

THE GLOBAL MENINGOCOCCAL INITIATIVE (GMI):

Efforts to control and prevent meningococcal disease in Latin America

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ABSTRACT

Background: The Global Meningococcal Initiative (GMI) is an international group of scientists and clinicians with expertise in meningococcal immunology, epidemiology, public health, and vaccinology. It aims to prevent meningococcal disease worldwide through education, research, cooperation, and vaccination. Given the marked geographical differences in disease epidemiology, prevention strategies should be country specific.

Methods: In May 2011, representatives from 7 Latin American countries participated in a GMI meeting, focusing on the burden of meningococcal disease and vaccination policies in the region.

Results: Meningococcal disease incidence varies widely (<0.1 [Mexico] to almost 2 cases [Brazil] per 100,000). Consistently, the highest age-specific incidence is in infants, with high case fatality rates reported (10–20%). Unlike in the US and Europe, there is no peak in adolescence, but during outbreaks increased case numbers among teenagers and young adults occur. Serogroups B and C are the dominant serogroups. Increases in serogroup W-135 and Y have recently been reported in some countries. Disease under-reporting/diagnosis is prevalent in Latin America. To facilitate comparisons across Latin America, a uniform meningococcal case definition combining World Health Organization criteria with diagnosis by reverse transcriptase polymerase chain reaction was recommended. Replacement of polysaccharide vaccines with conjugate formulations (wherever possible) was unanimously recommended. To reduce cost, technology transfer agreements with manufacturers should also be considered.

Conclusions: Meningococcal disease burden in Latin America is largely underestimated. Control efforts should focus on educating physicians and regulators on the importance of the disease, its diagnosis, and the need for uniform, quality data.

INTRODUCTION

- Neisseria meningitidis* is one of the leading causes of meningitis and septicemia worldwide, causing an estimated 500,000 cases of invasive disease and 50,000 deaths annually.¹
- Meningococcal disease is associated with high case fatality rates (10–20%) and substantial morbidity (up to 20% of survivors develop long-term sequelae including deafness, neurological deficit or limb amputation).^{2,3}
 - Although the disease is not common, occurring sporadically in most of the countries in the region, a single case of meningococcal disease frequently generates panic and fear among parents that is fueled by press coverage.
- Meningococcal disease incidence varies temporally and geographically, with the majority of disease occurring in the African Meningitis Belt.⁴
- Vaccination is considered the best strategy to prevent meningococcal disease. Plain polysaccharide (bivalent [MenAC], trivalent [MenACW], or tetravalent [MenACWY]), conjugate (monovalent [MenC] or tetravalent [MenACWY]), and serogroup B outer membrane vesicle (OMV) vaccines have been used and implemented in different countries to control outbreaks and epidemics or as part of routine immunization strategies.

THE GLOBAL MENINGOCOCCAL INITIATIVE

- The Global Meningococcal Initiative (GMI) was established to help prevent meningococcal disease worldwide through education, research, and cooperation. Issues are addressed at both global and regional levels.
- The GMI is supported by an unrestricted grant from Sanofi Pasteur.
- The GMI is a multidisciplinary group with expertise in public health, epidemiology/seroepidemiology, paediatrics, infectious disease, microbiology, and immunology.
- The GMI recommendations for preventing meningococcal disease are presented in **Table 1**.

TABLE 1. GMI Recommendations for Reducing the Global Burden of Meningococcal Disease⁵

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

- To gain insight into the burden of meningococcal disease and vaccination strategies employed in Latin America, the GMI convened its first Regional Roundtable Meeting on May 23–24, 2011 in Punta Cana, Dominican Republic.
 - The following Latin American countries were represented: Argentina, Brazil, Chile, Dominican Republic, Mexico, Panama, and Uruguay.

