Brief Original Article

Pneumococcal disease: emergence of serotypes 19A and 7F following conjugate pneumococcal vaccination in a Mexican hospital

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Abstract

Introduction: Mexico was the first country to initiate massive vaccination with heptavalent pneumococcal conjugate vaccine (PCV-7) in children. There is no information regarding pneumococcal invasive disease (PID) in children before and after implementation of PCV-7 in Mexico or elsewhere in Latin America.

Methodology: During October 2005 to September 2010, active surveillance for pediatric PID was initiated at Tijuana General Hospital. Only culture-confirmed cases from sterile fluids were included in the study. Serotype identification was also performed.

Results: Twenty-eight pediatric PID cases were confirmed. *Streptococcus pneumoniae* was the main cause of pleural empyema (n = 13). It was also the second most common cause of confirmed bacterial meningitis (n = 10), followed by *Neisseria meningitidis* (n = ?), and the only cause of otomastoiditis with bacterial isolation (n = 5). Vaccine-associated serotypes decreased from 54% before PCV-7 introduction to the vaccination schedule, to only 5.6% after PCV-7 implementation. Serotypes 19A and 7F (47% and 33% respectively) were predominant following PCV-7 vaccination.

Conclusions: Serotype substitution in PID is present in the northern border of Mexico following PCV-7 vaccination in children.

Key words: *Streptococcus pneumoniae;* pneumococcal invasive disease; pneumococcal conjugate vaccines; serotypes 19A and 7F; Mexico

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Introduction

Pneumococcal invasive disease (PID) in children is associated with high morbidity and mortality. In the United States, before implementation of heptavalent pneumococcal conjugate vaccine (PCV-7), *Streptococcus pneumoniae* annually caused five -to seven million cases of acute otitis media, 71,000 cases of pneumonia, 17,000 of bacteremia, and was the leading cause of bacterial meningitis with 1,400 cases per year [1]. Global immunisation with PCV-7 dramatically decreased PID in the US, including not only in vaccinated children, but also in the non-vaccinated population, the latter mostly associated with PCV-7 induced herd immunity [2]. Similar results were found in other countries where PCV-7 has been widely used [3]. In Mexico, studies performed in tertiary care hospitals have shown that PID is potentially the main cause of bacterial meningitis and pleural empyema [4,5]. Furthermore, a national study looking for asymptomatic carriage showed that 29% of children were colonized by *S. pneumoniae*, 56% of which were serotypes included in PCV-7 [6]. To date no prospective studies have yet been performed that examine serotype distribution and/or substitution as cause of PID, before and after global implementation of PCV-7, in Mexico. Tijuana is located in the northwest part of Mexico. It has a population of 1,637,000 people, of whom 30% are not insured and attend the only government-sponsored general hospital in the area. The border between Tijuana, Mexico, and San Diego, California, is one of the busiest in the world, with health issues affecting both countries and consequent programs being held

together. PID, a common health problem, does not have a binational program for prevention, when compared to other infectious diseases (such as TB, HIV, among others).

Methodology

From October 2005 to September 2010, active surveillance detecting PID in children from one month to 16 years of age was performed at Tijuana General Hospital (TGH). Aproximately 8 cultures were taken weekly from any pediatric patient with unknown fever, potential meningitis, and, patients with suspected pleural empyema and mastoiditis. Patients with nosocomial infections and newborns were excluded. Serotype identification was performed by the Quellung reaction using serotype-specific pneumococcal antisera from Statens Serum Institute (Copenhagen, Denmark). Only data from patients with confirmed isolation from a sterile body fluid (blood, cerebrospinal fluid (CSF), pleural fluid, surgically obtained mastoid pus) were included for analysis in this study. Both clinical and demographic analyses were performed for each patient with confirmed PID. Antibiotic susceptibility was not performed in the majority of cases. A descriptive analysis for both clinical and demographic characteristics was done, followed by chi square and *z* tests for comparisons of variables and proportions. $P < 0.05$ was considered to be statistically significant.

