The current situation of meningococcal disease in Latin America and recommendations for a new case definition from the Global Meningococcal Initiative

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Meningococcal disease (MD) is a serious, rapidly developing and potentially fatal infection. The causative bacterium for endemic and epidemic MD is *Neisseria meningitidis* [1]. Invasive disease is characterized by one or more clinical syndromes including bacteremia, sepsis or meningitis, the latter being the most common presentation. Pneumonia, conjunctivitis, arthritis, pericarditis and myocarditis are less common manifestations of *N. meningitidis* infection. In general, the highest incidence rates of MD are observed in children <1 year of age, both across the globe and in Latin America [2,3]. Additionally, in some areas of the world, other high incidence peaks are observed among adolescents (16 through 21 years of age [4–7]) (but this is not seen in all countries [8–10]) and older adults, that is, those aged ≥65 years [11]. Indeed, MD affects people of all ages, from the very young to the elderly across the globe, as well as in Latin America. However, the proportion of cases caused by each serogroup varies according to age group. Serogroup B *N. meningitidis* tends to be more prevalent among infants and young children, while serogroup Y affects more older individuals [3,12].

In general, six meningococcal serogroups (A, B, C, W-135, X and Y) are the etiological agents for nearly all clinical cases of MD [13]. However, the quality and the reliability of the information on MD are not uniform across the world. The reasons for this include, but are not limited to, differences in surveillance practices (or lack thereof), use of different diagnostic...
methods and protocols and application of different meningococcal case definitions.

Vaccination is considered the best strategy for MD prevention [14]. There are available meningococcal conjugate vaccines against serogroups A, C, W-135 and Y [11]. Vaccines composed of outer membrane vesicles (OMV) against serogroup B are also available and have proved to be efficacious to control specific outbreaks or epidemics. However, their modest immunogenicity in young children, short duration of protection and narrow strain specificity are limiting factors for their usefulness [15]. Recently, new serogroup B vaccines developed by reverse vaccinology or recombinant technology have shown high immunogenicity in children and adolescents in Phase II/III studies [16–18], and one such vaccine has already obtained marketing authorization and is approved for use in Europe [101]. These vaccines are expected to be available globally in the next few years.

The Global Meningococcal Initiative (GMI), founded in 2009, is led by a group of international scientists and clinicians with expertise in meningococcal immunity, microbiology, epidemiology, public health and vaccination. Its purpose is to promote MD prevention worldwide through education, research, international cooperation and vaccination. The GMI has proposed several recommendations to reduce the worldwide burden of MD [2] (Table 1). Because of geographic and temporal variations in disease, the GMI convened a roundtable meeting with 11 experts from seven Latin American countries (Argentina, Brazil, Chile, Dominican Republic, Mexico, Panama and Uruguay). As the epidemiology of MD in Latin America recently had been reviewed [3,19], the meeting’s primary objective was to tailor the global GMI recommendations to the region. Additionally, as robust, uniform epidemiologic data are required to make informed health policy decisions that result in the introduction and expanded use of life-saving meningococcal vaccines, a consensus-based meningococcal case definition for use throughout Latin America was proposed.

Table 1. Global Meningococcal Initiative recommendations for reducing the global burden of meningococcal disease.

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country-specific approaches to vaccine prevention are needed because of geographic and temporal variations in disease epidemiology</td>
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<tr>
<td>Country-specific meningococcal policy should be based on local epidemiology and economic considerations</td>
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<tr>
<td>Continued funding of the introduction of MenAfriVac™ is an important global and regional public health priority</td>
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<td>The MVP model should be considered when developing other products with markets that are primarily or exclusively in developing countries</td>
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<tr>
<td>Travelers to high-risk areas should be vaccinated against MD</td>
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<tr>
<td>Vaccines against all clinically relevant meningococcal serogroups (A, B, C, W-135, X and Y) should be developed</td>
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<tr>
<td>Conjugate vaccines should replace polysaccharide vaccines wherever possible, but polysaccharide vaccines are still recommended where conjugate vaccines are not available</td>
</tr>
<tr>
<td>Laboratory-based surveillance for MD should be strengthened (or initiated) to determine the true burden of disease</td>
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</table>

In Latin America, MD surveillance is largely passive, with heterogeneous reporting confounding inter-country epidemiologic comparisons. Moreover, concern exists over how representative the collected information is in terms of disease epidemiology, with a potential underestimation of the true burden of MD in the majority of the countries in the region, which can negatively impact data quality and hamper evidence-based health policy. However, since 2010, countries qualifying for Global Alliance for Vaccines and Immunization (GAVI) support – in partnership with the Family and Community Health (FCH/IM) unit at the Pan American Health Organization (PAHO) – have been strengthening existing surveillance and actively monitoring etiologic agents of meningitis and pneumonia, particularly in children <5 years of age [102,103].