EPIDEMIOLOGY OF MENINGOCOCCAL DISEASE IN LATIN AMERICA

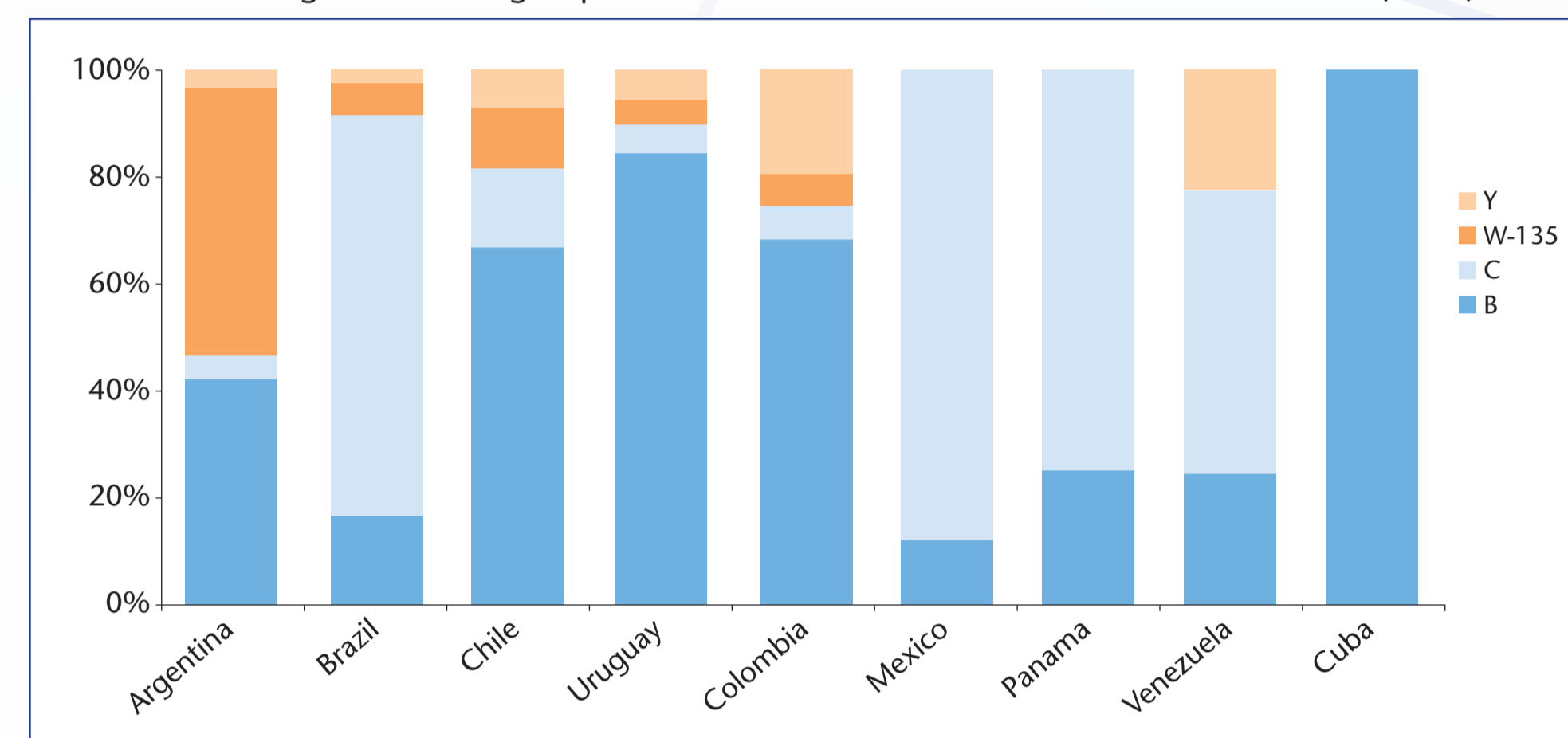
- Meningococcal disease incidence varies widely in Latin America⁶ (**Table 2**).
 - Some of these differences may be artefactual (ie, the result of discrepant surveillance practices).
- The highest age-specific incidence of meningococcal disease is consistently observed in infants <1 year of age.
- Unlike in Europe and North America, there is no peak in disease incidence among adolescents in endemic periods, but during outbreaks increased case numbers among teenagers and young adults are observed.

