

Impact of Universal Pneumococcal Vaccination on Hospitalizations for Pneumonia and Meningitis in Children in Montevideo, Uruguay

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Background: In March 2008, Uruguay included PCV7 into the routine vaccination program, in a 2 + 1 schedule for children <2 years of age. Catch-up immunization was offered to children born in 2007. Greater than 95% of children received their first and second doses. The aim of this study was to assess the effect of this strategy.

Methods: Annual hospitalization rates (per 10,000 discharges) for community-acquired pneumonia (CAP) in children <14 years of age and pneumococcal meningitis are described prior to PCV7 vaccination (2005–2007), during the year of implementation (2008) and following vaccine introduction (2009). Data regarding age, diagnosis, vaccination status, and pneumococcal serotype were obtained from Hospital Pereira Rossell databases and vaccination records.

Results: Comparison of hospitalization rates for CAP and pneumococcal CAP (P-CAP) between prevaccine years (2005–2007) and the year after vaccination (2009) decreased significantly in all children by 56% and 48.2%, respectively. Significant reduction was observed for vaccine serotype P-CAP (serotype 14 P-CAP decreased from 26.6 to 2.5 per 10,000 discharges) in children <2 years of age. A significant reduction in pneumococcal meningitis of 59% was seen in this age group; median rates prevaccination decreased from 17 (12.2–24.9) to 7 (3–11.8) after the administration of vaccine. No vaccine failures for P-CAP or pneumococcal meningitis were seen in fully immunized children.

Conclusions: One year after PCV7 introduction into the routine vaccination schedule of Uruguay, there was a rapid and significant reduction in rates of CAP, P-CAP, and pneumococcal meningitis in children <2 years of age.

Key Words: *Streptococcus pneumoniae*, pneumonia, meningitis, vaccine, Uruguay

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Pneumococcal disease is an important cause of morbidity and mortality globally.^{1,2} Surveillance data from Uruguay demonstrate that, before introduction of PCV7 into the routine immunization program, *Streptococcus pneumoniae* was the most important bacterial agent of community-acquired pneumonia (CAP) representing 9% of all admissions to the national reference pediatric hospital, Hospital Pediátrico—Centro Hospitalario Pereira

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Rossell (HP-CHPR), with a mean annual admission rate of 1126/10,000 during 2000–2004.³ *S. pneumoniae* was also the leading cause of acute suppurative meningitis in children and the case fatality rate for pneumococcal meningitis was 35%.⁴ Prior to PCV7 introduction, PCV7 serotypes accounted for 59% of invasive disease isolates in children <2 years of age in Uruguay.^{5–13}

PCV7 was incorporated into the routine childhood vaccination program for children <2 years of age in March 2008. A 2 + 1 schedule (doses at 2, 4, and 12 months of age) with catch-up immunization for children born in 2007 (2 doses, at 15 and 17 months of age) was initiated.¹⁴ Vaccination is free of charge and mandatory in Uruguay. National vaccination data demonstrate high compliance with PCV7 vaccination with 98% of children receiving the first dose and 96% the second dose. Partial data for the 2008 birth cohort demonstrate an 82% compliance rate with the third dose. Compliance with catch-up recommendations for the 2007 birth cohort was 85% for the first dose (at 15 months of age) and 70% for second dose (at 17 months of age) (Unpublished data from: Comisión Honoraria de la Lucha Antituberculosa y Enfermedades Prevalentes).

We assessed the impact of PCV7 introduction in Uruguay by comparing hospitalization rates for pneumonia and pneumococcal meningitis at HP-CHPR in the following 3 time periods: prior to PCV7 incorporation into the routine immunization program (2005–2007), during the initial year of vaccination (2008), and following vaccination (2009).