In 1993, PAHO and WHO implemented a Latin American laboratory-based passive surveillance program, named SIREVA, initially for cases of invasive Streptococcus pneumoniae infection. This network was extended in 1999 to cases of Haemophilus influenzae and in 2000 to cases of N. meningitidis. Currently, SIREVA II performs a systematic analysis of isolates recovered by the epidemiological survey network from countries in the Latin American and Caribbean region. The Instituto de Salud Carlos III, in Spain, is the international reference center, and the Adolfo Lutz Institute in São Paulo, Brazil, is the regional reference laboratory responsible for N. meningitidis characterization and other tests [20].

Laboratory-based diagnosis of suspected cases of MD in Latin America occurs almost exclusively via culture, in the absence of a standardized strategy based on nucleic acid amplification techniques and meningococcal genotype studies. However, previous antibiotic use is a risk factor for culture negativity [21], contributing to disease underreporting. Several countries in Latin America have regions with limited access to laboratory equipment and facilities, affecting the quality of the sample processing. Moreover, some hospitals cannot spare the funds to transport samples, further contributing to MD underreporting.

The Pan American Health and Education Foundation (PAHEF) Surveillance Study seeks to improve the surveillance and characterization of MD in Latin America and the Caribbean [104]. One of the first steps in improving surveillance is the standardization of case definitions for the disease.
Despite the existence of a PAHO-recommended case definition for MD in the region, the countries of Latin America employ different case definitions, complicating intercountry comparisons (Table 2). The attendees of the GMI Latin America Roundtable Meeting regarded the restrictive case definition criteria for MD in some countries, such as Mexico, as one of the potential determinants for the exceedingly low rates consistently reported in these countries. Evidence in support of this assumption is the recent increase in the number of cases detected after the implementation of multiplex PCR in Mexico City [23].

**Epidemiology**

As the epidemiology of MD in Latin America has been thoroughly and recently reviewed [3,19], only a brief overview will be provided here. In Latin America, the incidence of MD varies from <0.1 cases per 100,000 in countries including Mexico, Paraguay, Peru and Bolivia to almost two cases per 100,000 in Brazil. Although current estimates suggest that Brazil, together with the countries from the southern cone (Uruguay, Argentina and Chile), bear the highest burden of MD in Latin America, this rate may be the result of ascertainment bias. These countries, relative to others in the region, have a more robust surveillance system in place for MD and established laboratory infrastructure. In Brazil, for example, access to molecular diagnostics is available in sentinel sites in the state of São Paulo. In fact, the introduction of multiplex real-time PCR (RT-PCR) assay testing for *S. pneumoniae*, *N. meningitidis* and *H. influenzae* type B in sentinel hospitals in São Paulo provided an increase in the diagnostic yield for bacterial meningitis by 52, 85 and 20%, respectively, over culture-based methods [21]. In 2010, only a single isolate of *N. meningitidis* was reported to SIREVA from four Latin American countries: Costa Rica (serogroup Y), Ecuador (serogroup C), Nicaragua (serogroup B) and Peru (serogroup W-135 [183]), another likely illustration of ascertainment bias. However, although RT-PCR is the ideal, conventional PCR systems may be somewhat advantageous in some situations due to lower cost and ease of implementation [24] or in areas where RT-PCR facilities are not available.

Among the countries where information on incidence rates of MD is available, the highest burden of disease is consistently reported in infants and children younger than 5 years of age.

