*. Even though the SIREVA II network has assisted in this area, more work is required.

As mentioned, there is a lack of cost-effectiveness studies for the decision-making process in medicine regarding vaccines in Latin America. This lack of data is a major unmet need, and addressing this might bring more balance to the way vaccination is considered and carried out in the region. However, it should be recognized that it may be difficult to establish a cost-effectiveness argument for vaccination against a serious disease that has low prevalence, such as MD.

A number of other issues that need to be considered have been highlighted in the recent Joint Committee on Vaccination and Immunization position statement on meningococcal B vaccine in the United Kingdom [52]. These include the value society places on preventing disease in its youngest members, and potential litigation costs to health authorities associated with MD.

6. Recommendations for the control and prevention of meningococcal disease in Latin America

During its second Latin America Regional meeting, the GMI revisited the 2011 recommendations [6]. However, additional

Table 5

Updated Global Meningococcal Initiative recommendations for reducing the global burden of meningococcal disease (MD) in Latin America.

The establishment of a detailed and comprehensive national or regional surveillance system is critical to assess the epidemiology and the true disease burden of MD. In countries where limited information on the epidemiology of MD is available, the group recommends that active surveillance should be performed at selected sentinel sites. The data obtained can be used to estimate incidence rates of MD once the population under surveillance is characterized, and also provide more complete, detailed, and accurate data on serogroup distribution, sequelae, and CFR. The group supports standardization of laboratory procedures, including implementing molecular methods in routine testing, and reinforces the importance of establishing well-equipped sentinel and reference laboratories with properly trained personnel.

The group recommends adoption of a uniform case definition for MD. Supplementing PAHO criteria with diagnosis by PCR (where available) is necessary to improve surveillance in the region and facilitate data comparisons.

The group strongly supports the importance of maintaining laboratory-based surveillance relying on culture of CSF, blood, or other normally sterile body fluids from invasive MD cases. The use of molecular methods e.g., PCR and RT-PCR, provides results more rapidly than culture and improves detection rates from antibiotic-containing samples, and should supplement, not replace, culture methods. The availability of a representative proportion of isolates from invasive disease cases allows the determination of serogroup, and phenotypic and genotypic characterization of the strains, including antimicrobial resistance, and is of paramount importance in obtaining reliable information on the circulating strains in the region.

Replacement of polysaccharide vaccines with conjugate formulations (wherever possible) for outbreak control is still relevant. Recent experience in Brazil showed that the use of polysaccharide A/C vaccination was effective in controlling an outbreak of serogroup C disease that occurred among workers from an oil refinery [36]. However, the polysaccharide A/C vaccine had no effect on carriage and did not interrupt transmission to susceptible contacts. New cases of MD continued to occur in household contacts of vaccinated workers. These results represent a challenge to the previous policy of using the meningococcal polysaccharide A/C vaccine to control outbreaks of serogroup C MD, emphasizing the need to consider using MCC vaccines rather than meningococcal polysaccharide A/C vaccines to control serogroup C MD outbreaks.

Specific recommendations for vaccination of high-risk groups should be developed (where possible) that can be used throughout Latin America. For these high-risk groups, the quadrivalent (ACWY) conjugate vaccines should be the preferred vaccine. Once new protein-recombinant meningococcal vaccines become available, they should also be recommended for these patients. High-risk groups include those with complement deficiency, immunodeficiency (including functional and anatomic asplenia and HIV), and those at occupational risk, such as those working with microbiologic samples or in the military.

The group supports the conduct of cost-effectiveness studies in Latin America. Ideally, cost-effectiveness analyses would be based on US or European models, populated using data for the Latin American countries, and funded by organizations such as PAHO.

The group recommends closely monitoring and evaluating vaccination strategies implemented in selected countries in order to determine their impact and limitations. Sharing information can lead to the adoption of similar or improved strategies in countries confronting new epidemiologic situations.

Vaccination should be provided, whenever possible, free of charge to those traveling to endemic areas.

CFR, case fatality rate; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; MCC, meningococcal C conjugate; PAHO, Pan American Health Organization; PCR, polymerase chain reaction; RT-PCR, real-time polymerase chain reaction.

issues were addressed during the meeting and updated recommendations were proposed, not only to improve our understanding of the epidemiology of MD but also to reduce its public health impact in Latin America (Table 5) [47].

Author contributions

MAPS and MO wrote the initial draft of the manuscript. All authors have revised and reviewed the manuscript, and approved the final version.

Conflict of interest

The authors are all members of the Global Meningococcal Initiative (GMI). The GMI is funded by an educational grant from Sanofi Pasteur; however, the group is not led in any way by the company. GMI members determine meeting agenda items and lead the discussions and outputs. Sanofi Pasteur representatives may attend the meetings, but in the role of observers only, and they do not influence the findings of the group.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2015.10.055>.

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