EPIDEMIOLOGY AND RECOMMENDATIONS FOR CONTROL AND PREVENTION OF MENINGOCOCCAL DISEASE IN LATIN AMERICA: OUTCOMES OF THE GLOBAL MENINGOCOCCAL INITIATIVE MEETING

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INTRODUCTION

- *Neisseria meningitidis* remains a leading cause of meningitis and septicaemia worldwide, estimated to cause more than 1.2 million cases of invasive meningococcal disease (IMD) every year, and 135,000 deaths.[1,2]
- Meningococcal disease (MD) is associated with high case fatality rates (10–20%) and substantial morbidity.[3,4]
- MD incidence varies temporally and geographically, with the majority of disease occurring in the African meningitis belt.[5]
- Vaccination remains the best strategy to prevent meningococcal disease.

THE GLOBAL MENINGOCOCCAL INITIATIVE

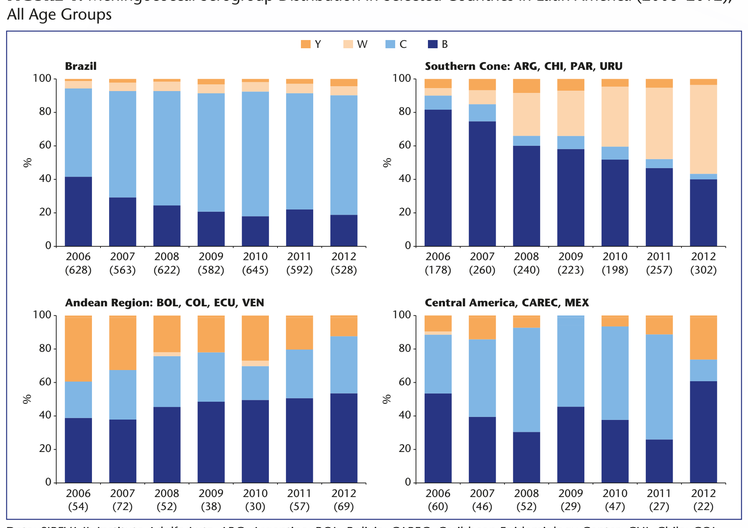
- The Global Meningococcal Initiative (GMI), supported by an unrestricted grant from Sanofi Pasteur, is a multidisciplinary group that was established in 2009 to help prevent MD worldwide.
- Live global and regional GMI meetings intend to promote education, research, and cooperation.
- A key paper has been published on the GMI recommendations for preventing MD (Harrison LH et al. The Global Meningococcal Initiative: recommendations for reducing the global burden of meningococcal disease. *Vaccine.* 2011;29(18):3363-71).[6]
- The latest Regional Roundtable Meeting was on June 25–26, 2013 in São Paulo, Brazil. The main objectives of this meeting were to gain further insight into the burden of MD, with a focus on serogroup W (formerly W-135), and to transfer knowledge to other Latin American countries in regard to the lessons learned from the Chilean outbreak situation and the Brazilian experience with meningococcal C vaccination.

MENINGOCOCCAL DISEASE IN LATIN AMERICA

Epidemiology

- MD incidence varies widely in Latin America.[7]
  - Data indicate, however, that serogroups B and C are dominant in the region, but an increase in the amount of disease attributable to serogroup W has been reported in several countries (eg, Argentina and Chile) (**Figure 1**).
  - Updated data regarding MD epidemiology in the region can be found at: http://www.paho.org/.
- The differences in incidence of MD across the Latin American region may be, in part, the result of discrepant surveillance practices.

FIGURE 1. Meningococcal Serogroup Distribution in Selected Countries in Latin America (2006–2012), All Age Groups



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.