### Table 2. Meningococcal meningitis and meningococcemia case definitions in a number of Latin American countries.

| Country      | Probable: person with compatible disease and purpura fulminans or antigen detection in CSF | Suspected: acute onset with high fever, meningeal syndrome, petechial or purpuric exanthem | Confirmed: person with compatible disease and isolation of *Neisseria meningitidis* from a normally sterile site or detection of *N. meningitidis* antigen in blood, CSF or other normally sterile site | Brazil Clinical: >1 year of age: fever, severe headache, vomiting, stiff neck, signs of meningeal irritation, seizures and/or red spots on the body; <1 year of age: irritability, persistent crying or bulging fontanelle | Confirmed: isolation of *N. meningitidis* from blood, CSF or skin lesion or detection of *N. meningitidis* antigen in blood or CSF or detection of intracellular Gram-negative diplococci or detection of bacterial DNA by RT-PCR or epidemiologic link with a laboratory-confirmed case or disease compatible with meningococccemia with petechial rash | Mexico Suspected: >1 year of age: fever (>38°C) and headache and vomiting and ≥ one of the following: stiff neck, altered consciousness, Kernig or Brudzinski sign or petechial or purpuric rash; <1 year of age: fever accompanied by bulging fontanelle, vomiting, drowsiness, irritability, seizures (with or without petechial rash) | Confirmed: isolation of *N. meningitidis* from normally sterile site or detection of *N. meningitidis* DNA in blood or CSF by RT-PCR OR epidemiologic link with a laboratory-confirmed case | Panama Meningococcal meningitis: any illness with sudden onset of fever and ≥ one of the following: stiff neck, altered consciousness, other meningeal sign or petechial or purpuric rash | Meningococcemia: sudden febrile episode with some kind of hemorrhagic rash and negative IgM against dengue | Confirmed: positive culture or epidemiologic link with a laboratory-confirmed case | PAHO Suspected: a case that meets the clinical case definition (an illness with sudden onset of fever (>38.5°C rectal or >38.0°C axillary) and ≥ one of the following: neck stiffness, altered consciousness, other meningeal sign or petechial or purpuric rash. For patients <1 year of age, suspect meningitis when fever accompanied by bulging fontanelle) | Probable: a suspected case as defined above and turbid CSF (with or without positive Gram stain) or occurring during an ongoing epidemic and with an epidemiologic link to a confirmed case | Confirmed: a suspected or probable case with laboratory confirmation (either detection of bacterial antigen(s) in CSF or positive culture) |
|--------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Argentina    |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |
| Brazil       |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |
| Chile        |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |
| Mexico       |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |
| Panama       |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |
| PAHO         |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |                                                                                                                                                             |

*In some hospitals, buffy coat smears are tested, particularly in patients with suspected meningococccemia and known previous antibiotic use.*

**CSF:** Cerebrospinal fluid; **PAHO:** Pan American Health Organization.

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**Epidemiology**

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Among the countries where information on incidence rates of MD is available, the highest burden of disease is consistently reported in infants and children younger than 5 years of age.
However, during epidemics and outbreaks (the majority of them associated with serogroup C and reported in Brazil, but also an outbreak of serogroup B in Argentina in 1993–1994), an increase in the incidence rates in adolescents and young adults is observed.

Regarding serogroup distribution, serogroups B and C have been responsible for the majority of cases reported in the region for the past two decades, although this may be biased as the vast majority of data come from Brazil. Serogroup B has been the prevalent cause of disease in Chile, Uruguay and Colombia, although a decreasing trend in the incidence rates of serogroup B has been observed in Latin America in recent years [19]. Serogroup Y has also been predominant in Colombia for several years. Serogroup W-135 has emerged in Argentina and Chile, with the prevalence of this serogroup increasing from no cases in 2001 to 34% of total cases in 2011 and 55% of all cases identified by December 2012 within Chile, with an increase in the case fatality rates from 10–15% (expected for the disease) to 26% in 2012 [105,106] and from 2% of cases with confirmed serogroup in 2000 to 50% in 2010 within Argentina [25]. Clusters of MD cases resulting from serogroup W-135 have also been reported in Brazil. The emergence of serogroup W-135 in Latin America is related to the hypervirulent Hajj clone W-135:P1.5,2:ST-11 (ST-11/ET-37 clonal complex), which emerged and has spread internationally since 2000 [26].

In Brazil, from 2002 onward, a significant increase in the proportion of cases attributed to serogroup C, associated with the ST-103 complex, has been observed and, currently, serogroup C is the most frequent serogroup causing MD in Brazil [26]. Serogroup C is also the predominant cause of disease in Mexico, Central America and the Caribbean. In the Andean region, limited information is available, although serogroups B and Y appear to be predominant in Colombia. Serogroup A has virtually disappeared from Latin America (Figure 1, based on the data from the 2011 SIREVA II report [20,103]).

Before implementing meningococcal vaccination strategies in the region, it is of paramount importance to have better information on representative carriage prevalence studies. This will have important implications in future vaccination strategies, optimizing the indirect effects provided by meningococcal C conjugate vaccines and also by other meningococcal vaccines with potential to induce indirect protection.

