Impact of the 13-valent pneumococcal conjugate vaccine on the incidence of consolidated pneumonia in children younger than 5 years old in Pilar, Buenos Aires: A population-based study

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ABSTRACT

Introduction. In January 2012, Argentina introduced the 13-valent pneumococcal Coverage in Pilar in 2012 reached>90% for the first two doses and 60% for the third dose. Objective. To measure the effectiveness of pneumonia (CP) in the two-year period following its introduction in the immunization schedule. and utpatients) in the first two years since the vaccine introduction (2012-2013) were included. radiological assessments were done as per the World Health Organization's criteria.

Results. Six hundred and sixty-six patients with clinical suspicion of pneumonia were included. others: 4). A significant reduction in the incidence old) was observed between the pre- and post-2013. No significant differences were observed

Conclusions. Following the introduction of PCV13 in Argentina's immunization schedule, a fast and significant reduction in the incidence of CP was observed, mainly in infants younger than 1 year old in 2012 and in children younger than 2 years old in 2013.

Key words: Streptococcus pneumoniae, pneumonia, conjugate vaccine, effectiveness, child.

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conjugate vaccine (PCV13) in its immunization schedule for children younger than 2 years old. PCV13 to reduce the incidence of consolidated Methods. Prospective, population-based study conducted in Pilar. All children younger than 5 year sold with clinical signs of pneumonia assisted at the reference hospitals (both inpatients The annual incidence of CP was compared to the 2003-2005 baseline period. Clinical and

CP was diagnosed in 309 patients; 52.1% were girls, 70.2% were younger than 2 years old, and 56.4% had been immunized with the PCV13; 4.5% (14/309) had bacteriological confirmation (S. pneumoniae: 4; N. meningitidis: 4; S. aureus: 2; of CP (per 100 000 children younger than 5 years immunization periods, from 750 (204/27 209) to 561 (171/30 475) in 2012 and to 453 (138/30 475) in 2013; effectiveness accounted for 25.2% and 39.6%, respectively. Reduction in infants younger than 1 year old: 33.9% in 2012 and 44.6% in 2013; and in children aged 12-23 months old: 57.9% in in the incidence of CP at an older age.

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INTRODUCTION

Streptococcus pneumoniae is the main bacterial cause of communityacquired pneumonia (CAP); however, establishing the burden of pneumococcal pneumonia accurately is difficult given that routine diagnostic tests have a low sensitivity. Microorganisms are isolated in the blood of less than 10% of patients hospitalized for CAP, and culture performance is greater when patients have empyema and there is a sample of pleural fluid available.1 Therefore, it is evident that microbiological diagnosis provides a very partial account of the impact of *S. pneumoniae*.

Due to such difficulties, the World Health Organization (WHO) developed a protocol based on the standardized interpretation of chest x-rays. The WHO proposed to measure vaccine effectiveness based on the reduction in "radiologicallyconfirmed consolidated pneumonia" as a reasonable approach to "bacterial pneumonia". The purpose was strictly epidemiological in order to provide an effective tool that would allow measuring the impact of introducing conjugate pneumococcal vaccines in national immunization schedules.2

In Argentina, a prospective, population-based study was conducted in Pilar between 2003 and 2005 (3-year period), that allowed to establish baseline data regarding the burden of consolidated pneumonia (CP) in children <5 years old, which accounted for an average of 750 cases per 100 000 (95% confidence interval

[CI]: 650-860), and 1922 per 100 000 in infants younger than 1 year old (95% CI: 1560-2330).³

In January 2012, the 13-valent pneumococcal conjugate vaccine (PCV13) was introduced in the national immunization schedule as of two months old, with a "2 + 1" schedule (one dose at 2 months old, another dose at 4 months old, and a booster dose at 1 year old). During the first year after introducing the vaccine, children aged between 12 and 24 months old were also immunized with two doses in order to achieve a greater impact on the reduction of invasive pneumococcal disease in the shortest period possible in Argentina.4 The national coverage of PCV13 for 2012 was 69% for the first dose and 22% for the third dose, while in 2013, it accounted for 96% and 81%, respectively.5 Coverage in the district of Pilar was estimated using nominal records and accounted for 100%, 83% and 48.3% for the first, second and third doses, respectively, out of a total of 6735 live newborn infants in 2012.6 In 2013, coverage accounted for 87.6%, 84.9% and 61.3%, respectively.7

OBJECTIVE

To measure the effectiveness of PCV13 to reduce consolidated pneumonia in the two-year period following its introduction in the national immunization schedule.

METHODS

Population

Pilar is located 54 km to the northwest of the province of Buenos Aires and, according to the 2010 National Population Census; it has 299 077 inhabitants, and 30 475 (10.2%) are younger than 5 years old. The latter made up the follow-up population.

Inclusion criteria

All children <5 years old with clinical signs of pneumonia were assisted either as inpatients or outpatients between January 1st, 2012 and December 31st, 2013 at the reference hospitals located in Pilar (two public hospitals: Hospital de Niños Federico Falcón, Hospital Juan Sanguinetti; and a private hospital: Hospital Universitario Austral). The algorithm in *Figure 1* shows how consolidated pneumonia was diagnosed.