MATERIALS AND METHODS

This is a retrospective study in which data from patients 1 month to 14 years of age hospitalized at HP-CHPR for pneumonia and pneumococcal meningitis were analyzed. HP-CHPR located in the capital, Montevideo is the *Administración de Servicios de Salud del Estado* (ASSE) reference pediatric hospital. It provides care of 3rd level to 306,657 children younger than 15 years old and care of 2nd level to about half of this population who lives in Montevideo. Data sources were as follows: Reports of Diseases of Mandatory Reporting issued by the Ministry of Public Health (www.msp.gub.uy), HP-CHPR databases, HP-CHPR Microbiology Laboratory database, and patient records. Standard of care at HP-CHPR dictates that a chest radiograph and blood culture be obtained for children requiring hospitalization for suspected pneumonia. In addition, pleural fluid is obtained upon admission, if applicable. Blood and cerebrospinal fluid cultures are obtained for children admitted with suspected meningitis. Standard laboratory practice at HP-CHPR includes microscopic examination, culture and susceptibility testing. In addition, *S. pneumoniae* isolates are sent for serotyping to Servicio Nacional de Laboratorios de Salud Pública, the national reference laboratory (CamouT, García Gabarrot G. Servicio Nacional de Laboratorios de Salud Pública. MSP. Montevideo, Uruguay).

Case definitions were based on published guidelines used at HP-CHPR¹⁵ and were as follows:

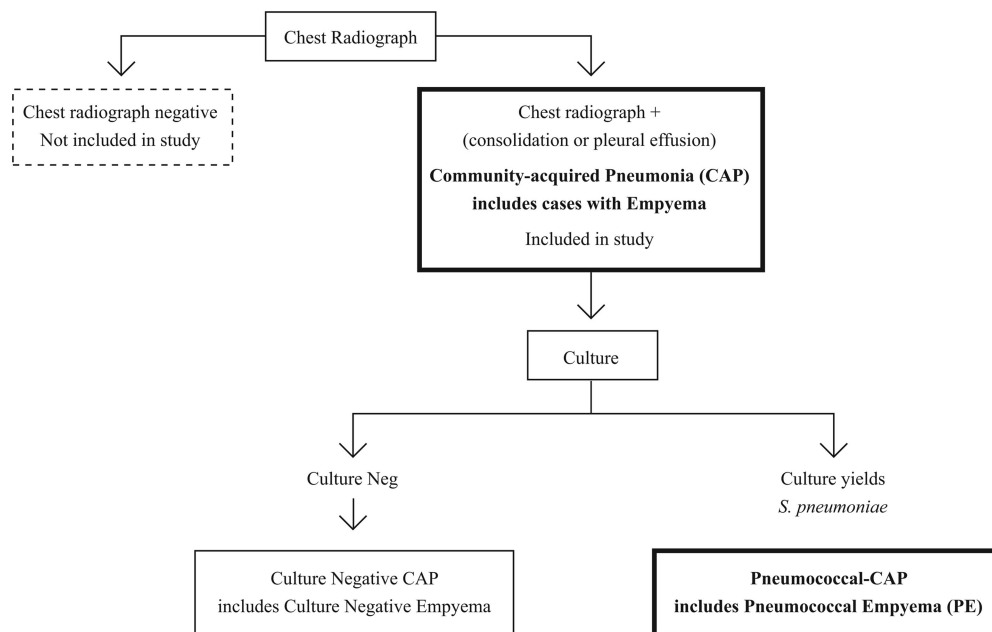


FIGURE 1. Patient flow and diagnoses. Suspected community onset pneumonia case.

Pneumonia. Only cases that had a community onset of disease were included. Thus all cases of pneumonia are referred to as CAP (Fig. 1). CAP was defined as any case with clinical signs of pneumonia and chest radiograph compatible with pneumonia of a probable bacterial etiology (alveolar or lobar consolidation with or without pleural effusion). Thus, CAP encompasses all pneumonia cases including those with empyema. Empyema was defined as CAP cases in which pleural fluid had at least one of the following: LDH >1000 U/L, pH <7.20, glucose <40 mg/dL, increased cellularity with predominance of polymorphonuclear leukocytes, and bacteria on direct microscopic examination. If *S. pneumoniae* was isolated from blood or pleural fluid, it was subcategorized as pneumococcal-CAP (P-CAP). P-CAP includes cases of bacteremic pneumonia without empyema and pneumococcal empyema (PE) cases.