Carriage prevalence studies proved to be crucial to understanding the dynamics of carriage and disease and also the potential effect of control programs, such as vaccination, on the
transmission of meningococci. European and North American studies showed that age was a key factor influencing meningococcal carriage rates. In these studies, carriage rates were low in young children, increasing in teenagers and reaching a peak in older adolescents and young adults, and then declining in adulthood [27]. However, it is important to acknowledge that very limited published data describing carriage prevalence of *N. meningitidis* in Latin America are currently available.

**Vaccination**

Polysaccharide, conjugate and OMV-based vaccines are available in Latin America (Table 3). Conjugate vaccines offer a number of advantages over polysaccharide formulations. The conjugation of polysaccharides with carrier proteins alters the nature of the anti-polysaccharide response to a T-dependent response, inducing the production of high levels of antibodies (even in infants), higher antibody avidity and increased serum bactericidal activity. The formation of populations of memory B lymphocytes, of long duration, provides an excellent anamnestic response (booster effect) on re-exposure. Furthermore, these vaccines have the ability to reduce nasopharyngeal colonization by serogroup C *N. meningitidis*, reducing the number of carriers among the vaccinated and, therefore, the spread of the disease in the population (indirect immunity or herd protection [1]).

Meningococcal C conjugate vaccines and quadrivalent A, C, W-135 and Y meningococcal conjugate vaccines are available in the private sector in Argentina, Brazil, Bolivia, Chile, Colombia, Costa Rica, Guatemala, Panama and Peru. In Argentina, quadrivalent meningococcal conjugate vaccines are available (without cost) to individuals at high risk of disease. In response to an increase in the number of serogroup W-135 cases in Chile during 2012 (incidence rates of serogroup W-135 disease were approximately three-times higher in 2012 compared with 2011), an immunization program in children aged between 9 months and 5 years old, with quadrivalent meningococcal conjugate vaccines, has recently been implemented [107]. These vaccines are also available to control outbreaks and epidemics.

Meningococcal vaccine use and scheduling vary by country. However, Cuba and Brazil are the only countries in Latin America with universal MD vaccine recommendations. In fact, Cuba was the first country in the Americas to implement mass vaccination against MD, specifically against serogroup B [28]. Cuba introduced a locally produced serogroup B OMV plus a serogroup C polysaccharide vaccine (VA-MENGOC-BC) in a catch-up campaign targeting individuals aged 3 months to 24 years in 1990. The program achieved 95% coverage. Since 1991, this vaccine has been routinely administered to infants at 3 and 5 months of age, as part of the national immunization schedule. In 2008, Cuba reported a low incidence of MD (0.1/100,000 inhabitants), but only a few isolates were sent to SIREVA II for analysis[29]. Most cases of MD that have occurred in Cuba since the availability of the OMV vaccine have been caused by ST-33 strains, with the same phenotype (B:4:P1.19,15) as the strain included in VA-MENGOC-BC [29].

In response to an increase in the amount of disease attributable to serogroup C, Brazil began to routinely immunize infants (two doses at 3 and 5 months plus a booster dose at 12–15 months) and toddlers (one dose between 12 and 23 months) with a meningococcal C conjugate vaccine in September 2010 [12]. Coverage for the two primary doses was >90% in late 2011, and a population-based analysis showed a 30% decrease in MD rates in this cohort, a significant early reduction relative to prevaccine disease incidence [26]. Mathematical modeling has shown the routine immunization of Brazilian infants against serogroup C to be cost effective [30], but no catch-up campaign of older age groups was done due to cost and resourcing constraints [12]. As a consequence, only the burden of MD borne by those <2 years of age is anticipated to be impacted in the immediate period after vaccine introduction.

