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Neisseria meningitidis and *Streptococcus pneumoniae* as leading causes of pediatric bacterial meningitis in nine Mexican hospitals following 3 years of active surveillance

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Abstract

Objectives: Meningococcal meningitis is reported as a rare condition in Mexico. There are no internationally published studies on bacterial causes of meningitis in the country based on active surveillance. This study focuses on finding the etiology of bacterial meningitis in children from nine Mexican Hospitals.

Methods: From January 2010 to February 2013, we conducted a three years of active surveillance for meningitis in nine hospitals throughout Mexico. Active surveillance started at the emergency department for every suspected case, and microbiological studies confirmed/ruled out all potentially bacterial pathogens. We diagnosed based on routine cultures from blood and cerebrospinal fluid (not polymerase chain reaction or other molecular diagnostic tests), and both pneumococcal serotyping and meningococcal serogrouping by using standard methods.

Results: *Neisseria meningitidis* was the leading cause, although 75% of cases occurred in the northwest of the country in Tijuana on the US border. Serogroup C was predominant. *Streptococcus pneumoniae* followed *Neisseria meningitides*, but was uniformly distributed throughout the country. Serotype 19A was the most incident but before universal implementation of the 13-valent pneumococcal conjugate vaccine. Other bacteria were much less common, including *Enterobacteriaceae* and *Streptococcus agalactiae* (these two affecting mostly young infants).

Conclusions: Meningococcal meningitis is endemic in Tijuana, Mexico, and vaccination should be seriously considered in that region. Continuous universal vaccination with the 13-valent pneumococcal conjugate vaccine should be nationally performed, and polymerase chain reaction should be included for bacterial detection in all cultures – negative but presumably bacterial meningitis cases.

Keywords: active surveillance, bacterial meningitis, children, meningococcal meningitis, pneumococcal meningitis

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Background

Meningococcal meningitis (MM) is considered to be a rare disease [Almeida-Gonzalez *et al.* 2004] in Mexico, despite proven endemicity in the northwestern part of the country and documented outbreaks [Chacon-Cruz *et al.* 2011, 2014a, 2015]. However, it is endemic in other Latin American countries [Safadi and Cintra, 2010], as

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well as in many other parts of the world [Chang *et al.* 2012; Baccarini *et al.* 2012]. Employing an active surveillance system throughout Mexico, we sought to examine the burden of MM, pneumococcal meningitis (PM) and other bacteria causing bacterial meningitis (BM) throughout Mexico. Furthermore, active surveillance for BM has never been published in Mexico, and in Latin America, is the third-published study also prospectively looking for pathogens causing BM and other invasive diseases in children [Sacchi *et al.* 2011; Gaensbauer *et al.* 2016]; all other information on pediatric BM in Mexico and Latin America we have is mostly based on passive surveillance (SIREVA report, 2012).

Incidence rates (IR) were obtained only for MM because it had been reported as a very rare disease in Mexico based on passive surveillance. Among nine hospitals included in this study, only five had a stable population who only attended that particular hospital. They were the only ones in which it was possible to estimate IR based on the following formula:

$$\mathrm{IR} = \frac{\text{Cases of MM} \times 100{,}000}{\text{Population by age group}}$$

Materials and methods

The main objectives of our study were to:

(1) Evaluate the real epidemiological situation of meningococcal disease in Mexican children.
(2) Estimate incidence rates of MM only in hospitals where a defined denominator was well defined.
(3) Identify all culture-positive bacterial causes of meningitis in children.
(4) Compare the clinical and demographic pictures of MM *versus* PM.
(5) Describe clinically and demographically other bacteria causing meningitis in Mexican children.

This study was initiated by physicians in charge of children with BM. The project guidelines were developed during the initial meeting and participating microbiologists from each hospital were trained in isolating and identifying bacterial pathogens that may cause BM. The study was approved by the ethics committees from all nine hospitals.

From February 2010 to January 2013, active surveillance for BM in children <16 years of age was implemented in 9 hospitals throughout Mexico: Tijuana General Hospital (northwest); Hospital Universitario of Monterrey (northeast); Children's Hospital of Culiacan (north-Pacific); Hospital Civil of Guadalajara (central-Pacific); three hospitals in Mexico City (National Institute of Pediatrics, Hospital Picacho–PEMEX and Hospital Medica-Sur); Children's Hospital of Morelia (southwest); and General Hospital of Tuxtla-Gutierrez (southeast).

All but two are tertiary hospitals (National Institute of Pediatrics and Hospital Civil of Guadalajara); the rest are secondary hospitals. All but one are public; the exception is a private hospital in Mexico City, Hospital Medica-Sur. These hospitals were chosen because they represent a geographical area, and by looking at their microbiological laboratories, they fulfilled the basic equipment and personnel for identification of invasive bacteria.

