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Streptococcus pneumoniae as cause of infection in infants less than 60 days of age: serotypes and antimicrobial susceptibility

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SUMMARY

Objective: The aim of this study was to determine the distribution of serotypes and the antimicrobial susceptibilities of *Streptococcus pneumoniae* clinical isolates causing invasive and non-invasive disease in children aged ≤60 days in hospitals in Mexico.
Methods: A 15-year retrospective study was conducted for the period 2000 to 2014. Pneumococcal clinical isolates were serotyped by Quellung reaction, and antimicrobial susceptibility testing was performed with the broth microdilution method.
Results: A total of 126 pneumococcal isolates were collected. Pneumonia was the most frequent diagnosis (40.5%), followed by meningitis (29.4%), septicemia (16.7%), and other clinical entities, including otitis media and conjunctivitis (13.5%). The most frequent serotypes before the introduction of heptavalent pneumococcal conjugate vaccine (PCV7) were 19F, 23F, 7F, and 35B. Serotypes 3, 6A, 10A, 12F, and 15A/B increased after the introduction of PCV7. Serotype 19A was isolated most frequently in the pneumonia and meningitis cases only after the introduction of PCV7, and it displayed a high resistance to penicillin.
Conclusions: Although the number of infections in infants aged ≤60 days was low, such infections were not unusual events. New vaccination strategies should be evaluated to limit the risks in this age group.

1. Introduction

Streptococcus pneumoniae causes invasive (IPD) and non-invasive (NIPD) pneumococcal disease, mainly in the pediatric population and among the elderly. It is considered an uncommon causative agent of neonatal sepsis, including serious infections such as bacteremia, pneumonia, and meningitis; however, in this age group and before the age of 2 months, such infections can become fatal and have mortality rates that range from 1% to 14%.[1–5] Reductions in the numbers of early-onset sepsis cases caused by *S. pneumoniae* have been reported in the international literature, including only a single case in Mexico,[6] and the majority of infections occur after 7 days of life.[1] The mechanisms of transmission of early and late infections are not entirely clear, but vertical transmission (e.g., maternal bacteremia, chorioamnionitis, prolonged membrane rupture, and cervico-vaginal colonization) has been shown to predominate in early cases, whereas horizontal transmission dominates in late cases, although these patterns are not exclusive.[1,6,7] Some neonatal conditions, such as preterm delivery and low birth weight, as well as pneumococcal virulence factors, can induce poor neonatal immune responses and increase the risk of infection.[4,8–10]

In Mexico, immunization with the heptavalent pneumococcal conjugate vaccine (PCV7) began in early 2006, when this vaccine was

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introduced gradually and only in the municipalities with the lowest human development indices. In 2008, universal vaccination with PCV7 was applied to the population aged under 1 year. During the period from 2008 to 2010, PCV10 was introduced in a three-dose schedule to the pediatric population insured by the Instituto Mexicano del Seguro Social (IMSS), which covers half of the population. Since 2011, PCV13 has been used in a 2-, 4-, and 12-month schedule as part of the universal immunization program.[11,12]

The aim of this descriptive, retrospective study was to analyze the distribution of serotypes and the antimicrobial susceptibilities of the pneumococcal strains that caused invasive and non-invasive disease in children aged less than 2 months during the 2000–2014 period.

2. Methods

2.1. Surveillance of S. pneumoniae and clinical samples

In 1993, Mexico entered the Sistema Regional de Vacunas (SIREVA) project for Latin America,[13] and since that time, pneumococcal isolates from patients with invasive and non-invasive disease from 23 participating hospitals have been sent voluntarily, along with demographic data, to the Instituto Nacional de Salud Pública (INSP) in Cuernavaca, Morelos, Mexico. As part of this passive laboratory surveillance, a retrospective study was conducted for the period 2000 to 2014 with data from the SIREVA–Mexico network, including *S. pneumoniae* isolates from unvaccinated infants younger than 2 months of age. Two sub-groups were considered: newborns aged 0–7 days and infants aged ≥8–60 days. Early-onset disease (EOD) cases were those that occurred within the first 7 days of life, and late-onset disease (LOD) cases were those that occurred in patients between the ages of 8 and 60 days. The analyses accounted for two periods: 2000–2007, before the introduction of PCV7 (pre-PCV7); and 2008–2014, after the introduction of PCV7 (post-PCV7).