Results

During the study period, 98 patients were admitted to our hospital with suspected meningitis, empyema, mastoiditis and/or clinical sepsis with purpura. Twenty-eight (28.5%) patients had confirmed PID by culture. Average age at admission was 61.6 months (7 months to 14 years). Fourteen males and 14 females were included in the study. Clinical diagnoses were pleural empyemas (n = 13), bacterial meningitis (n = 10), otomastoiditis (n = 5) and bacteremias in association with meningitis and/or pleural empyema (n = 3). From 23 cases with pleural empyemas, isolation was not obtained in 10 patients, but *S. pneumoniae* caused 100% of all culture-confirmed cases (n = 13), as well as 100% of culture-confirmed mastoiditis. From 55 CSF cultures, 38 were positive (10 for *S. pneumoniae*, 25 for *N. meningitidis*, 2 for *S. agalactiae*, and one for *E. coli*,). These results confirm *S. pneumoniae* as the second leading cause of culture-confirmed bacterial meningitis in our study. Overall mortality was 7% (two cases with meningitis). The average hospitalization stay was 19.2 days (range 10 to 47 days) and 61.5% of pneumococcal pleural empyemas resulted in pleural decortication.

As seen in Figure 1, from 2005 to 2006 during the period before the start of global PCV-7 vaccination in the state of Baja, California, Mexico, 66.6% of all PID cases were caused by PCV-7 associated serotypes, with a progressive decline, showing complete replacement by only non - PCV-7- associated serotypes in the 2008 to 2009 period. In Figure 2, serotypes found before and after PCV-7 introduction are described: as shown, before PCV-7 implementation (August to September 2007), 54% of all PID were caused by PCV-7 associated serotypes, followed by 23% non-PCV-7 associated serotypes, and 13% unknown. In contrast, following the introduction of the vaccine, only 5.6% of cases were caused by PCV-7-associated serotypes ($p < 0.001$). From PCV-7 non-associated serotypes following PCV-7 vaccination, 46.6% were 19A and 33.3% were caused by 7F. There was no statistically significant difference regarding use of antibiotics prior to admission between children before and after PCV-7 implementation (69.2% versus 73.3% respectively, p = NS). PCV-7 was not administered to any of the patients before PCV-7 introduction, while 33.3% following PCV-7 implementation in the region were fully immunized.

Discussion

This is the first Latin American study that prospectively shows serotype replacement in pediatric PID before and after introduction of PCV-7. our data is based on an active surveillance system for bacterial invasive diseases implemented at TGH since October 2005. Replacement of serotypes is evident, even though serotype identification was not performed on 13% of isolates during the pre-PCV-7 era due to lack of reagents for a short period of time. Although PID in Mexico is not a communicable health condition, previous studies have been well documented (4,5], all of which were done before the introduction of PCV-7 as part of the immunisation schedule in Mexico. In these reports, the majority of pediatric PID cases were caused by PCV-7-associated serotypes. Furthermore, in a Mexican national study,