TABLE 2. Meningococcal Disease Incidence in Selected Countries in Latin America⁶

	Argentina	Brazil	Chile	Mexico	Panama
Incidence per 100,000	0.6	1.5–2	0.5	0.06	0.5–1

- The dominant serogroups in Latin America are B and C. However, increases in serogroups W-135 and Y have recently been reported in some countries: in 2010, serogroup W-135 became the prevalent serogroup in Argentina, responsible for 50% of all identified cases⁷ (**Figure 1**).

FIGURE 1. Meningococcal Serogroup Distribution in Selected Countries in Latin America (2010)⁷



VACCINES

- Polysaccharide, conjugate, and OMV-based meningococcal vaccines are available in Latin America (**Table 3**).
- The GMI Latin American Regional Roundtable attendees unanimously recommended the replacement of polysaccharide vaccines with conjugate formulations—wherever possible.

TABLE 3. Meningococcal Vaccine Availability in Selected Countries in Latin America

	Polysaccharide	Conjugate	Other
Argentina	MenAC	MenC MenACWY	
Brazil	MenAC	MenC MenACWY	MenB (OMV)/C
Chile	MenAC	MenC	
Mexico		MenC	
Panama	MenAC		

CURRENT VACCINATION STRATEGIES

- Brazil and Cuba are the only countries in Latin America with universal meningococcal vaccine recommendations:
 - Brazil: routine administration of MenC conjugate vaccine to infants at 3, 5, and 12 months of age
 - Cuba: routine administration of MenB (OMV)/C vaccine to infants at 3 and 5 months of age
- Although meningococcal vaccination is recommended in Argentina, it is not part of the National Immunization Program—only high-risk individuals receive MenACWY conjugate vaccine at no cost.
 - Meningococcal vaccines are available in the private sector in many Latin American countries.

VACCINATION POLICY

- Government decisions on vaccine policy are based on disease prevalence; disease perception; and vaccine safety, cost, and availability.
- In most countries, vaccination policies are crafted centrally by the Ministry of Health. Thus, the focus must be on national versus regional immunization programmes.
- As elsewhere, vaccine costs are a concern in Latin America.
 - Technology transfer agreements can lead to significant reductions in cost and are not without precedent in the region. Rotavirus vaccine, pneumococcal conjugate vaccine, and MenC conjugate vaccine were recently introduced to Brazil via technology transfer.
 - Technology transfer requires the country to have the facilities and resources to manufacture the vaccine.
 - Revolving funds should also be considered. The Revolving Fund of the Pan American Health Organization (PAHO) has been critical to the introduction of new vaccines in the region and to the Region of the Americas becoming a global role model for the successful implementation of immunization programmes.

SURVEILLANCE

- Meningococcal disease under-reporting and under-diagnosis are prevalent in the region, and information is not uniform.
- With the exception of specific regions within Chile, meningococcal disease surveillance in Latin America is passive.
- Confirmatory diagnosis of suspected cases of meningococcal disease occurs almost exclusively via bacterial culture. Bacterial culture may be subject to low sensitivity, especially if a patient used antibiotics prior to sample acquisition.
- True disease burden can only be determined through the supplementation of culture-based methods with molecular diagnostics, such as reverse transcriptase polymerase chain reaction (RT-PCR).
 - RT-PCR has been incorporated into the public health surveillance system in São Paulo State, Brazil, providing an additional yield of 85% over culture-based detection.
- To obtain accurate estimates of meningococcal disease, improvements are needed within laboratory and surveillance networks. Recommendations include
 - Reducing bias
 - ≥50% of all suspected meningococcal cases should be sent to a country's National Research Laboratory (NRL).
 - Samples should derive from different regions within a country (ie, urban and rural locales) and different types of hospitals.