Active surveillance was as follows. At the emergency department, for every patient with suspected meningitis, lumbar punctures [cytochemical analysis including glucose, proteins and leucocytes from cerebrospinal fluid (CSF) and culture] and blood cultures were immediately performed along with other routine tests [cell blood count (CBC), serum biochemical profiles (glucose, liver and renal functional tests), erythrocyte sedimentation rate (ESR) and clotting times (prothrombin and thromboplastin times]. Diagnosis of BM was established by a positive CSF and/or blood culture, with abnormal CSF cytochemical analysis. Bacterial identification was performed using initially broth media followed by specific automatized methods for each pathogen. Standard isolation and identification of each pathogen was established during the first meeting of all investigators and microbiologists, and annual supervision by the principal investigator.

For all *Neisseria meningitidis* isolates, serogroup identification was performed using the Pastorex meningitis kit (Alere Ltd, Stockport, UK). For some *Streptococcus pneumoniae* isolates, serotype identification was performed using the Quellung reaction (Statens Serum Institute, Copenhagen, Denmark). We did not use polymerase chain reaction (PCR) or another molecular diagnostic tool due to lack of resources. For every culture-negative meningitis, a discussion took place within the

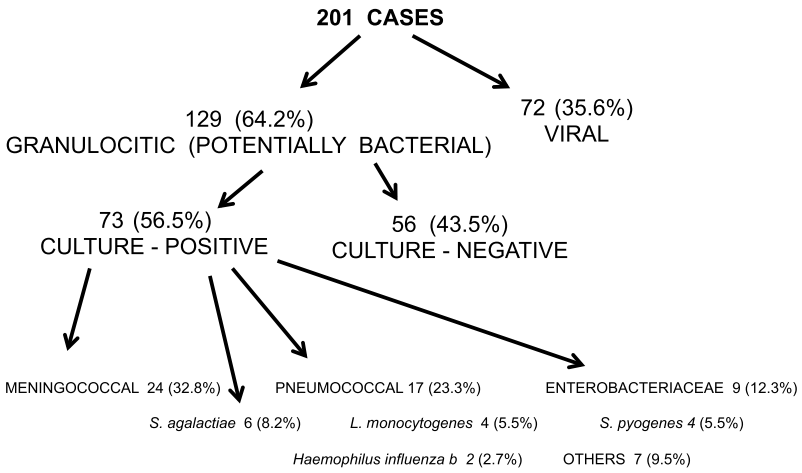

Figure 1. Pediatric meningitis surveillance in nine Mexican hospitals: number and percentage of cases by disease and agent.
Period: 1 February 2010 to 31 January 2013.

main investigators on an individual basis and it was decided whether it was viral meningitis (VM) or potential bacterial meningitis (PBM); decisions were made based on CSF cytochemical analysis (leucocytes, proteins and glucose), clinical picture at admission, and clinical outcome during hospitalization. All patients with VM received no more than 2 days of antimicrobials, a second lumbar puncture revealed a normal cytochemical analysis, and were discharged with at least 3 days without antibacterials. The reasons for a second lumbar puncture in all VM cases was to confirm they were not BM, mostly due to the lack of molecular tools for identification of viruses and because there are reports of BM without CSF pleocytosis [Hase *et al.* 2014]. Patients with PBM had a granulocytic CSF and a second abnormal granulocytic CSF again, but isolation of a bacterial pathogen was not possible.

The principal investigator supervised once a year all nine hospitals to assure compliance.

Results

There were 201 cases of meningitis; 72 (36%) were considered to be VM and 129 (64%) were considered to be PBM. Culture-confirmed BM cases were 73 (56.5% positivity) and isolates were as follows: *N. meningitidis* 24 (33%); *S. pneumoniae* 17 (23.3%); *Enterobacteriaceae* 9 (12%); *Streptococcus agalactiae* 6 (8%); *Listeria monocytogenes* 4 (5.5%); *Streptococcus pyogenes* 4 (5.5%); *Haemophilus influenzae* type b 2 (2.7%); and others 7 (9.5%) (Figure 1).

Culture-confirmed BM was from CSF only in 100% of cases and from both CSF and blood in 36% of patients.

MM incidence was significantly higher in the northwest (Tijuana, 75%); of these 41.6% were caused by serogroup C (Figure 2).

The median age of presentation for MM was 1 year (21 days to 15 years), 71% were <2 years old. Purpura and thrombocytopenia were present in 46% and 41.6%, respectively. A total of 6 children died (25%, between 1 and 3 days following hospitalization). Among survivors, 4 (22.2%) developed neurologic sequelae (motor and speech impairment) at discharge from the hospital. It was possible to estimate the IR of MM from five hospitals. The vast majority of cases were found in Tijuana, with annual rates in children <5 years old of 25/100,000, while the overall rate in that same age group was of 5/100,000 (Table 1).