Figure 1. Serotype distribution before and after pcv-7 implementation

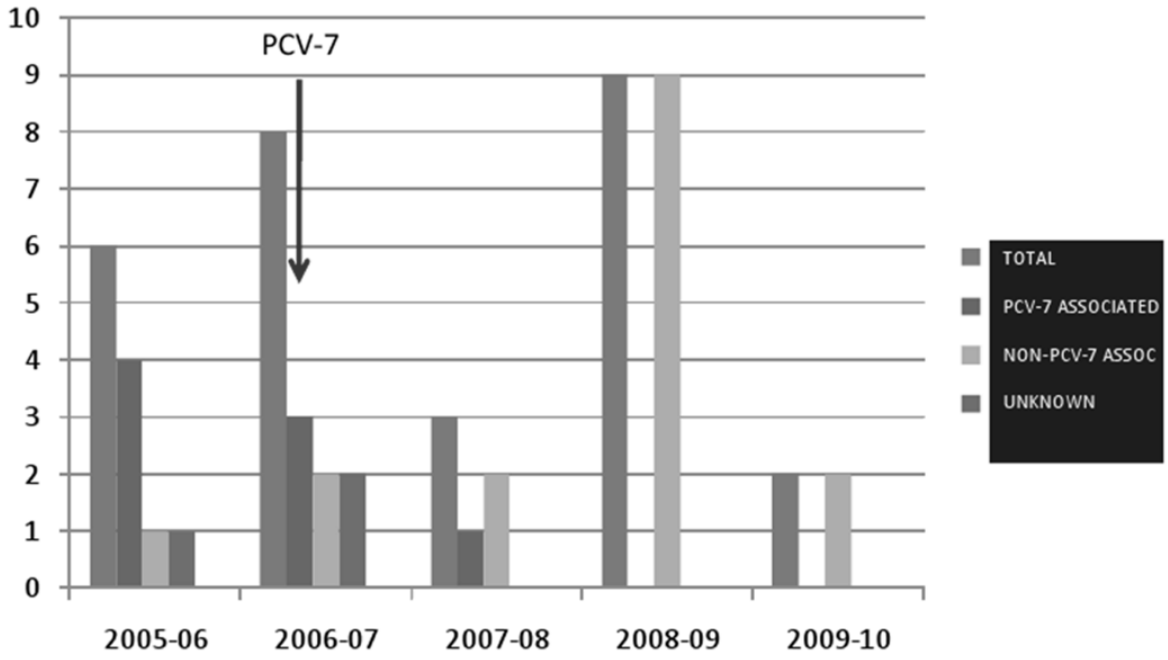
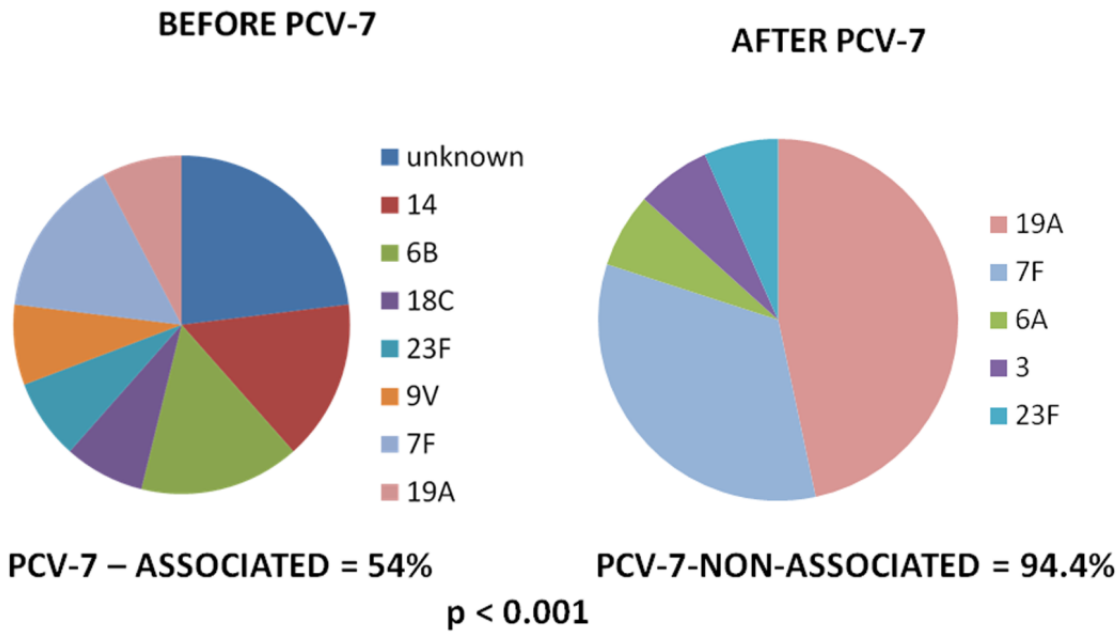