Meningitis. Only cases of pneumococcal meningitis were analyzed. Pneumococcal meningitis was defined as any case of suspected bacterial meningitis in which the cerebrospinal fluid was compatible with bacterial meningitis (at least one of the following applies: leukocytes >10/mm³, proteins >40 mg/dL, or glucose <40 mg/dL), and where *S. pneumoniae* was isolated in CSF and/or blood.

The following observational periods were defined: prior to implementation of the PCV7 vaccination program (January 1, 2005 to December 31, 2007), year of implementation of the program (January 1, 2008 to December 31, 2008), and following vaccination program implementation (January 1, 2009 to December 31, 2009).

Statistical considerations were as follows: discharge rates per 10,000 hospitalized children with 95% confidence intervals were described for CAP, CAP subcategories, and pneumococcal meningitis for each time period. For each clinical condition the percent change were calculated, comparing findings of previous (2005–2007 median rates) and following PCV7 vaccination (2009 rates). Analysis was performed by age groups (all up to 14 years of age, <2 years of age, 2 to 4 years of age, 5 to 14 years of age) and other parameters described, including doses of PCV7 received, and *S. pneumoniae* serotypes. Discharge rates for acute gastroen-

teritis were used as a control condition which is not expected to change with PCV7 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 $P < 0.05$ was considered statistically significant.

RESULTS

Impact of PCV7 Program on CAP

Discharge Rates for CAP and Subcategory of Empyema

Table 1 shows the annual number of cases, and discharge rates for CAP and the subcategory of empyema, during 2005–2009 in children <14 years of age. CAP discharge rates decreased from a median of 921 (865–979) prevaccination (2005–2007) to 406 (368–466) in 2009 in children <14 years of age, representing a significant reduction of 56%.

Analysis of discharge rates by age group demonstrates statistically significant reduction in CAP in children <2 years of age after the introduction of PCV7. Although discharge rates for CAP in children 2 to 4 years of age began to decline prior to implementation, but a sustained and statistical significance was achieved postimplementation of the PCV7 program. A significant reduction in CAP discharge rates was also observed in children ≥ 5 years of age after the implementation of the PCV7 program (Fig. 2).

Table 1 also shows the annual number of cases, and discharge rates for the subcategory of empyema in children <14 years of age. Empyema discharge rates decreased from a median of 111 (91.8–133) prevaccination (2005–2007) to 67.6 (53.7–83.9) in 2009 representing a significant reduction of 39.2% (Fig. 2).

Analysis of discharge rates by age group demonstrates statistically significant reduction in empyema in children <2 and 2 to 4 years of age after the introduction of PCV7. Empyema discharge rates decreased from a median of 106 (87.2–127.6) prevaccination (2005–2007) to 69 (54.1–86.9) in 2009 in children

TABLE 1. Number of Cases and Discharge Rates (per 10,000 Discharges) for Community Acquired Pneumonia (CAP), Pneumococcal-CAP (P-CAP), Emyema and Pneumococcal Emyema in Children 0–14 Years of Age at the Hospital Pediátrico - Centro Hospitalario Pereira Rossell (HP-CHPR), 2005 to 2009

