Changes in Hospitalizations for Pneumonia After Universal Vaccination With Pneumococcal Conjugate Vaccines 7/13 Valent and *Haemophilus influenzae* Type b Conjugate Vaccine in a Pediatric Referral Hospital in Uruguay

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Background: In 1994, Uruguay included *Haemophilus influenzae* b (Hib) conjugated vaccine in a 3 + 1 schedule. In March 2008, 7-valent pneumococcal conjugate vaccines (PCV7) was included in a 2 +1 schedule. In 2010, 13-valent PCV replaced PCV7. Catch-up immunization was offered. The aim of this study was to describe the etiology of community-acquired pneumonia (CAP) in children 0–14 years of age hospitalized at the Hospital Pediatrico-Centro Hospitalario Pereira Rossell between 2003 and 2012.

Methods: Annual hospitalization rates (per 10,000 discharges) for CAP and bacterial-confirmed CAP in children 0–14 years of age was described prior PCV7 vaccination (2003–2007), during the year of implementation of PCV7 (2008) and after the introduction of PCV7 (2009–2012). Data regarding age, strains isolated from pleural fluid and/or blood, vaccination status, pneumococcal and *H. influenzae* serotypes were obtained from Hospital Pediatrico-Centro Hospitalario Pereira Rossell databases and vaccination records.

Results: Hospitalization rates for CAP and pneumococcal CAP between prevaccine years and the last year after introduction of vaccination with PCV (2012) significantly decreased by 78.1% and 92.4%, respectively. Significant reduction for 13-valent PCV vaccine serotypes and significant increase for nonvaccine serotypes was observed. A decrease in *Staphylococcus aureus* pneumonia was observed. Hospitalization rates for *H. influenzae* CAP remain stable before and after pneumococcal vaccination.

Conclusions: Three years after PCV7/13 introduction into the routine vaccination schedule, there was a rapid and significant reduction in rates of CAP and P-CAP. An increase of etiology of CAP by other agents was not observed.

Key Words: *Streptococcus pneumoniae*, pneumonia, vaccine, *Haemophilus influenzae*, *Staphylococcus aureus*

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Universal vaccination against childhood communicable diseases is 1 of the most cost-effective public health interventions available to improve health care of children.[1] Pneumonia represents 1 of the most frequent causes of death in children <5 years of age and it could be considered a vaccine preventable disease.[2–4]

By reducing mortality and morbidity, vaccination can contribute substantially to achieve the Millennium Development Goal number 4: reduce mortality rate among children <5 years of age by two-thirds between 1990 and 2015.[1,5] Currently available vaccines against bacteria such as *Streptococcus pneumoniae* (pneumococcal conjugated vaccine 7, 10 or 13 valent), *Haemophilus influenzae* type b (Hib) and *Bordetella pertussis (*acellular or cellular vaccines) have demonstrated that it is possible to reduce significantly the pneumonia incidence of children[6,7]

In Uruguay, before 2008, pneumococcal serotypes 14, 1 and 5 were the leading cause of community-acquired pneumonia (CAP), because of the fact that *H. influenzae* type b is not a common cause of CAP among vaccinated children. In Uruguay, *H. influenzae* type b conjugated vaccine was incorporated to the routine childhood vaccination program in 1994 at 2, 4 and 6 months of age with a booster dose at 12 months. Since 1999, *H. influenzae* type b vaccine has been included in a pentavalent (Tetanus-*B. pertussis*-Diphtheria-Hepatitis B-Hib) vaccine with the same schedule. Coverage of 95% or more has been achieved since 2005 for all the doses of pentavalent vaccine. Other *H. influenzae* serotypes or *H. influenzae* nontypable were infrequent cause of CAP among healthy children.[6–10]

Staphylococcus aureus is not a very common cause of CAP in Uruguay but in 2001 community-acquired methicillin resistant *S. aureus* (CA-MRSA) emerged as a cause of skin and soft tissue infections, osteomyelitis, arthritis and pneumonia in children. In 2003, CA-MRSA caused severe cases of CAP.[11]

In March 2008, Uruguay included 7-valent pneumococcal conjugate vaccine (PCV7) into routine vaccination program, in a 2 + 1 schedule (given at 2, 4 and 12 months of age). Catch up immunization was offered to children born in 2007 (2 doses, at 15 and 17 months of age). Uruguay switched to 13-valent PCV (PCV13) with same vaccination schedule, in April 2010. A catch up immunization was offered to children born from January 1, 2005 to April 23, 2009, with a single dose of PCV13.