PM was more equally distributed throughout the country (Table 1). PM median age of presentation was 2.5 years (3 months to 16 years) and 47% were <2 years old. Purpura was not present in any case, thrombocytopenia was present in 11.7% of patients, and overall PM mortality was 5 (29.4%, between 1 and 8 days following hospitalization). Among survivors, 3 (25%) developed neurologic sequelae (motor and speech impairment) at discharge from the hospital. Pneumococcal serotype identification was obtained in seven patients, six of which were serotype 19A.

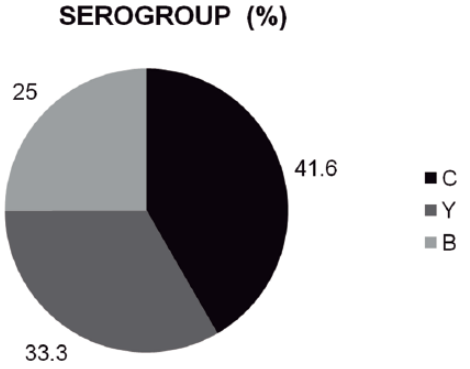

Figure 2. Pediatric meningitis surveillance in nine Mexican hospitals: meningitis due to *Neisseria meningitidis* by serogroup (n = 24)
Period: 1 February 2010 to 31 January 2013.

Table 1. Pediatric meningitis surveillance in nine Mexican hospitals.

	Geographical zone		
	North	Central	South
Number of hospitals	3	4	2
Meningococcal/ pneumococcal	20/7	4/8	0/2

Meningococcal and pneumococcal meningitis in children: regional distribution in Mexico from 1 February 2010 to 31 January 2013.

Among patients with PM, pneumococcal vaccination status was of at least 2 doses of 7-valent pneumococcal conjugate vaccine in 15 from 17 patients (88.2%); 2 patients were not vaccinated at all.

Other bacteria were much less common, with *Enterobacteriaceae* and *S. agalactiae* affecting mostly children less than 3 months old. *Enterobacteriaceae* caused three deaths and all patients were discharged with neurologic sequelae. Patients with meningitis due to *S. agalactiae* developed well, with no mortality and no apparent sequelae at discharge.

There were 4 cases due to *S. pyogenes*, affecting mostly older children (4–8 years of age) and 4 cases of *L. monocytogenes* affecting mostly young infants with a good clinical response. There were two cases of *Haemophilus influenzae* type b, both of which were unvaccinated children, one the son of parents belonging to anti-vaccine groups (this patient died).

All patients did not have any apparent immunological disorder, none had any kind of bacterial invasive disease in the past and all were human immunodeficiency virus (HIV) negative. No further immunological studies were performed.

Discussion

This is the first internationally published study performed in Mexico based on active surveillance (not retrospectively) looking for etiological bacterial pathogens of BM. Even though MM is a notifiable condition, the overall belief that MM is a rare disease persists. This assumption, however, is based only on observation. Nevertheless, MM was mostly present in Tijuana (75%), with indeed an outbreak due to serogroup C, MTLS ST-11 – an outbreak that occurred 1 month after this surveillance was finished [Chacon-Cruz *et al.* 2011, 2014, 2015]. We believe that meningococcal vaccination should be seriously evaluated in that region. In other areas than Tijuana, Mexico, we do not have enough information to recommend universal vaccination. However, we should encourage active, national surveillance.

PM presence was equally notable throughout all nine hospitals. Among the seven serotyped strains, six were caused by serotype 19A. This study was mostly conducted before initiation (May–June 2012) of the 13-valent pneumococcal conjugate vaccine (PCV-13). Currently, following PCV-13 universal introduction, serotype 19A and PM have dropped significantly in Tijuana [Chacon-Cruz *et al.* 2014b].

Other bacteria were much less common, with *Enterobacteriaceae* and *S. agalactiae* affecting mostly children <3 months old; there were also 4 cases each of *L. monocytogenes* and *S. pyogenes* and 2 children with *Haemophilus influenzae* type b meningitis who were not vaccinated.

The main limitation of our study is that we were unable to perform PCR for any PBM case due to lack of resources. We believe our results will bring more resources in the near future to continue active surveillance and to encourage the use of PCR as a common tool for all PBM cases as proven in many other studies [Salgado *et al.* 2013; Sacchi *et al.* 2011; Ubukata 2013; Diggle and Clarke, 2006; Mothershed and Whitney, 2006; Bennet and Cafferkey, 2006].

Conclusion

(1) Meningococcal meningitis is among the leading causes of BM in Mexico. However,

it is predominant only in the northwest of Mexico (Baja-California–California border) and universal vaccination should be seriously evaluated in that region [World Health Organization, 2011].