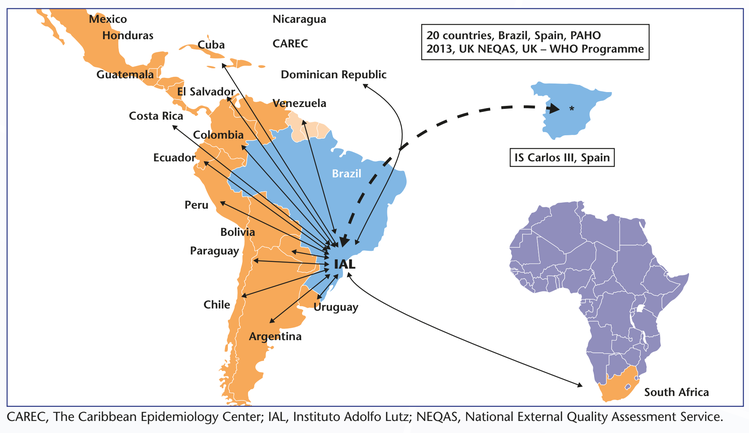
Vaccination

- Polysaccharide, conjugate, and OMV-based vaccines are available in Latin America. Meningococcal vaccine use and scheduling vary by country. Men C conjugate is licensed for use from 2 months of age. Men ACWY-D is currently licensed for use from 9 months of age. Additionally, by July 2013, Men ACWY-CRM had been licensed in the United States from 2 months of age and is currently being licensed in several countries in Latin America with a similar indication. Men ACWY-TT also is being licensed currently in some Latin America countries (from 1 year of age).
- Quadrivalent conjugate vaccines should be the preferred vaccine choice in the target populations.

Surveillance

- Different surveillance methods are utilized in the region, ie, with the exception of specific regions, MD surveillance in Latin America is passive and may be under-reported.
- The Pan American Health Organization (PAHO) proposed laboratory-based surveillance of invasive disease caused by *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *N. meningitidis* in Latin American and Caribbean countries.
  - This surveillance system, known as SIREVA (Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonías y Meningitis Bacterianas), initially focused on *S. pneumoniae* (1993–1999) and the surveillance was carried out in 6 countries (ie, SIREVA I). In 2000, the focus was expanded to include *H. influenzae* and *N. meningitidis*, and 20 countries are currently participating (SIREVA II) (**Figure 2**).

FIGURE 2. SIREVA II Network (2000–2013)



CAREC, The Caribbean Epidemiology Center; IAL, Instituto Adolfo Lutz; NEQAS, National External Quality Assessment Service.

Serogroup W in Latin America

- In 2004/2005, serogroup W first reached Southern Brazil and reached Argentina in the following year, when the number of cases attributed to this serogroup began to increase, becoming the prevalent serogroup now causing MD in Argentina.
  - Lessons can be gleaned from the situation in Chile to influence prevention and reduction of MD.
- Although serogroup W has now been reported in other Latin American countries, including Colombia, Paraguay, and Uruguay, significant increases are restricted to the Southern Cone at the moment.

The Chilean experience

Surveillance systems

- In Chile it is mandatory to report all suspicious clinical cases of MD. A suspicious case is defined as:
  - Patient with sudden fever ≥38°C and headache associated with:
    - Alteration of consciousness: drowsiness, confusion
    - Stiff neck
    - Signs of meningeal irritation (Brudzinski's and Kernig's signs)
    - Purpuric or petechial rash.
  - Cerebrospinal fluid (CSF) and culture are carried out locally.
    - All positive cultures and CSF should be referred to the public health centre if it adheres to definition of a suspicious case, where the result is confirmed and then sent out to all hospitals.
      - The information is also sent to the health ministry and regional ministerial centre.
      - Note: at the local level, if there is a suspicious sample, and CSF and blood culture are negative, the sample is referred to the Public Health Institute, and since May 23, 2013, polymerase chain reaction (PCR) is carried out on samples that are culture negative.
- Besides mandatory surveillance, there are other targets with which the health system must comply, such as:
  - Treating all contacts with chemoprophylaxis, within 24 hours after the patient has been hospitalized.

The epidemiology and disease burden of serogroup W

- Initially, few cases of disease attributable to serogroup W were observed in Chile. However, this number rose over the years and in 2012, 60 cases were reported.
  - More cases of serogroup W have already been identified in 2013 than were seen in all of 2012.
- Data show that:
  - All W cases submitted to characterization are sequence type (ST)-11 and accounted for 58.3% of cases in 2012 (the same ST as the strains of the Hajj-linked outbreak).
  - Strains are susceptible to antimicrobials such as chloramphenicol and beta lactams.
- In regard to MD caused by serogroup W:
  - The majority of cases (71.7%) presented as meningococcemia.
  - The fatality rate due to W is 28.6%.
    - The presence of diarrhoea is significantly associated with fatality.
    - The reason for the high fatality rate is unknown. However, it was suggested that a delay in diagnosis and management may play a part, as well as high rates of meningococcemia.
  - No secondary cases of W have been identified.
    - This could suggest that W has low transmissibility.