Vaccines included in the National Immunization Program are free of charge for the patients, universal and mandatory in Uruguay. National vaccination data demonstrated high compliance with PCV7/13 use: ≥93% of children received 3 doses (cohort 2008 and 2009) and 98% and 95% have been vaccinated with 1 and 2 doses of PCV13, respectively, for cohort 2010.[10]

PCV effectiveness against hospitalized pneumonia has been demonstrated in children.[12–15] In Uruguay, a significant reduction in hospitalization rates caused by pneumonia has been observed among children <5 years of age in different hospitals after the incorporation of PCV7 and PCV13 into the National Immunization Program.[16,17]

Surveillance is mandatory after PCV introduction to evaluate epidemiologic changes of *S. pneumoniae* serotypes causing pneumococcal CAP and/or a potential increase of other agents like *S. aureus* or *H. influenzae*.[18] The aim of this study was to describe etiology for CAP in children 0–14 years of age hospitalized at the Hospital Pediatrico-Centro Hospitalario Pereira Rossell from January 1, 2003, to December 31, 2012.

MATERIAL AND METHODS

This is an observational and retrospective study in which data from patients 0 month to 14 years of age hospitalized because of pneumonia at Hospital Pediatrico-Centro Hospitalario Pereira Rossell (HP-CHPR) from January 1, 2003, to December 31, 2012, were analyzed. HP-CHPR located in the capital, Montevideo, is a reference pediatric hospital of the most important health care provider from Uruguay (1,241,864 affiliates). It provides 3rd level care to around 300,000 children <15 years of age and 2nd level care to about half of this population who lives in Montevideo.

HP-CHPR databases, HP-CHPR Microbiology Laboratory database and patient records were used as a data source. HP-CHPR applies standardized protocols in the care of children with CAP including chest radiogram, blood culture and pleural fluid study if applicable. Standard laboratory practice at HP-CHPR includes microscopic examination, culture and susceptibility testing.[19,20] *S. pneumoniae* isolates were referred to the National Reference Laboratory for "quellung" serotyping (Camou T, Garcia Gabarrot G, Servicio Nacional de Laboratorios de Salud Pública, Ministerio de Salud Pública, Montevideo, Uruguay). Case definitions were based on HP-CHPR[21] published national guidelines are given below.

Pneumonia

Only cases that had a community onset of disease were included. CAP was defined as any case with clinical signs of pneumonia and chest radiograph compatible with pneumonia (alveolar or lobar consolidation with or without pleural effusion).

Empyema

Empyema was defined as CAP cases in which pleural fluid had at least 1 of the following: lactate dehydrogenase >1000 U/L, pH <7.20, glucose < 40 mg/dL, increased cellularity with predominance of polymorphonuclear leukocytes and bacteria on direct microscopic examination.

If a bacterium was isolated from blood and/or pleural fluid the case was subcategorized as bacterial-confirmed CAP. If *S. pneumoniae* was isolated from blood and/or pleural fluid, it was subcategorized as pneumococcal CAP (P-CAP). P-CAP includes cases of bacteremic pneumonia without empyema and pneumococcal empyema cases. If *S. aureus*, *H. influenzae* or other bacteria were isolated from blood or pleural fluid, the case was subcategorized as *H. influenzae* CAP or *S. aureus* CAP.

The following observational years were analyzed for P-CAP: before PCV7/13 vaccination program implementation (January 1, 2003, to December 31, 2007), year of implementation of PCV7 (2008) and after PCV7/13 vaccination program implementation (January 1, 2009, to December 31, 2012). The same observation periods were used to analyze *S. aureus* and *H. influenzae* pneumonia rates. For every year of the study, we collected the number of discharges and the number of CAP, bacterial-confirmed CAP and P-CAP.

Vaccine failure was defined as follows: according number of doses of PCV received (PCV7 or PCV13), year of birth, year of hospitalization and months of life, 3 categories were defined: nonvaccinated, incomplete immunization and complete immunization. Complete immunization was defined as 2 doses for children <12 months of age, 3 doses for children with ≥12 months, 2 doses of PCV7 in the second year of life for children born in 2007 and 1 dose of PCV13 for children born between January 1, 2005, and April 23, 2009. We also defined vaccine failure if 1 child completely vaccinated presented P-CAP with PCV7 or PCV13 2 weeks after the last dose received. The children categorized as vaccine failure were evaluated for detection of the most frequent primary or secondary immunodeficiencies (blood cells count, tests for investigation of HIV infection, immunoglobulin dosage, serum protein electrophoretic, complement factors dosage (CH50, C3, C4), pneumococcal and tetanus antibodies and isohemagglutinins).

Ethical Considerations

Data described belong to the systematically surveillance performed at the HP-CHPR about acute lower respiratory infections. The authors are members of the group in charge of this clinical and microbiology surveillance. The study has the approval of the Ethics Committee of HP-CHPR.

