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12 years active surveillance for pediatric pleural empyema in a Mexican hospital: effectiveness of pneumococcal 13-valent conjugate vaccine, and early emergence of methicillin-resistant *Staphylococcus aureus*

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Abstract

Background: Previous publications have proved the effectiveness of the 13-valent pneumococcal conjugate vaccine (PCV13) on pneumococcal pleural empyema (PnPE) in children, with little emergence of other pathogens. We searched the literature to establish whether PCV13 reduces PnPE, and to identify other pathogens causing pleural empyemas (PEs).

Material and methods: From October 2005 to January 2018 (12.3 years) we performed active surveillance for all cases of PE at the General Hospital of Tijuana, Mexico. Isolates from pleural fluid (PF) were identified by conventional culture, and since 2014, polymerase chain reaction (PCR) was added for all culture-negative PFs. *Streptococcus pneumoniae* serotypes were detected by either Quellung reaction (Statens Serum Institute®) or PCR. Clinical, imagenological, laboratorial and microbiological evaluation was performed on each patient. Statistical analysis was purely descriptive.

Results: A total of 64 PEs were identified (5.28/year). Median age was 51 months (1–191), hospitalization days 18 (4–35). Decortication was performed in 42%, and two children died (3.2%). Bacterial identification was obtained from 51 (80%). *S. pneumoniae* was the leading cause (29 = 56.8%), followed by *Staphylococcus aureus* (14 = 27.4%), *Streptococcus pyogenes* (3–5 = 9%) and others (5 = 9.8%). PCV13 was initiated in May 2012, and its impact on serotype-specific PnPE was 81% (much fewer than serotype 3) and for all PnPE 56.1%; however, for all PE –2.1% due to an increase of PE caused by *S. aureus* for all but one methicillin-resistant *S. aureus* (MRSA).

Conclusions: Following 12.3 years of active surveillance, PCV13 has shown impact on both serotype-specific and all PnPEs; however, an increase of PEs by MRSA has emerged. Continuous surveillance is crucial to establish whether this epidemiological finding is transitory or not.

Keywords: Methicillin-resistant *Staphylococcus aureus*, pleural empyema, pneumococcal conjugated vaccine, pneumococcal empyema, staphylococcal empyema

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Introduction

In countries where the 13-valent pneumococcal conjugate vaccine (PCV13) is widely used, its effectiveness on all invasive pneumococcal diseases (IPDs) in children has shown a decrease in incidence, mortality, and a great reduction of serotype 19A and many others included in this vaccine.[1–6] Previous publications from elsewhere, have also demonstrated the effectiveness of PCV13 on complicated pneumonia, including pneumococcal pleural empyema (PnPE) in children, with little emergence of other pathogens.[7–11] In this study, we investigated whether there was a reduction in PnPE cases in our hospital with the PCV13 based on prospective/active surveillance, as well to identify emergence of other pathogens causing pediatric pleural empyemas (PEs). The Tijuana, Mexico–San Diego, California (USA) border is the busiest crossing in the world and has very relevant health issues that concern both countries.[12–14]

Material and methods

From 1 October 2005 to 31 January 2018 (12.3 years) we performed active/prospective surveillance for all pediatric (<16 years of age) cases of PE at the General Hospital of Tijuana, Mexico. Surveillance was developed as follows: once a patient < 16 years of age was admitted with a clinical/radiological diagnosis of community-acquired pneumonia complicated with pleural effusion, a chest puncture was promptly performed, if a purulent extraction or PF with more than 1000 leukocytes was obtained (defined as case), an immediate inoculation of pleural fluid (PF) into a radiometric broth media (BACTEC®, Becton Dickinson, Franklin Lakes, NJ, USA) was followed, and incubated at 37°C with 5% CO_2, with final identification performed using Vitek/Microscan Vitek2®, BioMérieux, Hazelwood, Missouri, USA,). Since 2014, polymerase chain reaction (PCR) was added to all culture-negative isolates. For real-time (RT)-PCR, deoxyribonucleic acid (DNA) extraction from PF was performed using QIAGEN® QIAamp DNA blood mini kit (QIAGEN, Shanghai, China) following product instructions. An aliquot of 200 µl PF was processed, and the DNA eluted in 100 µl of TE buffer. An RT-PCR assay on Mx3000P qPCR Systems (Stratagene®, La Jolla, CA, USA) was used to identify seven common pathogens that cause bacterial PEs (targeted genes: 16S, *femA*, *hly*, *ctrA*, *lytA*, *bexA*, and *cfb*, for *Escherichia coli*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and group B streptococcus, respectively).