Year	Total Discharges	CAP		Emyema		Pneumococcal-CAP		Pneumococcal Emyema		
		No. Cases	Rate (95% CI)	No. Cases	Rate (95% CI)	No. Cases	Rate (95% CI)	No. Cases	Rate (95% CI)	
Prior to PCV7	2005	15,146	1515	1000.3 (950–1052)	188	124.2 (107.1–142.6)	115	75.9 (63–90.8)	66	43.6 (34–55.1)
	2006	14,799	1379	931.8 (883–982)	169	114.2 (97.3–132.4)	91	61.5 (49.8–75.1)	55	37.2 (28.2–48)
	2007	15,107	1265	837.4 (792–884)	144	95.30 (80.6–112)	69	45.7 (38.8–57.5)	43	28.5 (20.9–38)
Year of implementation	2008	12,979	828	637.9 (595–682)	85	65.40 (52.6–80.6)	42	32.4 (23.6–40.3)	28	21.6 (14.6–30.8)
Post PCV7	2009	11,382	463	406.8 (371–445)	77	67.60 (53.8–74.1)	37	32.5 (22.1–42.9)	23	20.2 (13.1–29.8)

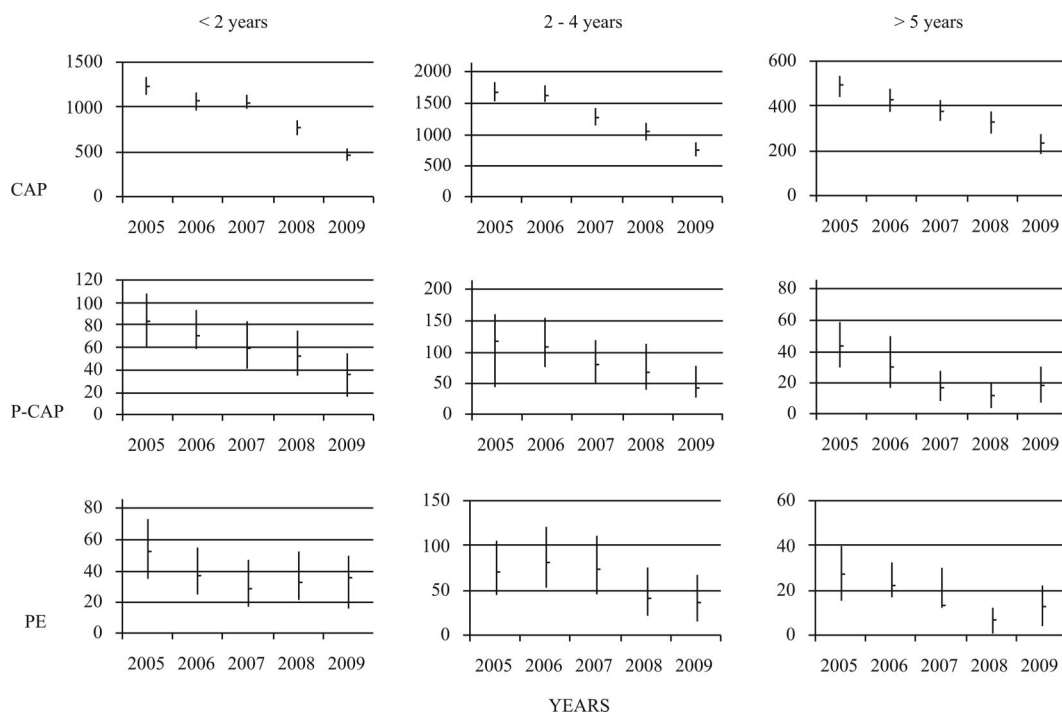


FIGURE 2. Discharge rates per 10,000 discharges (95% CI) for community acquired pneumonia (CAP), pneumococcal-CAP (P-CAP), and PE by age group at the Hospital Pediátrico - Centro Hospitalario Pereira Rossell (HP-CHPR), 2005–2009.

<2 years of age, representing a significant reduction of 35%. In children aged 2 to 4 years, the rates decreased from a median of 237 (208.6–268.2) prevaccination (2005–2007) to 143 (121.1–167.7) in 2009, representing a significant reduction of 40%. Emyema discharge rates in children ≥5 years of age decreased from a median of 63 (48.8–80) prevaccination (2005–2007) to 35 (24.7–48.9) in 2009, representing a nonsignificant reduction of 45%.