Statistical Considerations

Discharge rates and average annual rates per 10,000 hospitalized children with 95% confidence intervals were described for CAP and CAP subcategories. Analysis was done by P-CAP, P-CAP by PCV7 serotypes, P-CAP by 6 additional serotypes included in PCV13 and by nonvaccine serotypes and finally for CAP caused by another bacteria. For each subcategories of CAP, the percent of change was calculated, comparing findings before and after PCV7/PCV13 vaccination.

The descriptive statistical analysis included performance of specific univariate association assessments. The degree of univariate association was examined by use of Fisher exact test and/or χ^2 test (2-tailed) with Yates correction, as appropriate. All reported probability values were 2-tailed and $P < 0.05$ were considered statistically significant.

RESULTS

CAP Discharge Rates

Table 1 shows the total number of discharges, number of cases and CAP discharge rates during 2003–2012 in children 0–14 years of age. CAP discharges rates per 10,000 before PCVs vaccination (2003–2007) period was 879.1 (833.4–924.7) versus 193 (167.8–219.7) in 2012 (post PCV7/13 implementation), a significant reduction of 78.1% was observed.

Bacterial-confirmed CAP

Table 1 also shows the total number of CAP with identified bacteria in blood and/or pleural fluid (bacterial-confirmed CAP). The average annual rate per 10,000 discharges for bacterial-confirmed CAP during the period 2003–2007 was 74.3 (60–88). It decreased to 9.2 (3.5–14.9) in 2012. It was a significant reduction of −87.7%. The numbers of P-CAP and annual rates were described in Table 1.

S. pneumoniae was the most frequent cause of pneumonia in the whole period, 630 children were hospitalized by P-CAP. *S. pneumoniae* was isolated from blood in 338, from pleural fluid in 235 and from blood and pleural fluid in 57 children, corresponding to bacteremic P-CAP 73.5% of the cases. About 597 of the *S. pneumoniae* isolated were serotyped.

H. influenzae was isolated in 46 children, 39 were classified as CAP caused by *H. influenzae* as a single etiology and 7 as co-infections. In 5 children, *H. influenzae* type b was isolated. Within the remaining children hospitalized with CAP because of *H. influenzae*, 2 strains were *H. influenzae* type a, 1 *H. influenzae* type

TABLE 1. Annual Discharges, Number of Cases and Rates (Per 10,000 Discharges) for CAP; Number of Bacterial-confirmed Pneumonia and Number of Cases and Rates for P-CAP (Per 10,000 Discharges) in Children 0–14 Years of Age

		CAP		Bacterial-confirmed Pneumonia	P–CAP	
Year	Total Discharges	N	Rate (95% CI)	N	N	Rate (95% CI)
2003	13,531	1032	762 (717.9–807.4)	99	84	62 (54.1–82.3)
2004	15,413	1318	885.1 (810.9–899.2)	151	130	84.3 (69–99)
2005	15,146	1515	1000 (952–1048)	128	115	75.9 (63–90.8)
2006	14,799	1379	931.8 (883–982)	98	91	61.5 (49.8–75.1)
2007	15,107	1265	837.4 (792–884)	76	69	45.7 (38.8–57.5)
2008	12,979	828	637.9 (595–682)	48	42	32.4 (23.6–40.3)
2009	11,382	463	406.8 (371–445)	41	37	32.5 (22.1–42.9)
2010	10,885	331	304 (271.8–336.3)	34	32	29.4 (19.2–39.5)
2011	10,523	234	222.3 (194.1–250.5)	27	23	21.8 (12.9–30.8)
2012	10,835	210	193 (167.8–219.7)	10	7	6.4 (1.6–11.2)

HP-CHPR, 2003–2012.

f and 38 nontypable. The *H. influenzae* CAP average annual rate before PCV vaccination (2003–2007) was 3.3 (0.4–6.3) and after vaccination (2009–2012) was 3.6 (0.07–7.26). *H. influenzae* was isolated from blood in 30 children, from pleural fluid and blood in 4 children and from pleural fluid in 12 children.

During the study, 5 children were hospitalized for CAP with isolation of methicillin susceptible *S. aureus*, all of them before 2008 and 32 with CAP because of CA-MRSA, 27 of them before 2008, 2 in 2008 and 2 as a single etiology and 1 as co-infections with *H. influenzae* during the period after PCV7 implementation. The average annual rate before vaccination (2003–2007) for *S. aureus* CAP was 4 (0.8–7.2) and it was 0.68 (−0.8 to 2.4) after vaccination (2009–2012). *S. aureus* was isolated from pleural fluid in 26 children, from pleural fluid and blood in 5 children and from blood in 1 child. During this period of analysis, 3 children were hospitalized because of *Streptococcus pyogenes* pneumonia; 2 as a single etiology and 1 as co-infection with *H. influenzae*. All *S. pyogenes* strains were isolated from blood and in the case of co-infection also from the pleural fluid.