S. pneumoniae serotypes were detected by either Quellung reaction (Statens Serum Institut®, Copenhagen, Denmark) or PCR: for *S. pneumoniae* molecular serotyping, a sequential multiplex PCR method approved by the CDC (Center for Disease Control and Prevention) was performed. All serotype-specific primers were first tested with individual isolates of the targeted serotypes. To ensure that the primers would detect all strains within the given serotype, an additional 5–10 different clinical isolates within each targeted serotype were amplified with its corresponding primer sets.

For *S. aureus* strains, methicillin resistance was identified by either using 6 µg/ml of oxacillin in Mueller-Hinton agar supplemented with 4% NaCl, or by PCR detecting the *mec*A gene. The reaction protocol was as follows: an initial FastStart DNA *Taq* polymerase activation phase at 95°C for 10 min; a 45-cycle amplification phase consisting of a 95°C segment for 10 s, a 50°C segment for 10 s, and a 72°C segment for 20 s; a melt phase from 45 to 75°C with a temperature transition rate of 0.1°C/s; and a rapid cooling phase. The presence of amplified DNA was measured by detection of energy emitted at 640 nm (for the presence of the *mecA* gene). The temperature at which the hybridization probes dissociated from the target sites was determined by melting curve analysis, as provided for by the LightCycler® software (Roche Molecular Systems, Belmont, CA, USA), this served as an independent indicator of the specificity of hybridization.

Demographic, clinical, tomographic/radiological, laboratory and microbiological evaluations were performed on each patient prospectively. Statistical analysis was purely descriptive. This study was accepted by the hospital's internal review board. No additional interventions were added to the gold-standard treatment each child received. Follow up was undertaken for every child with community-acquired PE.

Results

A total of 64 PEs were identified (5.28/year). Median age was of 51 months (1–191), and median hospitalization period was 18 days (4–35). Decortication was performed in 42% of the cases, and two children died (3.2%). Bacterial

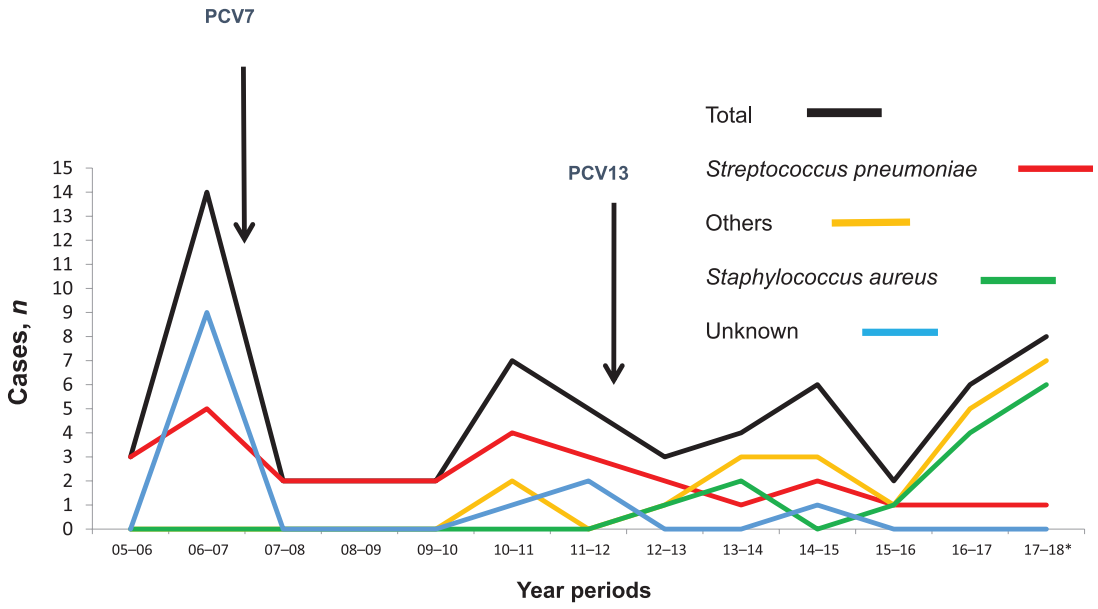

Figure 1. Pediatric pleural empyemas Tijuana General Hospital, Mexico October 2005–January 2018 (n = 64).
The line 'Others' (in orange) includes empyemas caused by *Staphylococcus aureus* (in green).
PCV (Pneumococcal Conjugate Vaccine)

identification was obtained from 51 (80%) cases. During the 2006–2007 period, there were nine cases without bacterial isolation. However, during the following years, the percentage for bacterial identification improved. From 2014 onward, PCR was performed on all culture-negative PFs. The microbiological etiology was identified in all but one case of PF (see Figure 1).