**Outbreak management**

In most situations, the number of cases of MD during an outbreak is not substantial, emphasizing the importance of a well-established surveillance system, with quality information on baseline

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**Table 3. Meningococcal vaccine availability in the public and/or private markets in a number of Latin American countries.**

<table>
<thead>
<tr>
<th>Country</th>
<th>Polysaccharide</th>
<th>Conjugate</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td></td>
<td>C, ACWY</td>
<td>BC</td>
</tr>
<tr>
<td>Bolivia</td>
<td></td>
<td>ACWY</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>AC</td>
<td>C, Hib-C, ACWY</td>
<td>BC</td>
</tr>
<tr>
<td>Chile</td>
<td></td>
<td>C, ACWY</td>
<td></td>
</tr>
<tr>
<td>Colombia</td>
<td></td>
<td>ACWY</td>
<td>BC</td>
</tr>
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<td>ACWY</td>
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</tr>
<tr>
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<td>BC</td>
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<tr>
<td>Dominican Republic</td>
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<td>ACWY</td>
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<tr>
<td>Ecuador</td>
<td></td>
<td>AC</td>
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<tr>
<td>Guatemala</td>
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<td>Mexico</td>
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<td>Panama</td>
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<tr>
<td>Paraguay</td>
<td>AC</td>
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<tr>
<td>Peru</td>
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<td>ACWY</td>
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<tr>
<td>Venezuela</td>
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</tbody>
</table>

AC: Polysaccharide vaccine against *Neisseria meningitidis* serogroups A and C; ACWY: Polysaccharide or conjugate vaccine against *N. meningitidis* serogroups A, C, W-135 and Y; C: Conjugate vaccine against *N. meningitidis* serogroup C; Hib-C: Conjugate vaccine against *N. meningitidis* serogroup C and *Haemophilus influenzae* type B; BC: *N. meningitidis* serogroup B outer membrane vesicles (OMV) plus a serogroup C polysaccharide vaccine.
patterns of disease that can identify whether the occurrence of cases represents an outbreak.

PAHO defines an epidemic/outbreak as occurring or likely to occur in areas considered hyperendemic when an average of 15 cases per 100,000 per week occur over 2 consecutive weeks. Once epidemic disease is detected in a given area, a lower value (e.g., five cases/100,000 per week) may be used as a threshold in contiguous areas. In non-hyperendemic areas, the occurrence of an epidemic can be defined when a three to fourfold increase in disease incidence relative to previous years or a doubling in the number of cases from 1 week to the next over 3 weeks is observed [31] (however, other thresholds have been proposed [32]). In general, outbreaks are difficult to declare in countries with scant information on endemic disease, underscoring the need for improvements in case reporting and laboratory capabilities.

Outbreak preparedness and responses vary from one Latin American country to the next and are dependent on local disease epidemiology and policies (Figure 2). However, containment efforts that have been employed in the region include augmented disease monitoring; chemoprophylaxis of close contacts (such as, household contacts; other close contacts, especially children (school contacts, people who have eaten or slept with the patient at least 4 h a day within a radius of 1 m in the 7 days preceding illness onset); health workers in contact with the patient’s oral secretions (e.g., mouth-to-mouth resuscitation) and reactive vaccination to the population age groups with higher risk of disease.

In Brazil, recent serogroup C MD outbreaks are typically contained via chemoprophylaxis of close contacts and reactive vaccination of high-risk groups if the attack rate exceeds 10 cases/100,000 population over a 3-month period (three or more confirmed or probable primary cases of MD of the same serogroup). The population at risk is used as the denominator in calculations of the disease attack rate. The population at risk is usually defined on the basis of organizational affiliation or community of residence. Outbreaks can be classified as organization-based (common affiliation but no close contact with each other, e.g., a school or a university) or community-based (persons residing in the same area who are not close contacts of each other and who do not share a common affiliation). Given the poor immunogenicity of polysaccharide vaccines in infants and young children, meningococcal C conjugate vaccines are administered to those <2 years of age, while meningococcal A/C polysaccharide formulations are given to those ≥2 years of age [33]. Although reactive meningococcal A/C polysaccharide vaccination prevented new cases of disease among vaccinated workers during an organization-based outbreak at a food-processing facility in Midwestern Brazil, it did not prevent the surrounding community from experiencing an attack rate of 12 cases per 100,000 [32]. Reactive vaccination has also failed to control serogroup A meningococcal epidemics in the African Meningitis Belt [33,34]. Reactive vaccination has met with limited success because it is difficult to determine when sporadic disease incidence becomes an outbreak, especially in countries without routine disease surveillance. Second, there may be delays in acquiring and/or shortages in vaccine supply and manpower to initiate any proposed reactive immunization strategy [34]. Mathematical modeling of MD in the African Meningitis Belt has shown that preventative vaccination in these settings is more cost effective than reactive immunization, avoiding more cases of disease and costing less per case [35].