(2) PM is the most frequent bacterial pathogen found, but cases are more equally distributed throughout the country. Serotype identification was performed only in 41% of cases, all of which were 19A, suggesting that PCV-13 should be continued as a universal antipneumococcal vaccination in Mexican children.

(3) PCR or other molecular diagnostic tools should be included to increase the yield of diagnosis of all cases of BM.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

References

Almeida-Gonzalez, L., Franco-Paredes, C., Perez, L. and Santos-Preciado, J. (2004) Meningococcal disease caused by *Neisseria meningitidis*: epidemiological, clinical, and preventive perspectives. *Salud Publica Mex* 46: 438–450.

Baccarini, C., Ternouth, A., Wieffer, H. and Vyse, A. (2012) The changing epidemiology of meningococcal disease in North America 1945–2010. *Hum Vaccin Immunother* 9: 162–171.

Bennet, D. and Cafferkey, M. (2006) Consecutive use of two multiplex PCR-based assays for simultaneous identification and determination of capsular status of nine common *Neisseria meningitidis* serogroups associated with invasive disease. *J Clin Microbiol* 44: 1127–1131.

Chacon-Cruz, E., Espinosa-De Los Monteros, L., Navarro-Alvarez, S., Aranda-Lozano, J., Volker-Soberanes, M., Rivas-Landeros, R. *et al.* (2014a) An outbreak of serogroup C (ST-11) meningococcal disease in Tijuana, Mexico. *Ther Adv Vaccines* 2: 71–76.

Chacon-Cruz, E., Rivas-Landeros, R. and Volker-Soberanes, M. (2014b) Early trends in invasive pneumococcal disease in children following the introduction of 13-valent pneumococcal conjugate vaccine: results from eight years of active surveillance in a Mexican hospital. *Ther Adv Vaccines* 2: 155–158.

Chacon-Cruz, E., Rivas-Landeros, R. and Volker-Soberanes, M. (2015), Pediatric meningococcal disease in a northern Mexican hospital: results of nine years of active surveillance. *Open Forum Infect Dis* 2(Suppl. 1): abstract 1755.

Chacon-Cruz, E., Sugerman, D., Ginsberg, M., Hopkins, J., Hurtado-Montalvo, J., Lopez-Viera, J. *et al.* (2011) Surveillance for meningococcal disease US–Mexico border, 2005–2008. *Emerg Infect Dis* 17: 543–546.

Chang, Q., Tzeng, Y. and Stephens, D. (2012) Meningococcal disease: changes in epidemiology and prevention. *Clin Epidemiol* 4: 237–245.

Diggle, M and Clarke, S. (2006) Molecular methods for the detection and characterization of *Neisseria meningitidis*. *Expert Rev Mol Diagn* 6: 79–87.

Gaensbauer, J., Asturias, E., Soto, M., Holt, E., Olson, D., Halsey, N. *et al.* (2016) Pediatric invasive pneumococcal disease in Guatemala City: Importance of serotype 2. *Pediatr Infect Dis J* 35: e139–e143.

Hase, R., Hosokawa, N., Yaegashi, M. and Muranaka, K. (2014) Bacterial meningitis in the absence of cerebrospinal fluid pleocytosis: a case report and review of the literature. *Can J Infect Dis Med Microbiol* 25: 249–251.

Mothershed, E. and Whitney, A. (2006) Nucleic acid-based methods for the detection of bacterial pathogens: present and future considerations for the clinical laboratory. *Clin Chim Acta* 363: 206–220.

Sacchi, C., Fukasawa, L., Goncalves, M., Salgado, M., Shut, K., Carvalhanas, T. *et al.* (2011) Incorporation of real-time PCR into routine public health surveillance of culture negative bacterial meningitis in São Paulo, Brazil. *PLoS One* 6: e20675.

Safadi, M. and Cintra, O. (2010) Epidemiology of meningococcal disease in Latin America: current situation and opportunities for prevention. *Neurol Res* 32: 263–271.

Salgado, M., Gonçalves, M., Fukasawa, L., Higa, F., Paulino, J. and Sacchi, C. (2013) Evolution of bacterial meningitis diagnosis in São Paulo State-Brazil and future challenges. *Arq Neuropsiquiatr* 71: 672–676.

SIREVA REPORT (2012) http:www.paho.org/index.php?option=com_docman&task=doc_download&gid=22372&ltemid=270&lang=es

Ubukata, K. (2013) Rapid identification of meningitis due to bacterial pathogens. *Rinsho Shinkeigaku* 53: 1184–1186.

World Health Organization (2011) Meningococcal vaccines: WHO position paper, November 2011. *Wkly Epidemiol Rec* 86: 521–540.