Regarding co-infections, 11 children hospitalized with P-CAP presented a co-infection with nontypable *H. influenzae;* 9 with *S. pneumoniae*, the pneumococcal serotypes were 3, 8, 22F, in 2 cases 14 and in other 2 children 7F. Five children were hospitalized in the prevaccine period, those with serotype 14, 1 child with serotype 8 and 2 strains were not serotyped. The other co-infections were during the period 2009–2012. In 2012, a child was hospitalized because of a CA-MRSA and nontypable *H. influenzae*, another child was hospitalized because of *S. pyogenes* and nontypable *H. influenzae* pneumonia. In 10 cases of co-infection, the strains were isolated from the pleural fluid and in 1 from blood culture.

P-CAP and PCV13 P-CAP

P-CAP discharge rates decreased from an average of 66.2 (53.1–79.2) prevaccination (2003–2007) to 6.4 (1.6–11.2) in 2012, representing a significant reduction of 90.4% (Table 1). A significant reduction of 97.1% was also observed for P-CAP caused by PCV13 vaccine serotypes with a decrease from an average annual rate prior vaccination of 60.8 (48.3–3.3) to 1.8 (−0.7 to 4.4) in 2012 (Table 2).

P-CAP by the 7 PCV7 Serotypes, PCV13 6 Additional Serotypes and Nonvaccine Serotypes

Table 2 and Figure 1 show annual rates for P-CAP by the 7 common serotypes in PCV7 and PCV13, the 6 additional serotypes in PCV13 and nonvaccine serotypes. Before universal vaccination, serotypes included in PCV7 and PCV13 represented 98.2% of P-CAP hospitalized cases (450 of 458 cases). Before PCV7 introduction, serotypes 14 and 6B were the most common isolates in PCV7 group representing 73% (131/179) and 9% (16/179), respectively. P-CAP discharges rates because of PCV7

TABLE 2. Annual Discharges, Number of Cases and Discharges Rate (Per 10,000 discharges) for CAP, Discharge Rates for P-CAP by PCV7 Serotypes, 6 Additional Serotypes in PCV13 and Nonvaccine Serotypes in Children 0–14 Years of Age

Years	Total Number of Discharges	P-CAP PCV7 Serotypes	Rate per 10,000 Discharges (95% CI)	P-CAP PCV13 6 Additional Serotypes	Rate per 10,000 Discharges (95% CI)	Nonvaccine Serotypes	Rate Per 10,000 Discharges (95% CI)
2003	13,531	49	36 (26 to 46.3)	31	23 (14.8 to 31)	2	1.4 (−0.5 to 3.5)
2004	15,413	42	27.9 (19.5 to 36.2)	74	48 (37 to 59)	2	1.29 (−0.5 to 3.09)
2005	15,146	30	19.8 (12.7 to 26.8)	75	49.5 (38.3 to 60.7)	2	1.32 (−0.5 to 3.15)
2006	14,799	28	19 (12 to 26)	56	37.8 (28 to 47.7)	1	0.67 (−0.6 to 2)
2007	15,107	30	20 (12.8 to 27.1)	35	23.3 (15.6 to 31)	1	0.66 (−0.6 to 2)
2008	12,979	20	15.4 (8.6 to 22.1)	20	15.4 (8.6 to 22.1)	2	1.5 (−0.6 to 3.6)
2009	11,382	7	6.15 (1.6 to 10.7)	26	23 (14 to 31.6)	4	3.5 (0.07 to 6.9)
2010	10,885	4	3.67 (0.07 to 7.3)	20	18.73 (10.3 to 26.4)	7	6.4 (1.6 to 11.1)
2011	10,523	0	0	14	13.3 (6.3 to 20.2)	8	7.6 (2.3 to 12)
2012	10,835	0	0	2	1.84 (−0.7 to 4.4)	5	4.6 (0.5 to 8.6)
Total	120,100	210		353		34	

HP-CHPR, 2003–2012.