2.2. Isolation and identification

Invasive pneumococcal disease (IPD) was defined by the isolation of *S. pneumoniae* from blood, cerebrospinal fluid (CSF), and/or pleural fluid. Bacteremic and/or complicated pneumonia was defined in the presence of a clinical diagnosis of pneumonia and positive culture from blood and/or pleural fluid. Non-bacteremic pneumonia was considered when the treating physician defined an episode as pneumonia and the bronchial and/or tracheal aspirates were positive for *S. pneumoniae* as a single culture. Non-invasive pneumococcal disease (NIPD) included those isolates from non-bacteremic pneumonia patients and isolates from non-sterile sites, such as middle ear fluid and eye discharge; these sites were considered as 'other sites'. The isolates were identified by standard procedures that included tests for bile solubility and optochin sensitivity. Pneumococcal isolates were serotyped by the Quellung reaction with type- and factor-specific antisera (Statens Serum Institut, Copenhagen, Denmark).

2.3. Antimicrobial susceptibility

Antimicrobial susceptibility tests for penicillin (PEN), cefotaxime (CTX), vancomycin (VAN), erythromycin (ERY), and chloramphenicol (CHL), all from Sigma-Aldrich USA, were performed by broth microdilution method to determine the minimum inhibitory concentration (MIC); the procedures of the Clinical and Laboratory Standards Institute (CLSI) were followed, using cation-adjusted Mueller–Hinton broth (CAMHB) supplemented with 3% lysed horse blood. Interpretative criteria were differentiated for meningitis and non-meningitis isolates according to CLSI guidelines; *S. pneumoniae* ATCC 49619 was used as the control strain.[14]

2.4. Statistical analysis

Chi-square statistical analyses were performed using IBM SPSS Statistics version 20.0 software (IBM Corp., Armonk, NY, USA); *p*-values of ≤0.05 were interpreted as statistically significant.

3. Results

A total of 1763 *S. pneumoniae* isolates from children younger than 17 years of age with IPD and NIPD were collected during the years 2000–2014. One hundred and twenty-six isolates (7.2%) came from children ≤60 days of age. Twenty-five isolates (19.8%; 25/126) were obtained from newborns aged between 0 and 7 days and 101 (80.2%; 101/126) from infants aged between 8 and 60 days. Males represented 67.5% (85/126) of the patients.

Meningitis was diagnosed in 29.4% (37/126) of the patients; 16.7% (21/126) had sepsis/bacteremia and 40.5% (51/126) had pneumonia. Only 21.6% (11/51) of the isolates that caused pneumonia came from blood cultures and/or pleural fluid. Non-bacteremic pneumonia was present in 78.4% (40/51) of the cases and was significantly more frequent in infants aged 8–60 days ($p = 0.0001$). Other diseases, such as acute otitis media and conjunctivitis, were diagnosed in 13.5% (17/126) of the cases. IPD represented 54.8% (69/126) of the cases, whereas 45.2% (57/126) corresponded to NIPD. There were 17 deaths, giving a lethality rate of 13.5% (17/126) in both IPD and NIPD cases, as shown in Table 1.

Table 1
Demographic features and clinical diagnoses of infants with IPD and NIPD in Mexico

Variable	*N* (%)	Age sub-group (days)			Pre- and post-PCV7 era		
		0–7 (*n* = 25), *n* (%)	8–60 (*n* = 101), *n* (%)	*p*-Value	2000–2007 (*n* = 60), *n* (%)	2008–2014 (*n* = 66), *n* (%)	*p*-Value
Sex							
Female	41 (32.5)	11 (44.0)	30 (29.7)		22 (36.7)	19 (28.8)	
Male	85 (67.5)	14 (56.0)	71 (70.3)		38 (63.3)	47 (71.2)	
Diagnosis							
Meningitis	37 (29.4)	4 (22.2)	33 (64.7)	0.0025[a]	17 (60.7)	20 (48.8)	
Sepsis	21 (16.7)	10 (55.6)	11 (21.6)	0.0151[a]	6 (21.4)	15 (36.6)	
Bacteremic pneumonia	11 (8.7)	4 (22.2)	7 (13.7)		5 (17.9)	6 (14.6)	
IPD total	69 (54.7)	18 (72.0)	51 (50.5)		28 (46.7)	41 (62.1)	
Non-bacteremic pneumonia	40 (31.7)	3 (42.9)	37 (74.0)	0.0001[a]	22 (68.8)	18 (72.0)	
Other sites	17 (13.5)	4 (57.1)	13 (26.0)		10 (31.2)	7 (28.0)	
NIPD total	57 (45.2)	7 (28.0)	50 (49.5)		32 (53.3)	25 (37.9)	
Lethality	17 (13.5)	5 (20.0)	12 (11.9)		3 (5.0)	14 (21.2)	0.0089[a]

IPD, invasive pneumococcal disease; NIPD, non-invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine.
[a] Significant *p*-values (≤0.05).