Exclusion criteria

Patients with nosocomial pneumonia were excluded; as per the WHO, this is defined as pneumonia that had neither developed nor was in the incubation period, i.e., it was acquired during hospitalization and is not the reason for hospitalization.⁸

Figure 1. Inclusion criteria: operational algorithm

Suspected case of pneumonia: Child <5 years old with clinical signs of pneumonia Clinical pneumonia Chest X-ray Chest X-ray Clinical card and digital image of chest X-ray Assessment by pediatrician and reference radiologist Yes Bacterial pneumonia Probable bacterial pneumonia (consolidated pneumonia)

Design

Prospective, population-based study conducted following the introduction of PCV13 in 2012 in the national immunization schedule.

Data collection

Data were obtained from medical records of patients assisted either as inpatients or outpatients who complied with inclusion criteria. Relevant data were summarized in a standard card and included age, sex, socioeconomic level as per Graffar's modified method, history of pneumococcal immunization (type of vaccine and number of doses), cohabitation with five or more people in the same house and with more than three people in the same room, prior hospitalizations, perinatal history, presence of underlying diseases, antibiotic treatment in the three previous months and in the week prior to hospitalization, selected respiratory signs and symptoms, complications, treatment and course.

Underlying diseases were defined as those indicated in the national recommendations for pneumococcal immunization in special hosts. ¹⁰ In addition, other risk conditions were studied, such as second-hand smoking and acute respiratory disease in the previous week.

Complications were defined as effusion, pneumothorax, atelectasis, necrotizing pneumonia, abscess, and respiratory failure.

Microbiological study

A microbiological study was conducted only in hospitalized patients. Bacterial etiology was studied in blood and/or pleural fluid. Pleural tap was performed when thoraco centesis was therapeutically indicated.

Isolations of *S. pneumoniae* were submitted to the National Infectious Disease Institute (*Instituto Nacional de Enfermedades Infecciosas*, INEI), National Administration of Health Institutes and Labs (*Administración Nacional de Laboratorios e Institutos de Salud*, ANLIS) "Dr. Carlos G. Malbrán" in order to confirm identification and serotyping by means of the Quellungreaction. Antimicrobial susceptibility was studied using the agar diffusion method and the minimum inhibitory concentration (MIC), established by means of broth or agar micro dilution method or E-test, according to the current standards of the Clinical Laboratory Standards Institute (CLSI).¹¹

Viral etiology was studied as per the treating pediatrician's clinical judgment. The indirect immunofluorescence (IIF) rapid diagnostic method was used for nasopharyngeal aspirates to look for the following respiratory viruses: respiratory syncytial virus (RSV), adenovirus, influenza A and B, and *para influenza* 1, 2 and 3.

Radiological assessment

Chest X-rays were captured in digital images and were interpreted by the investigator pediatrician and the reference radiologist in a blinded and independent manner as per the WHO methodology. Discrepancies were resolved through a third reading.

Definition of consolidated pneumonia

Pneumonia with dense opacity and cotton wool-like appearance (alveolar infiltrate), involving one or more segments or lung lobes, or an entire lung. It usually presents with an air broncho gram, and sometimes in association with pleural effusion.

Data analysis

Statistical analysis was done using the Epi Info software, version 6.4 (CDC, Atlanta), and the Epidat software, version 3.1.

Qualitative outcome measures were expressed

Table 1. Studied population: comparison of pre- and post-introduction of the 13-valent pneumococcalconjugate vaccine

Population included as per the algorithm		713 period 3-2005)	Post-PCV13 period (2012-2013)		
	n	%	n	%	
Total number of patients with clinical suspicion of pneumonia	1220	100.0	666	100.0	
Suspected cases of pneumonia with digital images of chest X-ray	1108	90.8	642	96.4	
Cases of consolidated pneumonia	611	55.1	309	48.1	
Cases of bacterial consolidated pneumonia	15	2.5	14	4.5	
Cases of pneumococcal consolidated pneumonia	7	1.2	4*	1.3	

PCV13: 13-valent pneumococcal conjugate vaccine. No significant differences between both periods.

^{* 2012:} n= 2; and 2013: n= 2.

in terms of percentage and analyzed using a χ^2 test with Yates' correction. Numerical outcome measures were described using mean value, standard deviation (SD), median and range.

The annual incidence of CP cases and the average annual incidence in the pre-immunization period with a 95% CI were estimated. The difference between pre-immunization and post-immunization incidence were expressed as effectiveness and estimating the percentage of reduction with a 95% CI.

A probability lower than 0.05 was considered significant.

Ethical aspects

No informed consent was requested for this research because it was a surveillance study. This study was approved by the Research Ethics Committee of participating hospitals.

RESULTS

During the two-year period following the introduction of the PCV13, 666 patients with clinical suspicion of pneumonia were included.