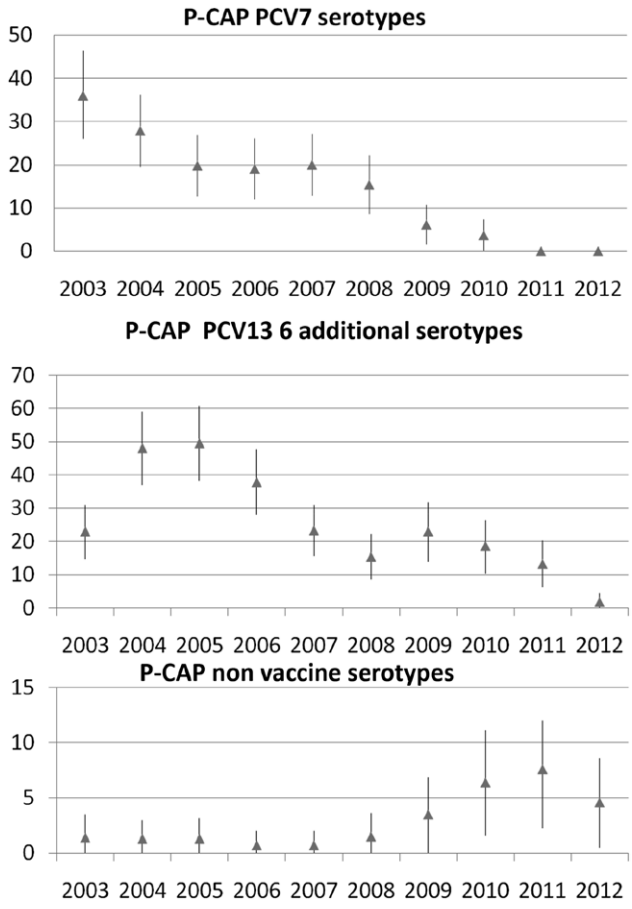

FIGURE 1. Annual discharges rates 95% CI (per 10,000 discharges) for P-CAP by PCV7 serotypes, 6 additional serotypes in PCV13 and nonvaccine serotypes in children 0–14 years of age. HP-CHPR, 2003–2012.

serotypes were 36 (26–46.3) in 2003; the average annual rate was 21.8 (14.3–29.2) during the period 2004–2006 and it was 20 (12.8–27.1) in 2007.

After PCV7 implementation, P-CAP discharge rates because of 7 vaccine serotypes had a significant and rapid decline and the average annual rate during the period post vaccination (2009–2012) was 2.7 (−0.3 to 5.8), comparing with the average annual rate of 30.4 (21.5–39.2) during the pre vaccination period (2003–2007). It represents a significant reduction of 91.2%.

Discharges rates per 10,000 for P-CAP caused by 6 additional serotypes had spontaneous and significant fluctuations during 2003–2007. During 2004–2006, the average annual rate reached 50 (34.3–55.6); however, the rate was 23 in 2003 (14.8–31) and it was pretty similar in 2007, 23.3 (15.6–31), showing a significant increase during 2004–2006. P-CAP discharges rate caused by 6 additional serotypes in PCV13 prior any PCV vaccination (2003–2007) was 36.4 (26.7–46.2); during 2008, it was 15.6 (8.6–22) and it fell to 1.84 (−0.7 to 4.4) in 2012 representing a significant reduction of 95% after PCV7/13 implementation (Table 2).

Other serotypes not included in PCV7 neither in PCV13 had a significant increase after PCVs introduction. The average annual rate per 10,000 discharges before (2003–2007) vaccination was 1.6 (−0.6 to 4), and after PCV7/13 vaccination (2009–2012) was 5.5 (1.1–10).

Discharge Rate by Pneumococcal Serotype

Vaccine Serotypes

During all the study period, the most frequent serotypes were 14, 1, 5, 6B, 7F, 3, 19F and 19A. Table 3 and Figure 2 show rates per 10,000 discharges for those serotypes. Discharge rates declined after PCV7/PCV13 implementation. Rates reduction was significant for serotypes 14, 1 and 5.

Before PCVs implementation, the most frequent serotypes were 14, 1 and 5. Particularly, serotypes 1 and 5 were associated with fluctuations during 2003–2007. Serotype 1 discharges rates were 6 (1.8–10) in 2003; 18 (11.6–25.3) during the period 2004–2006 and 12 (6.4–17.4) in 2007. Serotype 5 had a similar behavior with smaller numbers; in 2003, discharge rate was 6 (1.8–10) and during the period 2004–2006, it was 14.5 (8.4–20.6) and finally it was 2 (−0.2 to 4.2) in 2007.

Nonvaccine Serotypes

During the period before PCVs universal use (2003–2007), the nonvaccine serotypes were: 15 (2), 22 (1) and 12F (1); in 2008, 1 strain 24F was isolated and during the period after universal vaccination (2009–2012), the nonvaccine serotypes were: 12F (5), 24F (3), 22F (2), 33 (2), 24A (1), 23A (1), 15C (1), 16A (1), 11A (1), Pool G (1) and Pool C (2).

PCV7 and PCV13 Vaccination Status and P-CAP

During 2008–2012 period, 114 children were hospitalized because of P-CAP, 64 of them, according to age, had indication for pneumococcal conjugated vaccine. During PCV7 universal vaccination period (2008–2009), 21 children with indication of PCV7 were hospitalized for P-CAP. PCV7 serotype strains were isolated in 4 children: serotype 14 was isolated in 2 nonvaccinated children. Serotype 6B was isolated in 2 children, 1 child was 10 months of age and had received 1 dose at 2 months old and the other child was 2.5 years of age and had received 1 dose in the second year of life; both were incompletely immunized.