**GMI recommendations**

**Surveillance**

As inadequate surveillance and heterogeneous reporting severely hamper evidence-based immunization policy, the GMI encourages 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; the introduction of quality controls, so that data from different laboratories can be harmonized; consistent and universal use of standardized diagnostic protocols, such as those set forth by SIREVA II or PAHO; 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) and the implementation of active population- and laboratory-based surveillance for invasive MD in determined sites to assist in early outbreak detection and estimation of age-specific incidence rates and serogroup distribution.

PAHO recognizes the utility of laboratory diagnostics in analyzing clinical samples [109], considering culture positivity and cerebrospinal fluid (CSF) antigen detection as acceptable confirmatory evidence of meningococcal infection [108]. However, given the potential for antibiotic-induced culture negativity and for prolonged transport times to compromise sample integrity, the GMI also endorses the use of PCR, at least at the National Reference Laboratory (NRL), but ideally at designated regional reference laboratories. PCR techniques have demonstrated a high impact on the diagnosis of MD [36]. However, the GMI understands that low-income countries may not have the resources to implement PCR techniques and therefore may need to continue with the PAHO confirmed case definition as it stands unless of course financial support can be identified.

The GMI acknowledges that if a case definition does not include a requirement for laboratory confirmation, it would be difficult for Latin American hospitals to justify the costs of such tests. To this end, there was unanimous agreement among the meeting attendees to amend the existing PAHO case definition for confirmed MD to include molecular diagnostic techniques, like PCR, if available (RT-RCR if possible) (Table 4). RT-PCR is associated with high sensitivity and specificity for N. meningitidis [37–40], especially relative to culture-based detection methods [38,39,41]. Even when the organisms are nonviable after antibiotic treatment, PCR can still detect N. meningitidis DNA [21].

As mentioned, laboratory infrastructure is limited in many parts of the region. Although some countries have NRLs, they are not intended to serve as central processing/diagnostic facilities, but rather to lend guidance to smaller institutions, train staff and oversee quality control. Having multiple laboratories coordinated by a NRL would alleviate resource constraints and promote the generation of more robust, uniform epidemiologic data. Data generated at satellite laboratories can then be sent to the NRL for
Figure 2. Outbreak preparedness and response in a number of Latin American countries.
collation. To minimize costs, equipment and manpower dedicated to the monitoring of other infectious organisms could be coopted for MD surveillance. Multiplexed versions of RT-PCR that simultaneously target \textit{N. meningitidis}, \textit{S. pneumoniae} and \textit{H. influenzae} have been developed \cite{41}. Another solution lies in the forging of partnerships between resource-rich and resource-constrained countries. Such relationships are not without precedent in the region: the Instituto Nacional de Salud (Bogotá, Colombia), the Instituto Adolfo Lutz (São Paulo, Brazil) and other regional NRLs participate in an international quality assurance program with the Instituto de Salud Carlos III in Madrid, Spain \cite{3,8,10}.

In an effort to reduce bias and to gain a more accurate understanding of the burden of MD in Latin America, the GMI recommends that >50\% of a country’s suspected clinical cases be sent for central processing and that samples derive from different areas (i.e., urban and rural locales) and different hospital types (e.g., pediatric and general) to be representative. In many Latin American countries, the proportion of clinical samples being sent to NRLs is unacceptably low. For example, in Colombia, only 27\% of the total samples of meningococcal isolates recorded nationally were analyzed at the NRL \cite{8,10}. The corresponding values for isolates received at the NRLs in Argentina, Brazil, Chile and Costa Rica were 45, 25, 65 and 40\%, respectively \cite{10}. Moreover, in Argentina, pediatric hospital facilities are known to be overrepresented at the NRL, biasing data toward children \cite{10,25}.

**Outbreak prevention**

The GMI and local representatives unanimously supported the replacement of polysaccharide vaccines with conjugate formulations, wherever possible. Because infants and young children bear the highest burden of MD in a number of Latin American countries \cite{103}, use of vaccines that stimulate adequate immune responses are desired. Meningococcal C conjugate vaccines have proved to be immunogenic in children <2 years of age \cite{1}. In contrast to conjugate vaccines, serogroup C polysaccharide vaccines lack satisfactory immunogenicity in infants and are associated with hyporesponsiveness, a phenomenon by which immune responses are blunted upon revaccination \cite{1,42,43}. Conjugate vaccines may overcome – at least partially – the refractoriness associated with repeat administration of polysaccharide formulations \cite{44}. Moreover, in countries where serogroup C conjugate vaccines were introduced in large catch-up programs, including adolescents and young adults, they contributed to the development of herd immunity \cite{45,46}, a phenomenon whereby unvaccinated individuals are at a reduced risk of disease because those who have been vaccinated are less likely to carry and transmit \textit{N. meningitidis} \cite{1}. Although herd immunity has only been demonstrated in a population immunized with meningococcal C conjugate vaccine \cite{46}, this vaccination benefit is believed to extend to conjugate formulations targeting other meningococcal serogroups. In light of the recent demonstration of waning antibody titers a few years after being vaccinated \cite{47-52}, revaccination is necessary with conjugate vaccines, especially in places where herd immunity effects were not observed after vaccination.