Discharge Rates for P-CAP and Subcategory of PE

P-CAP was diagnosed in 5% to 7.9% of CAP cases. The annual number of cases and discharge rates for P-CAP and the subcategory of PE in children <14 years of age are noted in Table 1. A significant 52% reduction in P-CAP discharge rates was seen in children <14 years of age, from a median of 61 (47.1; 77.8) prevaccination (2005–2007) to 31.6 (22.7; 38.8) in 2009. In children <2 years of age, there was a trend toward reduction of

P-CAP rate but statistical significance was not achieved. No significant reduction was achieved in the other age groups (Fig. 2).

There was also a nonsignificant 45.4% reduction of PE in the overall studied children from a median of 37 (27–46.7) prevaccination (2005–2007) to 20.2 (12–28.4) in 2009. This subcategory did not reach statistical significance reduction in any age group (Fig. 2).

Serotype Distribution of Vaccine Serotype (VST) Specific Discharge Rates for P-CAP

The distribution of *S. pneumoniae* serotypes are described in Table, Supplemental Digital Content 1, <http://links.lww.com/INF/A779>. The discharge rates of VST P-CAP by age group are shown in Table 2. The largest reduction in VST P-CAP was demonstrated in children <2 years of age with a significant reduction of 84.2%. A significant reduction was also seen in the 2- to

TABLE 2. Number of Cases and Discharge Rates (per 10,000 Discharges) for Pneumococcal CAP by PCV7 Serotypes by Age Group at the Hospital Pediátrico - Centro Hospitalario Pereira Rossell (HP-CHPR), 2005 to 2009

	<2 Years			2–4 Years			>5 Years		
	TD	P-CAP PCV7 Serotypes		TD	P-CAP PCV7 Serotypes		TD	P-CAP PCV7 Serotypes	
		n	Rate (95% CI)		n	Rate (95% CI)		n	Rate (95% CI)
2005	5728	21	36.6 (23.3–55)	2814	8	28.4 (13.2–53.9)	6810	1	1.4 (0.07–7.2)
2006	5364	20	37.2 (23.4–56.5)	2814	7	24.9 (10.8–49.2)	6812	1	1.5 (0.07–7.2)
2007	5628	19	33.7 (20.9–51.7)	2855	8	28 (13–53.2)	6729	2	3 (0.49–9.82)
2008	4931	14	28.3 (16.1–46.5)	2306	5	21.7 (7.9–48)	5839	1	1.7 (0.08–8.44)
2009	4048	2	4.9 (4.2–15.9)	1963	2	10.2 (1.7–33.6)	5218	2	3.8 (0.64–12.66)

TD indicates total discharges.

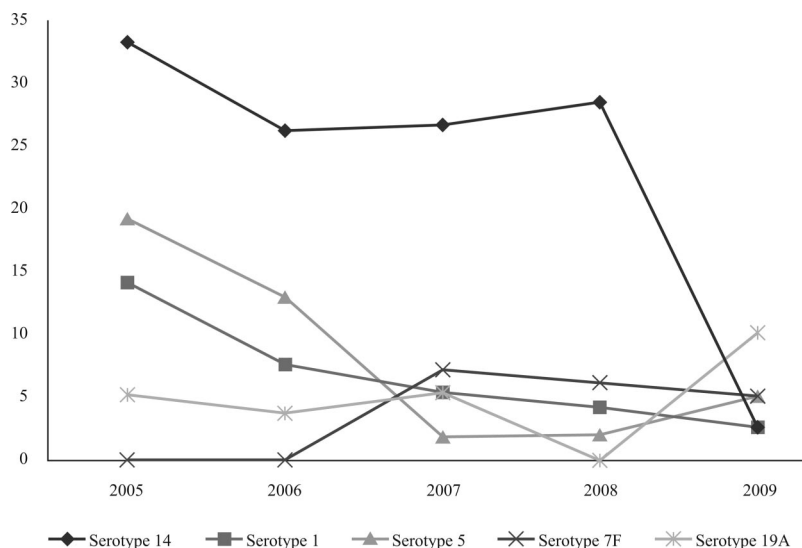


FIGURE 3. Annual discharge rate (per 10,000 population) of the most common serotypes in children less than 2 years of age in the Hospital Pediátrico - Centro Hospitalario Pereira Rossell (HP-CHPR), 2005–2009.