Containing the outbreak in Chile

- To contain the outbreak in Chile, it was necessary to develop a legal and organizational structure and institute technical resources (and economic incentives).
- In October 2012, strategic vaccination of children aged 9 months to 5 years was initiated.
  - Since October 2012, no case due to serogroup W has been identified in a vaccinated child in this age group.
  - By February 2013, coverage had reached 100% of the target population.
  - Cases occurring in adolescents are very low. Occurrence peaks in infants and the aging population, ie, those aged >60 years, with a high rate in those aged 3–4 months (19/100,000).
- The increase in the lethality of MD in Chile led to the reaction of the health authorities and the action plan for serogroup W.
  - The plan requires that the Ministry of Health and public health centres work together and provides an outline for combined surveillance.
  - The plans can be viewed online at: http://www.minsal.cl/portal/url/page/minsalcl/g_varios/boletin/meningitis/page_1.html.
- The Chilean experience has highlighted the importance of an integrated surveillance system, rapid response, and transparent dissemination of data to the public.

Brazil: Experience of Routine Immunization Against MD

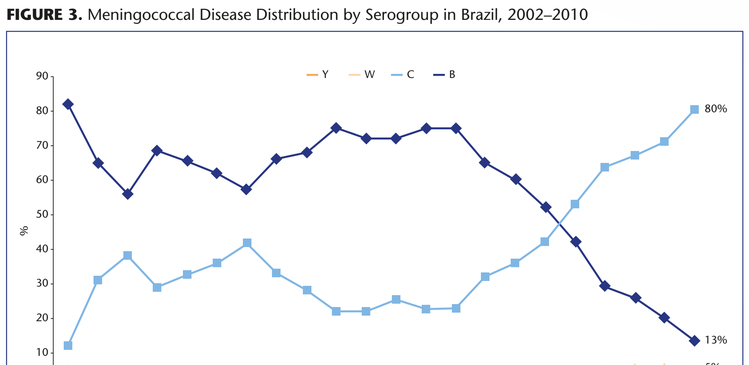
Epidemiology of MD in the pre-Men C routine vaccination era

- Men C conjugate vaccine was available in Brazil from 2001/2002 and was recommended for use in high-risk patients (funded by the government).
- By 2010, serogroup C accounted for the vast majority of MD cases (**Figure 3**).
- Case fatality rates due to MD in Brazil were approximately 20% between 2000 and 2010.
  - Higher incidence rates were observed in infants and young children.

Epidemiology of MD in the post-Men C vaccination era

- Brazil started vaccination of all children aged <2 years in late 2010 (2+1 schedule).
  - Infant immunization (3 and 5 months) with booster dose at 12 months
  - Children aged between 12 and 23 months: 1 dose
  - No catch-up campaign in older age groups
  - Coverage for the primary 2 doses was ~85% in late 2011 and 90–95% in 2012.

FIGURE 3. Meningococcal Disease Distribution by Serogroup in Brazil, 2002–2010



- To evaluate the early impact of vaccination, population-based surveillance data were analysed to examine trends in the burden of MD before and after the introduction of Men C conjugate vaccine. Changes in the incidence of MD in 2011 and 2012 were assessed against baseline values from 2001–2010.
  - Data showed:
    - In Brazil, there was a one-third reduction in the number of cases of MD in children aged < 2 years.
    - Additionally, the incidence rate of MD decreased by 15% (2008–2010 vs 2012; total population).
    - In São Paulo, the rates of MD in children aged <2 years declined from an average of 25.9/100,000 population in the pre-vaccination baseline period to 18.8/100,000 in 2011 and 10.9/100,000 in 2012 (**Figure 4**).
    - There were reductions of 27% and 55%, respectively, ($P<0.01$) in incidence rates in children aged <2 years.
    - Mortality rates of MD decreased in those aged <4 years following introduction of Men C vaccination in Brazil (by 35% in those <1 year of age and 50% in those aged 1–4 years).
    - In São Paulo, the number of deaths due to MD in children aged <2 years declined from an average of 72 in the pre-vaccination baseline period to 29 in 2011 (**Figure 4**).