During 2010 (transition year from PCV7 to PCV13), 20 children with indication of PCV were hospitalized for P-CAP. PCV13 serotypes were isolated in 11 children; none of them had received any doses of PCV13. PCV7 serotypes were isolated in 4 children; in 3 of them, incompletely immunized serotype 14 was isolated. During 2011 and 2012 (PCV13 universal vaccination period), 22 children with indication of PCV13 were hospitalized for P-CAP. PCV13 serotypes were isolated in 11 children, 5 of them were nonvaccinated as they did not receive the offered catch-up dose. Otherwise, 3 children were classified as incompletely immunized. Vaccine failure was observed in 3 children: 1 child was 3 years of age and serotype 1 was isolated, he had received 2 PCV7 doses during his first year of life and 1 PCV13 dose at 18 months of age. Another child was 16 months of age, serotype 3 was isolated and he had received 3 PCV13 doses at 3, 5 and 12 months of age. The last 1 was 19 months of age, serotype 3 was isolated and he had received 3 PCV13 doses at 3, 5 and 13 months of age. A primary or secondary immunodeficiency was excluded in 2 of the 3 children, 1 is still under evaluation. The 5 children with Hib-CAP were categorized as incompletely vaccinated for *H. influenzae* type b conjugate vaccine.

Antimicrobial Susceptibility

S. pneumoniae Penicillin Susceptibility

All isolates were susceptible to penicillin (≤ 2 μg/mL) according to Clinical and Laboratory Standards Institute 2010 except one of the 630 strains that had a minimum inhibitory concentration of 4 μg/mL and was a serotype 14 isolated in 2004.[20]

TABLE 3. Annual Discharge Rates (Per 10,000 Discharges) for Most Common Serotypes for P-CAP in Children 0–14 Years of Age

	Rate Per 10,000 Discharges (95% CI)										
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
14	26.6 (17.9 to 35.3)	18.2 (11.4 to 24.9)	18.5 (11.6 to 25.3)	11.5 (6 to 16.9)	14.6 (8.5 to 20.6)	14.6 (8 to 21.2)	2.6 (−0.3 to 5.6)	2.8 (−0.4 to 5.8)	0	0
1	6 (1.8 to 10)	22 (14.6 to 29.5)	23.1 (15.5 to 30.7)	18.9 (11.9 to 25.9)	12 (6.4 to 17.4)	6.9 (2.4 to 11.5)	8 (2.7 to 13)	9 (3.5 to 15)	1.9 (−0.7 to 4.5)	0.92 (−0.8 to 2.7)
5	6 (1.8 to 10)	3.2 (0.4 to 6.1)	21.1 (13.8 to 28.4)	13.5 (7.6 to 19.4)	2 (−0.2 to 4.2)	1.5 (−0.6 to 3.7)	7 (2 to 12)	1.8 (−0.7 to 4.4)	2.8 (−0.3 to 6)	0
7F	3.69 (0.4 to 6.9)	5.8 (2 to 9.7)	2 (−0.2 to 4.2)	1.4 (−0.5 to 3.2)	6 (2 to 9.8)	3.1 (0.06 to 6.1)	3.5 (0.07 to 7)	1.8 (−0.7 to 4.4)	2.8 (−0.3 to 6)	0
3	2.95 (0.06 to 5.8)	5.8 (2 to 9.7)	1.3 (−0.5 to 3.2)	2 (−0.2 to 4.3)	1.9 (−0.2 to 4.2)	2.3 (−0.3 to 4.9)	0	4.6 (0.6 to 8.6)	4.8 (0.5 to 8.9)	0.92 (−0.8 to 2.7)
6B	3.69 (0.4 to 6.9)	3.2 (0.4 to 6.1)	1.3 (−0.5 to 3.2)	2.7 (0.05 to 5.5)	0	0.8 (−0.7 to 2.3)	1.8 (−0.7 to 4.2)	0	0	0
19 A	3.69 (0.4 to 6.9)	1.9 (−0.2 to 4.1)	2 (−0.2 to 4.2)	2 (−0.2 to 4.3)	1.9 (−0.2 to 4.2)	0.8 (−0.7 to 2.3)	3.5 (0.07 to 7)	0.9 (−0.9 to 2.7)	0.95 (−0.9 to 2.8)	0
6 A/C	0.73 (−0.7 to 2.2)	0.6 (−0.6 to 1.9)	0	0.67 (−0.6 to 2)	0.66 (−0.6 to 1.9)	0.8 (−0.7 to 2.3)	0.9 (to 0.8 to 2.6)	0	0.95 (0.9 to 2.8)	0

HP-CHPR, 2003–2012.