4-year-old age group. In children ≥5 years of age, no changes were observed.

Prior to the introduction of PCV 7, the rank order for the 3 most common serotypes causing P-CAP in children <2 years were 14, 1, and 5. In children older than 2 years of age, the rank order was 1, 5, and 14. The 7 serotypes included in PCV7 accounted for 33.6% of all P-CAP in the overall group and accounted for 52.1% and 27.3% cases in children aged <2 and 2 to 4 years of age, respectively. Post PCV7 program implementation (2009), nonvaccine serotypes (NVST) 1, 5, 7F, 19A, and 24F became the most frequent causes of P-CAP. In children <2 years, serotype 19A was the most common serotype while in those 2 to 4 years of age, serotypes 1 and 5 were the most common (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/A779>; and Fig. 3).

Significant serotype-specific reduction in P-CAP was demonstrated for serotype 14. In children <2 years of age, the rate of serotype 14 P-CAP decreased from a median prevaccination for the years 2005 to 2007 of 28.4 (20.2–39.2) to 2.5 (1–5.5) postvaccination (2009); a significant reduction of 91.2%. Discharge rates for serotype 14 P-CAP also decreased significantly in children 2 to

4 years of age from 17.6 (11.4–25.9) to 5.1 (2.8–10.2), a 71.1% decrease. In children ≥5 years of age, serotype 14 was less frequent and no changes were observed.

No significant reductions were seen for P-CAP caused by NVST 1 and 5 in all age groups.

Prior to the introduction of PCV7, 40.3% of PE in children <2 years of age were caused by VST, mostly serotype 14. Post PCV7 implementation, only 9% was caused by a VST. NVSTs associated with PE in this age group were as follows: 19A, 5, 7F, 1, 9N, and 24F. In the 2 older groups of children, serotypes 1 and 5 caused the majority of PE cases pre- and post PCV7 implementation.

Serotype-specific significant reductions of VST 14 PE were seen in all age groups with a 100% reduction. No significant reductions were seen for NVST 1 and 5 PE in all age groups (Table, Supplemental Digital Content 2, <http://links.lww.com/INF/A781>).

PCV7 Vaccination Status and P-CAP

During the vaccine introduction year, 620 children <5 years of age were admitted with CAP, 17 had a history of PCV7

vaccination. *S. pneumoniae* was isolated in 3 children. Two children who had received 1 vaccine dose had NVST (3 and 7F). Serotype 14 was isolated in 1 child who had not received vaccine despite being eligible.

In the year after vaccination, 343 children ≤ 4 years of age were admitted to hospital with CAP, 170 had a history of PCV7 vaccination. *S. pneumoniae* was isolated in 27 children. Fifteen children had received at least one dose of PCV7, the remainders were unimmunized. A vaccine serotype was isolated in 3 children 6B (2) and 14 (1) all of them were partially vaccinated with PCV 7. No fully immunized child developed VST P-CAP. A NVST was isolated in 12 children. The serotypes isolated from those children were as follows: 19A (4); 5 (2); 7F (2); 24F (2); 9N (1); and 6A/C (1).