- Implementing RT-PCR
 - Diagnoses based solely on clinical examination are not reliable because the clinical symptoms of meningococcal disease are not unique or always obvious.
 - Definitions that do not include laboratory diagnostics are not sufficiently specific to meningococcal disease.
- Standardizing diagnostic protocols
- Standardizing case definitions
 - Meningococcal case definitions vary from one Latin American country to another.
 - The case definition employed in Mexico is too restrictive, as evidenced by the:
 - Higher incidence of disease along the US border versus elsewhere in the country
 - Increase in the number of cases detected since the introduction of PCR in Mexico City.

A UNIFORM MENINGOCOCCAL CASE DEFINITION FOR LATIN AMERICA

- One way to improve surveillance—and thus gain a better understanding of the true burden of meningococcal disease in Latin America—is for the region to adopt a uniform meningococcal case definition.
- To obtain accurate disease estimates, molecular diagnostics (eg, RT-PCR) should supplement culture. However, if a case definition does not include a requirement for laboratory confirmation, it will be difficult for hospitals in the region to justify the costs of such tests.
- There was unanimous agreement among the attendees to amend the existing PAHO case definition for meningococcal disease to include confirmatory diagnosis by RT-PCR, as indicated in boldface in **Table 4**.

TABLE 4. GMI-Proposed Universal Case Definition for Meningococcal Disease in Latin America (PAHO Case Definition Plus Confirmatory Diagnosis by RT-PCR)

Clinical case definition ⁸
An illness with sudden onset of fever (>38.5°C rectal or >38.0°C axillary) and ≥1 of the following: neck stiffness, altered consciousness, other meningeal sign, or petechial or purpurral rash <ul style="list-style-type: none"> In patients <1 year of age, meningitis should be suspected when fever accompanied by bulging fontanelle.
Laboratory criteria for diagnosis
Positive CSF antigen detection or positive bacterial culture or detection of the bacterial genome by RT-PCR
Case classification
Suspected: A case that meets the clinical case definition.
Probable: A suspected case as defined above and turbid CSF (with or without positive Gram stain) or an ongoing epidemic and epidemiological link to a confirmed case.
Confirmed: A suspected or probable case with laboratory confirmation.

CSF, cerebrospinal fluid; RT-PCR, reverse transcriptase polymerase chain reaction

- However, access to laboratory equipment and facilities is limited in Latin America.
 - There is only one NRL in all of Argentina. It is unfeasible for one facility to process an entire country's samples. Moreover, sample quality is jeopardized by prolonged transit times (ie, those associated with travel from more distant regions to the central laboratory).
- Having multiple reference laboratories within a country will alleviate resource constraints and lead to the generation of more robust epidemiologic data. The GMI proposes that smaller laboratories be coordinated by the NRL.

PROPOSED RECOMMENDATIONS FOR THE PREVENTION OF MENINGOCOCCAL DISEASE IN LATIN AMERICA

- Replace polysaccharide vaccines with conjugate formulations—wherever possible.
- Improve disease recognition.
- Strengthen invasive meningococcal disease surveillance:
 - Employ RT-PCR and other laboratory methods, in addition to culture.
 - Expand use of Gram stain AND rapid test AND culture in smaller hospitals.
 - Expand laboratory capabilities beyond the largest cities through the establishment of sentinel AND reference laboratories.
 - Standardize sample acquisition and diagnostic protocols.
 - Share reference strains and clinical samples for quality control.
- Adopt a uniform case definition.
- Implement novel business models to reduce vaccine cost:
 - Technology transfer agreements
 - Revolving funds
 - Partnerships (eg, public-private, philanthropic)
- Develop vaccination policies specific to each country's disease epidemiology, resources, and health priorities.

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