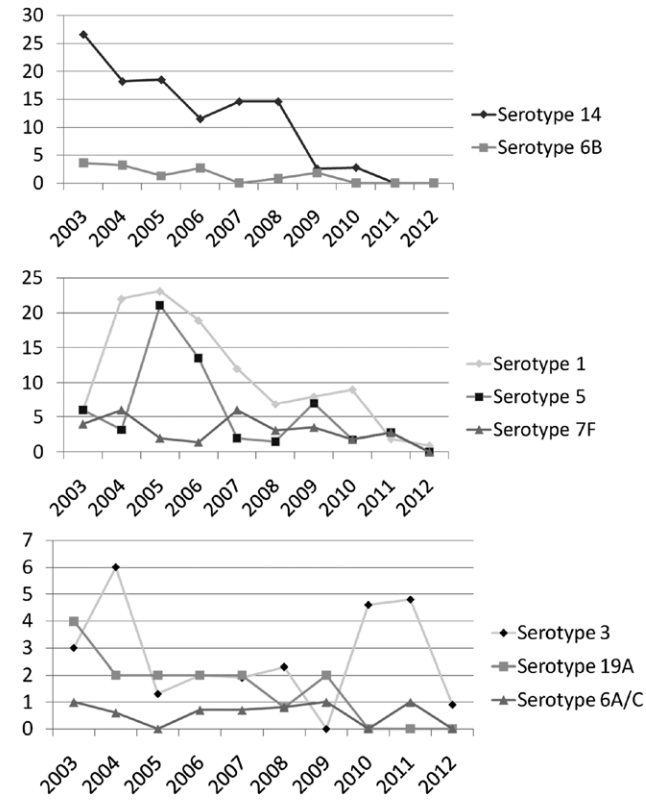

FIGURE 2. Annual discharge rates (per 10,000 discharges) for most common serotypes for P-CAP in children 0–14 years of age. HP-CHPR, 2003–2012.

H. influenzae, β-lactamase Production

Information about β-lactamase production was available for 42 (21 in each period, pre- and postvaccine) of the 46 strains of *H. influenzae*. There were no β-lactamase producing strains in the prevaccine period, whereas in the postvaccine period 19% (4/21) produced the enzyme.

S. aureus Susceptibility

Five strains were methicillin susceptible. The 32 strains CA-MRSA isolated were susceptible to gentamicin, trimethoprim-sulfamethoxazole and vancomycin and 8 were resistant to erythromycin and inducible clindamycin resistant (25%).

DISCUSSION

CAP is 1 of the most frequent vaccine preventable infectious diseases.[1,3,4] Pneumonia caused by *S. pneumoniae* is 1 of the most important public health problems worldwide. It causes around 1 million deaths among children <5 years of age.[22]

S. pneumoniae classically produces a lobar pneumonia that is characterized on physical examination by decreased breath sounds and/or rales; in infants, clinical manifestations can be only cough and rapid breathing.[3,23] A clinical picture of pneumonia because of *H. influenzae* and *S. aureus* are similar and CA-MRSA pneumonia presentation is usually more severe.[11,18] Bacterial pneumonia may have complications: respiratory failure, pleural effusion, empyema and necrotizing pneumonia are the most common.[6,7,23–26]

In Uruguay like in other Latin America countries prior PCVs universal vaccination, the most common *S. pneumoniae* serotypes associated with pneumonia were 14, 1, 5, 6B, 19A, 3

and 7F.[7,27–29] In our country, before PCV universal vaccination, in children <2 years of age, the most common P-CAP serotypes in order of frequency were 14, 6B, 5, 3 and 1 and in children 2–4 years of age were 14, 1, 5, 3 and 7F.[6,7,16] Serotypes 1, 3, 5, 7F, 14 and 19A are associated to pleuropneumonia and necrotizing pneumonia worldwide.[7,16,24,26] PCV7 effectiveness on CAP was observed after vaccination in several regions in vaccinated and nonvaccinated population.[12–16,30]

In Uruguay after PCV7 universal vaccination, a significant decrease in CAP hospitalization among children ≥2 years of age was seen.[16,17] PCV13 also demonstrated an impact in hospitalization for CAP in Uruguay among children <2 years of age.[17] A significant decrease for P-CAP hospitalization by PCV7 serotypes was observed in children <5 years of age.[16] Universal vaccination with an immunogenic and safe vaccine, which includes pneumococcal serotypes associated with pneumonia and pleuropneumonia, like PCV13, may improve PCV7 effectiveness against pneumonia.[6,16,31,32]

PCV13 effectiveness data against invasive pneumococcal disease and nasopharyngeal colonization have been published.[33–35] In 8 US hospitals, a decline of invasive pneumococcal disease cases because of 1, 5, 19A and 3 has been observed.[33] In our study, hospitalization for P-CAP caused by PCV7 strains showed a significant decrease during the period 2008–2009; a second step of reduction has been observed during the period 2011–2012, after PCV13 introduction. P-CAP due to PCV7 strains had a significant and sustained decrease during the period 2009–2012. Nonvaccine failure for PCV7 serotypes was observed. We observed a reduction of P-CAP hospitalization for serotypes 1 and 5 before 2008. This secular trend was reflected in the overall decrease of CAP at that time.