Impact of PCV7 Program on Pneumococcal Meningitis

Thirty-five cases of pneumococcal meningitis were identified in children less than 14 years of age at HP-CHPR during the study period; 30 prior to the implementation and 5 during and after PCV7 implementation. In the pre- PCV7 years, discharge rates (95% CI) for pneumococcal meningitis showed yearly decreases; 11.2 (5.87–16.53), 5.5 (1.7–9.3), and 3.3 (0.4–6.2) in 2005, 2006, and 2007, respectively. Discharge rates were 0.8 (–0.7–2.3) in the year of implementation and 2.6 (–0.3–5.5) in the year post PCV7.

In children < 2 years of age, a significant reduction in pneumococcal meningitis discharge rates of 59% was seen; median rates prevaccination decreased from 17 (12.2–24.9) to 7 (3–11.8) postvaccination. Prior to PCV7, the serotypes causing pneumococcal meningitis in children < 14 years of age were as follows: 14 (7); 5 (8); 1 (3); 7F (3); 6B (3); 12F (2); 6A/C (1); 23B (1); pool D (1) and 1 was not serotyped. In children < 2 years, VST accounted for 28.5% of the pneumococcal meningitis cases. During and postimplementation, the serotypes causing pneumococcal meningitis were the following: 18C (1); 3 (1); 7F (1); 6A/C (1); and 10A (1). Of the 5 cases of pneumococcal meningitis, 3 children were < 2 years of age (serotypes 7F, 6 A/C, and 10A), 1 (serotype 3) was in the 2- to 4-year age group, and 1 (serotype 18C) was ≥ 5 years. The only child with a VST (18C) was unvaccinated. None of the 4 children with NVST meningitis were fully vaccinated with PCV7 (1 had received one PCV7 dose and the remainder were unimmunized despite 2 of them were eligible).

Penicillin Susceptibility

Before the introduction of PCV7, the only P-CAP isolates that were resistant to penicillin was serotype 14. Serotypes 19A, 24F, and 6B showed penicillin minimum inhibitory concentrations ≥ 0.12 $\mu\text{g}/\text{mL}$, these are considered susceptible according to Clinical and Laboratory Standards Institute 2010.¹⁶ Prior to the introduction PCV7, 7 (23.4%) serotype 14 strains isolated in meningitis were penicillin nonsusceptible, with minimum inhibitory concentrations of 0.12 to 2 $\mu\text{g}/\text{mL}$. After the introduction of PCV7, all the pneumococcal meningitis isolated were penicillin susceptible.

Discharge Rates for Acute Gastroenteritis

Discharge rates (95% CI) by year for acute gastroenteritis, used as control condition, were 350 (range, 302–372) in 2005; 270 (248–306) in 2006; 240 (215–275) in 2007; 340 (301–379) in 2008; and 350 (318–382) in 2009. No significant changes were found between the median rates (95% CI) of gastroenteritis discharges in 2005–2007: 287 (250–324) versus 2009: 350 (318–382) for all children < 14 years of age.

DISCUSSION

Pneumococcal disease is the leading cause of vaccine preventable mortality in children < 5 years of age, globally. In Latin

America, it is estimated that between 20,200 and 33,100 children die yearly from pneumococcal disease, mainly from pneumonia and meningitis.¹⁷ Thus, prevention with conjugate pneumococcal vaccination is a priority for the region.^{17,18} Uruguay was one of the first countries in Latin America to introduce vaccination with the heptavalent conjugate vaccine.¹⁹ PCV7 vaccination was incorporated into the national routine immunization program in March 2008. The vaccine schedule consists of 2 doses at 2 and 4 months of age followed by a dose at 12 months of age. Catch-up immunization was given to children up to 2 years of age. Uptake of vaccine was rapid with high compliance rates $> 95\%$ for the first and second doses.