S. pneumoniae was the leading cause of all culture-/PCR-confirmed PE (29 = 56.8%), followed by *S. aureus* (14 = 27.4%), *Streptococcus pyogenes* (3 = 5.9%) and others (peptostreptococcus, *Pseudomonas aeruginosa, Klebsiellla oxytoca, Streptococcus salivaris, Streptococcus milleri*, one of each; 5 = 9.8%; see Figure 1). Most strains were isolated by conventional culture (46/51, 90%), with a higher recovery rate on *S. pneumoniae* by PCR (50% of the last six isolates since PCR introduction).

There were no differences in clinical manifestations prior to admission, outcomes during hospitalizations, or laboratory findings between PnPEs and non-PnPEs. Both groups had a high percentage of thrombocytosis on the Cell Blood Count (CBC), which has been mentioned previously in several studies.[15,16]

In May 2012, PCV13 was initiated, with a 56.1% relative reduction on all PnPEs, a clear 'elimination' of serotype 19A (a well-known replacing and severe pathogenic pneumococcal serotype),[3–5] an 81% decrease in all serotypes included in the vaccine, with little emergence of other serotypes (see Figure 2). Nevertheless, the number of cases with serotype 3 dropped from four to two cases before and after PCV13 introduction, consistent with other publications showing the relatively poor efficacy of this vaccine on this particular serotype.[8]

To measure the impact of PCV13 *versus* PnPE and nonpneumococcal PE, we compared number of cases per month (79 months of surveillance before, and 69 months following PCV13 introduction, respectively) and then calculated the reduction of those 'cases per month' after PCV13 was initiated. As seen in Figure 3, PCV13 showed high impact on all PnPEs (indeed, higher on PCV13-specific serotypes); however, due to an increase in the last 3 years of PE due to *S. aureus* (13 cases following PCV13 implementation, see Figures 1 and 3), we could assume that the impact of PCV13 on all causes of PE is absent (Figure 3). All but one isolate of *S. aureus* from PF were methicillin-resistant *S. aureus* (MRSA), including one D-test-positive (inducible resistance of clindamycin) strain. PE caused by MRSA did not develop more complications when compared with both PnPE and other causes (bacteria) of PE,

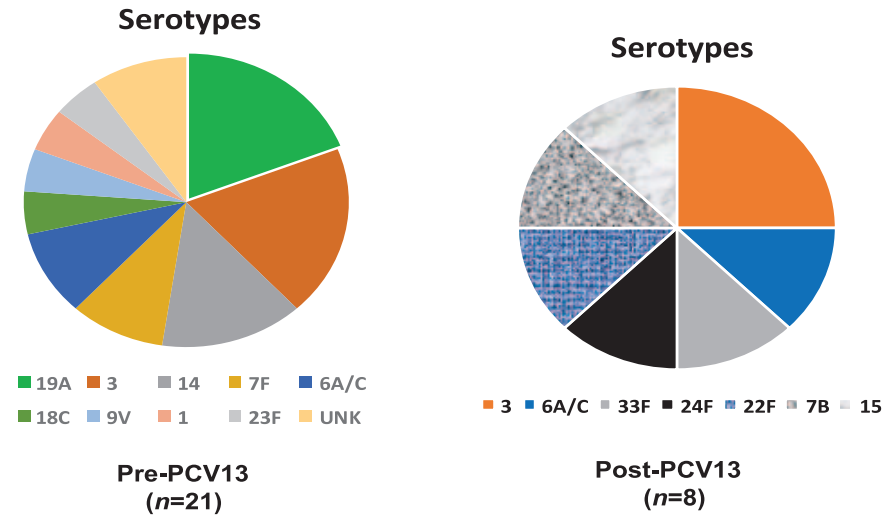

Figure 2. Pneumococcal pediatric serotypes.
Associated with pleural empyema (n = 29–56.9%): serotype distribution based on the PCV introduction (%).
PCV (Pneumococcal Conjugate Vaccine).