As government decisions on vaccine policy are based (in part) on disease prevalence, robust epidemiologic data are needed. Disease perception and vaccine safety, cost and availability also play a role in such decisions. The GMI stresses that proposed vaccination policies against MD be country-specific and based on local disease dynamics and health priorities. Although an understanding of disease burden makes the implementation of immunization policy easier, vaccines have been introduced in Latin America using international data, such as those directed against rotavirus (Brazil) and human papillomavirus (HPV, Panama); pressure from academic societies and the press also played an important role in the availability of HPV vaccines to Panamanians. While robust epidemiologic data are always desirable, prophylactic strategies should be implemented prior to large numbers of fatalities. Recently, an increase in the number of cases of MD caused by serogroup W-135 in Chile led to a massive vaccination campaign in the country for children between 9 months and 5 years of age with the quadrivalent conjugate vaccine \cite{107}. Although more than 80\% of the cases were concentrated in the country’s metropolitan region, the impact of this national campaign will be seen in the coming months.

As vaccine costs are a concern in Latin America – as in other parts of the world – novel financing arrangements should be considered. For example, technology transfer agreements have been used to introduce vaccines against rotavirus \cite{110}, yellow fever \cite{53}, serogroup C MD \cite{12}, pneumococcal disease in Brazil \cite{53,54} and an influenza vaccine in Argentina with an Argentinean private laboratory drug producer, called Synergium Biotech, which represents a joint effort between Novartis, ELEA and Biogenesis Bagó. However, technology transfer requires that countries have the facilities and resources (human and technological) to manufacture vaccines. A provision allowing for the exportation of regionally produced vaccines to neighboring countries that lack manufacturing capabilities would further expand access to life-saving vaccines. The PAHO Revolving Fund, which purchases vaccines in bulk through the consolidation of orders from countries in the region, represents another innovative financial arrangement. A revolving fund facilitated the introduction of rotavirus vaccine to 12 Latin American and Caribbean countries \cite{55}. A third option lies in Advanced Market Commitments (AMC), which use donor funds, from nonprofit organizations, companies or countries, to supplement the costs associated with a certain amount of vaccine for a prespecified period of time. Such an arrangement resulted in US$1.5 billion being committed to incentivize manufacturers to supply pneumococcal vaccines that met specific criteria needed in developing countries at a lower price, and this allowed Nicaragua and other countries to receive these vaccines in 2010–2011 \cite{111}.

**Expert commentary**

MD remains an important health concern in Latin America, where high morbidity and mortality rates are still reported in many countries. Additionally, few countries have established surveillance programs, and the information gathered is not standardized. As accurate epidemiologic insight (i.e., disease burden, serogroup distribution and better characterization of the carrier...
Finally, although the authors report herein the challenges faced by Latin America and a case definition specific for the region, it should be remembered that the key conclusions and general recommendations can be extrapolated to all other regions of the world. Control efforts, for example, should always focus on educating physicians and regulators on the importance of the disease, its diagnosis, improving meningococcal surveillance and the need for uniform, quality data, and this should be a key aspect for consideration globally (indeed, a separate GMI meeting held in India identified similar key conclusions as noted herein for the Latin American region) [56]. Additionally, other regions should consider developing a uniform meningococcal case definition relevant to their needs to improve surveillance and facilitate data comparisons in that region.

Five-year view
MD will continue to be mostly endemic in Latin America, with periodic occurrences of outbreaks and epidemics in future years. It is possible that the recently observed increase of serogroup W-135 disease in Southern Brazil, Argentina and Chile (which was linked to the hypervirulent Hajj clone W-135:P1.5,2:ST-11 (ST-11/ET-37 clonal complex), that emerged in 2000 and has since spread internationally) will gain in importance and be observed in other Latin American countries. It is also likely that the increase in serogroup C disease reported in Brazil, associated with the ST-103 complex, where it currently represents 80% of cases, will also gain in importance and become widespread in the Latin American countries.