FIGURE 4. Impact of Meningococcal C Vaccination on Disease Incidence in Varying Age Groups (Panels A-C), and Mortality (Panel D)

Summary of the impact of routine meningococcal C vaccination in Brazil

- The introduction of Men C conjugate vaccine into the routine vaccination programme provided an immediate reduction in incidence rates of MD in children aged <2 years, the age group targeted for vaccination.
  - No early impact was observed in other age groups, probably reflecting the lack of a catch-up programme targeting adolescents, the age group responsible for carriage.
  - Brazil will be the first country to provide experience with Men C vaccine against non–ST-11 *N. meningitidis*.

GMI RECOMMENDATIONS FOR REDUCING AND PREVENTING THE GLOBAL BURDEN OF MD

- The Latin American recommendations, initially developed at the 2011 meeting, and the 2013 updates/discussion are summarized in **Table 1**.

TABLE 1. GMI-Latin American Recommendations for the Prevention and Reduction of the Burden of MD: 2011 Recommendations and 2013 Updates

2011 Recommendation	2013 Update/Discussion
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	General agreement with 2011 Culture should be recommended and supplemented with PCR, where possible (PCR to supplement culture not replace it) Epidemiologic surveillance is crucial. We need to ensure it is continued Strengthen and maintain normal culture technique and PCR availability. Ensure training of providers/centres, etc, is carried out/continued Algorithm could be developed (could take other aspects into account, such as the limited resources of some countries, if using private laboratories where samples may be left overnight, number of samples to be analysed at same time, etc)
The introduction of quality controls, so that data from different laboratories can be harmonized	Standardization of surveillance is important Recommendation remains
Consistent and universal use of standardized diagnostic protocols, such as those set forth by SIREVA II or PAHO	2011 recommendation remains
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)	2011 recommendation remains
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	2011 recommendation remains
Replacement of polysaccharide vaccines with conjugate formulations—wherever possible Proposed vaccination policies against MD should be country specific and based on local disease dynamics and health priorities	No change. GMI agrees this is still relevant Consensus remains that regional strategy is difficult to develop based on country differences (eg, epidemiologic data, resource availability, etc) Socioeconomic situation of importance
Novel financing arrangements should be considered: Technology transfer agreements The PAHO Revolving Fund AMC	2011 recommendation remains
	Develop specific recommendations for vaccination of high-risk groups (where possible) that can be used throughout Latin America Risk groups include those with complement deficiency, immunodeficiency (including asplenia, HIV) and those at occupational risk such as those working with microbiological samples, military, etc
	Vaccination should be provided free of charge to those travelling to endemic areas
	Outbreak definition and control recommendation(s) to be developed

AMC, Advance Market Commitment; PAHO, Pan American Health Organization; PCR, polymerase chain reaction.

A UNIFORM MENINGOCOCCAL CASE DEFINITION FOR LATIN AMERICA

- Based on the previous finding that the countries of Latin America employ different case definitions for MD, to facilitate comparisons across the region a uniform meningococcal case definition combining PAHO criteria with confirmatory laboratory diagnosis by real-time PCR was recommended by the GMI and has recently been published[8] (**Table 2**).
  - The GMI hope that adoption of a uniform MD case definition in the region will improve surveillance—and thus allow us to gain a better understanding of the true burden of MD in the region.

TABLE 2. GMI-Proposed Universal Case Definition for MD in Latin America (PAHO Case Definition Plus, Where Available, Confirmatory Diagnosis by PCR)[8]

Suspected
- 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 purpuric rash
- For patients aged <1 year, MD should be suspected when fever is accompanied by bulging fontanelle

Confirmed (≥1 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; MD, meningococcal disease; PCR, polymerase chain reaction. Reproduced with permission.

CONCLUSIONS

- Since the first Latin American Roundtable meeting held in 2011, there have been great strides in the prevention, control, and diagnosis of MD in the region.
- However, MD remains an important healthcare concern in several Latin American countries, and the occurrence (and rise) of serogroup W in some areas is of great concern.
  - Countries should consider the Chilean experience and the plans that have been implemented, and strengthen surveillance systems wherever possible.
  - As more data amass from Chile, the world will learn more about this relatively new serogroup.
- The GMI will continue to re-evaluate trends in epidemiology and the impact of proposed recommendations on public health in Latin America.
- Vaccination remains the most effective method of disease prevention, and routine vaccination, in target populations, can have significant impact on the burden of disease, as highlighted by the introduction of the monovalent C vaccine in Brazil.

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