Vaccination with PCV7 has proven to be effective in significantly reducing invasive pneumococcal disease,^{20–23} pneumonia,^{24–27} and otitis media^{28,29} in countries that have incorporated it into their routine pediatric immunization programs. In addition, protection of the unimmunized by the indirect or herd effect has also been documented.^{20,30} The impact of PCV7 vaccination has been demonstrated in routine vaccination programs using a 4-dose schedule (3 infant doses followed by a toddler dose, 3 + 1)^{20,23–25,28,30} and also with the alternate 3 dose schedule of 2 infant doses followed by a toddler dose (2 + 1).^{21,22,26,27,29} Our study is the first publication of PCV7 effectiveness data in Latin America. Significant reductions in hospitalizations for CAP and the subcategories of empyema and vaccine serotype CAP were documented after PCV7 introduction in the vaccine target group of children < 2 years of age. In addition, significant decreases in these diagnoses were also seen in unimmunized older age groups, potentially being the first indication of the herd effect, although a more prolonged period of surveillance may be necessary to ascertain the degree of protection in the unimmunized.

The impact we observed in reduction of hospitalizations for CAP and pneumococcal meningitis were in line with what others have demonstrated.^{24–27,30–32} The largest reduction, 90.7%, was observed for serotype 14 P-CAP in children in the target vaccine age group of < 2 years, and a significant reduction was also demonstrated in serotype 14 P-CAP in unimmunized children 2 to 4 years of age. Since it is not characteristic for serotype 14 to exhibit large natural fluctuations over time it is very likely that this dramatic and rapid decrease was secondary to PCV7 vaccination. Remarkably, in the year after PCV7 implementation there were no hospitalizations for vaccine serotype P-CAP or pneumococcal meningitis in fully immunized children.

Although these reductions in hospitalizations are likely due to the PCV7 vaccination program, several other factors may have contributed to the decreases seen. (1) In 2008, Uruguay implemented a National Integrated Health Program which has led to a reduction in the number of hospital admissions. In the population < 15 years, rate of comparison made between 2008 and 2007 was -23% . The use of rates per 10,000 discharges when comparing hospitalizations previous to and following PCV7 implementation allows for accurate interpretation of the data. Importantly, the change in the healthcare system did not affect the rates of hospital discharges for acute gastroenteritis, the control disease analyzed. (2) In addition to the predictable decrease in VST disease, we observed a reduction of hospitalization for P-CAP caused by NVST 1 and 5. The reduction in these 2 NVST was reflected in the overall decrease of CAP. Serotypes 1 and 5 are well known to behave in a different epidemiologic pattern than other serotypes in that they are associated with waves or epidemics, becoming prevalent over a period of time, then decreasing naturally.^{33–35} Therefore, reductions in disease due to these NVST are likely due to natural fluctuations and merely coincident in time with the

implementation of the PCV7 program. (3) Reduction in P-CAP were already evident before the implementation of universal PCV7 vaccination; however, these only reached statistical significance when comparing prevaccine with postvaccine years. The natural fluctuation in disease due to serotypes 1 and 5 is likely the explanation of the nonsignificant reduction prior to PCV7 implementation.

Although there was a reduction in VST PE, we were unable to demonstrate a significant reduction in discharge rates for PE. This highlights the importance of NVST as a cause of PE and although serotypes 1 and 5 are important in this disease, NVST 3 and 19A are also important causes of empyema in Uruguay.

The PCV7 vaccine program in Uruguay has been highly successful in significantly reducing overall CAP as well as CAP and meningitis caused by the serotypes included in the vaccine, but disease caused by serotypes not included in PCV7 persists, particularly empyema. Postintroduction of PCV7, the serotypes most frequently associated with CAP in children were 19A, 7F, and 5, and PCV13 covered 92% of the remaining invasive disease. To further decrease the burden of pneumococcal disease in Uruguay, the National Vaccination Program transitioned from PCV7 to PCV13 in March 2010. Children who had received PCV7 finished their schedule with PCV13. Catch-up vaccination with 1 dose of PCV13 was given to children 2 to 5 years of age. The inclusion of PCV13 in the vaccination schedule will likely provide protection against the remaining disease. Surveillance for CAP and pneumococcal meningitis is ongoing to assess the impact of PCV13.

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