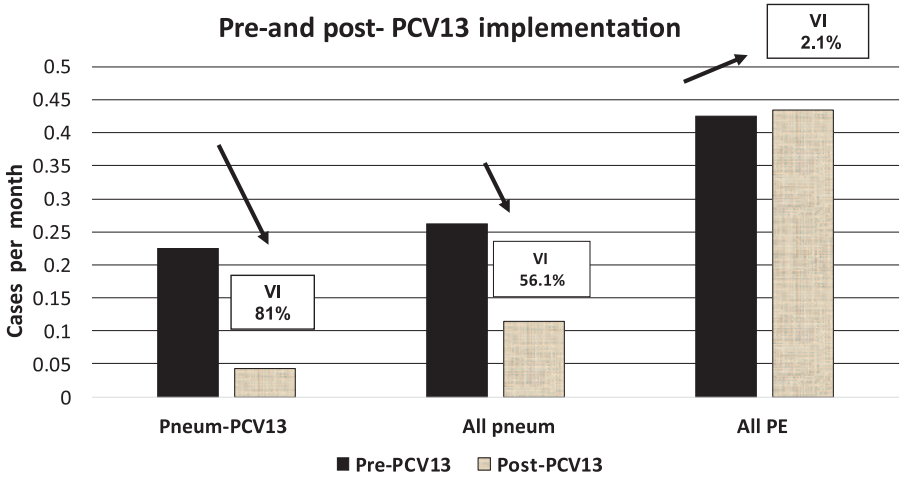

Figure 3. PCV13 impact (VI) on PCV13-serotype-specific pneumococcal empyemas, all pneumococcal-serotype empyemas, and all causes of pleural empyemas (n = 51).
Impact measured by cases per month before and after PCV13 implementation.
PCV13, (13-valent pneumococcal conjugate vaccine); PE, (pleural empyema); VI, Vaccine Impact; pneum, (pneumococcal serotype(s)).

however, the number of cases is still low to establish a more precise difference.

Discussion

Morbidity for PEs is high and is associated with hospital costs, even sequelae, and frequently requires surgery (decortication) or causes other complications, including respiratory sequelae and death.[17,18]

S. pneumoniae has been identified as the leading cause of PE both in children and adults worldwide, particularly in children before introduction of PCVs.[7–9,11,19–21]

In the USA, many European countries, Israel, and other countries in which PCV13 has been introduced as part of the pediatric immunization scheme, both IPD and PnPE have significantly decreased. As in our study, a decrease in PnPE from serotypes included in the vaccine has been observed, as well as little emergence of other non-vaccine serotypes.[7–9,11,19–22] Indeed, even with a good vaccine coverage (78–83%), the impact of

PCV13 on PnPE in our population was rapid. We do not have a concise explanation for that result, but maybe there is indirect immunization from vaccinees coming from San Diego, California (the highest-transit border in the world),[12–13] a city with a much longer PCV13 immunization time than Tijuana, but again, this is a mere speculation.

PE caused by *S. aureus* had been well documented prior to the introduction of PCVs (including PCV13).[23–25] There have been reports documenting a potential increase in the number of PEs caused by *S. aureus* following PCV13 implementation;[26] however, from reports in the US, this problem seems to be decreasing following vaccination.[27]

In Latin America, the most reliable data come from Uruguay and Argentina. However, the emergence of staphylococcal PE has not yet been reported despite several years of PCV massive immunization in children.[7,11]

The CDC considers community-acquired MRSA (CA-MRSA) infections an international problem, mostly due to misuse of antibiotics.[28] Most of CA-MRSA acquisitions have been related to soft tissue or osteoarticular infections;[29–32] however, reports of CA-MRSA PE have also been received in recent years.[26,33]

This is the first Latin American study with active/prospective surveillance that demonstrated CA-MRSA PEs in children. We are aware that our data come only from one hospital in Northern Mexico and cannot be applied to all of Mexico. It is possible these data could represent a transitory event, even an outbreak.

Furthermore, given the similarities in our data with previous reports, we can conclude continued surveillance is required and crucial. An increase in the overall global awareness on CA-MRSA infections is necessary.[28,31,33]

Regarding PCV13 administration, the rise of CA-MRSA PE does not change, at this point, its impact on PnPE in children. Furthermore, based on active surveillance, its global administration at this point should not be stopped but should be continuously monitored.

We are still concerned regarding our 2006–2007 period, in which culture-negative samples were very high, and at that time, we lacked molecular tools for clearer bacterial identification. Nevertheless, it is likely that those culture-negative specimens were due to *S. pneumoniae*, based on its unique characteristic of being a 'fastidious bacteria,' as published by Blasche et al.[34]

Conclusions

Following 12.3 years of active surveillance, PCV13 has shown impact on both serotype-specific and all PnPEs. Nevertheless, an increase of PE by CA-MRSA has emerged. Continuous and close surveillance is crucial to determine if this epidemiological behavior is transitory, and to continue monitoring the PCV13 impact on PnPE in children.

Ethical statement

Our study did not require an ethical board approval because it did not contain human or animal trials. All procedures undertaken on patients of this study were part of gold-standard care.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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