Figure 2. Specific serotype isolation before and after pcv-7 implementation



investigating *S. pneumoniae* asymptomatic carriage, 29% of 3,144 collected samples from nasopharynx of children attending day-care centers were positive for *S. pneumoniae*, from which 56% were PCV-7-associated serotypes [6]. The Regional Vaccine System (SIREVA), a passive surveillance system for bacterial invasive diseases in Latin America, also showed a higher prevalence of PCV-7- associated serotypes. According to the latest available report in children younger than 16 years of age, which shows the data for 2007 (just before PCV-7 global implementation), 57% of isolates were PCV-7-associated serotypes, including the following: serotype 6B = 20.4%, serotype 14 = 18.1%, serotype 6A = 12.7%, serotype 19F = 9.1%, serotype 23F = 6.8%, serotype 19A = 3.4%, serotype 18C = 2.3%, serotype 3 = 2.3%, 1 = 1.1%, serotype 7F = 1.1% and 22.7% were of unknown serotype [7]. However, Mexico is the first country in Latin America to introduce PCV-7 as part of the universal immunisation schedule, so information regarding circulating serotypes following PCV-7 introduction in Latin America is still unknown. A study by Arrendondo *et al*., the most recently published information available on *S. pneumoniae* causing invasive disease in Mexico [12], was performed before the initiation of PCV-7 as part of the National Immunisation Program. From 115 isolates of invasive strains of *S. pneumoniae,* 59.4% were serotypes now included in PCV-7 (personal communication Dr. Arredondo). There are many studies showing serotype replacement after the introduction of PCV-7 in the US and elsewhere [9-13]. Serotype 19A has been of particular concern in the US due to its virulence and high rates of resistance to both penicillin and third -generation cephalosporins [14,15].

Our study has three limitations: 1. Antibiotic susceptibilities were not included; 2. The precise immunisation with PCV-7 in Tijuana is unknown, but estimates of coverage are of 36% to 40%, with potentially higher coverage due to changes in vaccinating reporting policies (personal communication with Dr. Karzali Trasviña, Head of Immunisation of the Tijuana Health Department); and 3. The number of isolates seems to be low. The number of isolates included in this study are from only one hospital (TGH) that admits only non-insured population in Tijuana, mostly people who live in precarious conditions. It is clear to us that with these data we cannot prove that PCV-7 implementation caused serotype replacement on PID. However, two hypotheses have been advanced for why 19A may have become predominant serotype causing PID in many geographic areas [14,16]: 1. Selective pressure and colonization due to overuse of antibiotics, and 2. Replacement as a consequence of PCV-7 vaccination. Accordingly, in our study, there were no significant differences regarding previous antibiotic use prior to admission between patients before and after PCV-7 implementation. Furthermore, in a study done in the Netherlands, *S. pneumoniae* serotype 19A replacement in nasopharynx was more common in PCV-7 vaccinated children when compared to PCV-7 non vaccinated subjects, and in this same study, there were also no differences in the use of antibiotics between the two groups [16].

In summary, our data shows that *S. pneumoniae* is the leading cause of pleural empyema and mastoiditis, the second leading cause of bacterial meningitis. Furthermore, serotypes 19A and 7F are presently predominant following implementation of PCV-7 in the area. There are approximately 150,000 children younger than 16 years of age in Tijuana, Mexico, without social security (based on a Baja-California State-Department statistical database [17]), and whose only government-based hospital is TGH. We are aware that the data is limited for just one (but epidemiologically very important) geographic area, and that the number of isolates is not high; nevertheless, it is the first report of serotype replacement by 19A and 7F in Latin America, and in contrast to other studies, our data comes from an active and reliable surveillance system. Further studies are needed in Mexico and elsewhere in Latin America to prove that serotype substitution of pediatric PID is a global phenomena in regions where PCV-7 has been implemented, which in turn would influence the implementation of different vaccination strategies such as the use of the newer conjugate vaccines, with a higher number of serotypes included, especially 19A and 7F.

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