In 2009, once again serotypes 1 and 5 increased compared with 2008, but not at the level it arrived during 2004–2006. After the PCV13 universal vaccination, once again serotypes 1 and 5 significantly decreased. The significant increase of PCV13 in 6 additional serotypes during 2004–2006 can be described as an outbreak caused by serotypes 1 and 5. In HP-CHPR, during the period 2000–2002, the median rate per 10,000 discharges for the 6 additional serotypes was 22,[14–23] similar to 2003 and 2007 where serotypes 1 and 5 accounted for 75% of the 6 additional serotypes.[6]

Serotypes 1 and 5 are well-known to behave in a different epidemiologic pattern than other serotypes. They are associated with waves or epidemics, becoming prevalent over a period and then naturally decreasing.[36,37] Reduction of P-CAP were already evident before PCV7/13 implementation; however, the reduction on rates of hospitalization for P-CAP caused by serotype 1 and 5 only reached statistical significance decrease comparing prevaccination period (2003–2007) with the PCV13 vaccination period (2010–2012). During this period, we did not observe an expected outbreak for serotypes 1 and 5. Serotypes 1 and 5 continue to be at the lowest figures. During the study period, serotype 14 did not have significant fluctuations. Decrease of serotype 14 and the other 6 common vaccine serotype in PCV7/13 reached statistical significance only in the postvaccine period (2009–2012).

Other less frequent serotypes like serotypes 3, 7F, 19A and 6A/C showed a non significant decrease in the postvaccine period. Serotype 3 is an important serotype in Latin America and in other regions all over the world.[6,7,16,27,29,38] In Uruguay, it is associated with empyema.[6,7,16] During the whole period, we observed variations in serotype 3 hospitalization rates at the HP-CHPR. Three vaccine failures of PCV13, according to our definition, were observed. Of the 3, 2 were in children with 2 doses in the first year of life and a booster in the second year of life, both had serotype 3 P-CAP and the other 1 with a single dose in the second year of life had a serotype 1 P-CAP. In an immunogenicity study, serotype 3 elicited lowest immune response than the other PCV13 serotypes in healthy infants who received PCV13 at 2, 4, 6 and 12 months of age.[35] In our study, the children with vaccine failure did not receive a 3 + 1 schedule. Although the incidence of hospitalizations for serotype 3 P-CAP had a nonsignificant reduction after universal vaccination, the effectiveness of 2+1 schedule of PCV13 on serotype 3 P-CAP will need to be closely monitored.

CAP caused by nonvaccine serotypes had a significant increase during the period 2009–2012 and the rate per 10,000 discharges was higher than the P-CAP vaccine serotypes; however, it is important to highlight that, for example, regarding 2012 P-CAP nonvaccine serotypes rate was 4.6 (0.5–8), up to 10 times smaller comparing prevaccination rates of vaccine serotypes. There were diversity of nonvaccine serotypes causing P-CAP after 2008 and the most common were 12F, 24F, 22F and 33. Similar findings were reported in 8 children hospitals of United States.[33] *H. influenzae* pneumonia hospitalization rates among children before and after PCV introduction remained unchanged. We did not observe an increase of *S. aureus* pneumonia cases; the hospitalization rate for this agent, in fact, declined.

This is an important data, because Uruguay was 1 of the countries where CA-MRSA emerged as an important cause of severe bacterial infections in the previous decade.[39,40] *H. influenzae*, *S. aureus* and *S. pyogenes* remain a nonfrequent cause of pneumonia, but in 2012 they represented 30% of the confirmed bacterial pneumonia at the HP-CHPR.

CONCLUSIONS

Significant reduction on CAP after PCV7/13 introduction has been seen in the reference pediatric hospital HP-CHPR, Uruguay, after universal vaccination with a 2 + 1 schedule with a catch-up program. Four years after PCV7 implementation, there was a rapid and significant reduction in rates of P-CAP. P-CAP caused by serotypes included in PCV7 practically disappeared. P-CAP caused by additional serotypes showed a significant reduction. A clear 2-step reduction after each introduction of PCV (PCV7 and PCV13) was seen, attesting for the addition beneficial effect of PCV13 over PCV7. An increase in etiology of CAP by other agents was not observed and serotypes replacement is not relevant. Continued surveillance will be able to prove the consolidation of the success of PCV13 and clarify the effectiveness for each serotype as well as the occurrence of any serotype replacement.

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