Although progress has already been made in improving and coordinating the surveillance of invasive disease in the region, with the implementation of a laboratory surveillance network (SIREVA), there is a clear need to improve and establish more uniform quality surveillance across the region and standardized case definitions. The establishment of sentinel-based active surveillance incorporating population-based data, the adoption of a universal case definition together with an expanded use of molecular-based diagnostic techniques into routine surveillance of invasive disease will be crucial for a better understanding of the true MD epidemiology in the region.

The authors anticipate increased use of the meningococcal multivalent conjugate vaccines in the Latin American region, replacing the use of polysaccharide vaccines in the near future. In particular, they believe these vaccines will be used for the control of outbreaks/epidemics, high-risk groups, travelers or even in routine immunization programs where the disease is hyperendemic. Over the next 5 years, it is also expected that currently investigation recombinant protein vaccines will be licensed.

With this in mind, the authors have developed a new case definition for MD, specific for the unique Latin American situation.

**Table 4. GMI-proposed universal case definition for meningococcal disease in Latin America (PAHO case definition plus, where available, confirmatory diagnosis by PCR).**

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<th>Suspected (positive)</th>
<th><strong>An illness with sudden onset of fever (&gt;38.5°C rectal or &gt;38.0°C axillary) and ≥one of the following: neck stiffness, altered consciousness, other meningeal sign or petechial or purpuric rash</strong></th>
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| For patients <1 year of age, MD should be suspected when fever is accompanied by bulging fontanelle | **Confirmed (≥one of the following)**
Detection of bacterial antigen(s) in CSF or
Positive bacterial culture or
Detection of bacterial DNA by PCR, where available

CSF: Cerebrospinal fluid; GMI: Global Meningococcal Initiative; MD: meningococcal disease; PAHO: Pan American Health Organization.
Adoption of this revised universal case definition over the next few years may:

- Improve surveillance in the region;
- Provide us with a better understanding of the true burden of disease in Latin America;
- Allow cross comparisons of epidemiological data;
- Improve evidence-based immunization policies;
- Enable vaccine and control strategies to be better tailored to region’s needs, thereby markedly reducing the burden and impact of disease.

Within the next 5 years, the authors also anticipate that enhanced surveillance and indeed surveillance networks in the Latin American region, combining laboratory and clinical reporting, will be further developed at all levels and enable better systematic gathering and collating of country and regional data. They also hope that mandatory reporting of the disease will be implemented in all Latin American countries in the coming years. To anticipate the potential coverage of the new recombinant protein-based Men B vaccines, baseline information on molecular and phenotypic characterization of the diverse invasive strains is needed. Together, this will provide us with a better understanding of the epidemiology of MD and may allow for the monitoring of the effectiveness and long-term impact of the new recombinant protein-based vaccines (once introduced in national immunization programs). The effect of recombinant protein Men B vaccines on carriage, yet not clearly defined, is likely to be an important factor in assessing their potential impact and cost–effectiveness across all age groups. These improved, and more encompassing, surveillance networks are likely to be formed by a number of strategic alliances, and to include passive and active sentinel surveillance methods. Additionally, once these newer vaccines are introduced the authors feel that in all likelihood PAHO will expand their surveillance recommendations, ensuring that individual countries and the Latin American region gather data using agreed standards and definitions. Such recommendations may include gathering of strain data, case numbers, among others, as well as vaccine-specific aspects such as vaccine failures, examination of defined correlates of protection and adverse event monitoring.

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Key issues

- The Global Meningococcal Initiative (GMI) is an international group of scientists and clinicians with expertise in meningococcal immunology, epidemiology, public health and vaccination that aims to promote meningococcal disease (MD) prevention worldwide.
- GMI representatives from seven Latin American countries discussed the burden of MD and vaccination practices/policies in the region.
- MD burden in Latin America was concluded to be largely underestimated. Serogroups B and C are dominant in the region, however, we have seen a recent emergence of serogroups W-135 and Y in several countries.
- 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, quality data.
- To improve surveillance in the region, and facilitate data comparisons, a uniform meningococcal case definition supplementing Pan American Health Organization (PAHO) criteria with diagnosis by PCR (where available) is proposed herein.

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**Websites**


Present situation of meningococcal disease in Latin America


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