Of all X-rays, 96.4% (642/666) were photographed, and CP was diagnosed in 48.1% (309/642). *Table 1* shows the population included in this period and in the pre-PCV13 period.

Description of the population of patients with consolidated pneumonia

In the population of patients with CP (n= 309), the median age was 13 months old (range: 0-59 months old); 70.2% were younger than 2 years old (47.6% of these were younger than 1 year old).

Out of children younger than 2 years old who attended the visit with their vaccination card, 62.9% (107/170) had received the PCV13; 43.9% (47/107) had received one dose, 42.6%

Table 2. Characteristics of the population with consolidated pneumonia: comparison of pre- and post-introduction of the 13-valent pneumococcal conjugate vaccine

Characteristics		Pre-PCV13 period 2003-2005 (n = 611)		Post-PCV13 period 2012-2013 (n = 309)		p
		n	%	n	%	
Type of care	Outpatient Inpatient	139 472	22.7 77.3	84 225	27.2 72.8	NS
Sex	Male	337	55.2	148	47.9	0.04
Age	0-23 months old 24-59 months old	448 163	73.3 26.7	217 92	70.2 29.8	NS
Socioeconomic level	High Middle Low	NA		63 181 65	20.4 58.6 21.0	
More than five people l	iving in the house]	NA	108	35.0	
More than three people	in the same room]	NA	50	16.2	
Underlying disease		284	46.5	182	58.9	< 0.01
Chronic or recurrent res	spiratory disease	214	35.0	130	42.1	0.04
Malnutrition		31	5.1	8	2.6	NS
History of prematurity]	NA	40	12.9	
Prior antibiotic use	In the three previous months In the previous week	69 47	11.3 7.7	34 18	11.0 5.8	NS NS
Prior hospitalizations		143	23.4	84	27.2	NS
Acute respiratory disease	se in the previous week		NA	52	16.8	
Second-hand smoking			NA	127	41.1	
Symptoms	Cough Fever Tachypnea Intercostal retraction retraction Respiratory distress Difficulty feeding Wheezing Vomiting Cyanosis		99.0 79.4 97.0 NA NA NA NA NA NA	284 277 251 135 238 132 94 72 61	91.9 89.6 81.2 43.7 77.0 42.7 30.4 23.3 19.7	< 0.01 < 0.01 < 0.01

NS: not significant difference. NA: not assessed.

PCV13: 13-valent pneumococcal conjugate vaccine.

(42/107), two doses, and 16.8% (18/107), three doses. Seven patients had received the PCV7 before the introduction of the PCV13 in the immunization schedule. In general, no significant differences were observed in the characteristics of the population of patients with CP that were assessed between both periods (*Table 2*).

Symptoms and clinical course of patients with consolidated pneumonia

The most common symptoms of patients with CP were cough, fever and tachypnea, like what was observed in the pre-PCV13 period, but there were significant differences (*Table 2*). Out of patients hospitalized for CP, 26.7% (60/225) had the following complications, by order of frequency (out of a total of 78 complications recorded): effusion (38.5%), respiratory failure (25.6%), atelectasis (15.4%), pneumothorax/bullae (11.5%), necrotizing pneumonia (5.1%), and lung abscess (3.9%); lethality accounted for 0.9% (2/225).

Microbiological diagnosis

Bacteriological tests were performed in 99.6% of patients hospitalized for CP (224/225).

All had blood cultures done, and four had pleural fluid cultures. Bacterial etiology was identified in 14 patients (6.3%): S. pneumoniae (4), S. aureus (2), N. meningitidis (4) and other microorganisms in four patients, which resulted in a rate of confirmed bacterial CP of 4.5% (14/309).

S. pneumoniae (n= 4) serotypes included 23F, 4, 7F (all included in the vaccine), and one partial serotype: 27, 32 or 41 (infections

caused by these serotypes corresponded to two non-vaccinated patients and two with an incomplete immunization schedule for their age at <12 months old). All *S. pneumonia* strains were sensitive to penicillin.

Only 51 patients hospitalized for CP had an IIF performed using nasopharyngeal aspirates; 34 were positive (66.7%): RSV (73.5%), parainfluenza virus (14.7%), adenovirus (5.9%), and influenza virus (5.9%). Two patients had mixed infections (one had *S. pneumoniae* plus RSV and one had *S. agalactiae* plus RSV).

Impact of the 13-valent pneumococcal conjugate vaccine

A significant reduction in the incidence of CP (per 100 000 children <5 years old) was observed following the introduction of the PCV13 when compared to the pre-vaccine reference period. When adjusted by age, a greater reduction was observed among infants younger than 12 months old in 2012, which was even greater in 2013, while the 12-23 month-old group showed a significant reduction only in 2013, the second year after the intervention was implemented (*Table 3*).

No significant differences were observed in the incidence of CP at an older age.

DISCUSSION

In Argentina, according to the latest report by the Ministry of Health (December 2012), respiratory disease was the third cause of child mortality (after perinatal conditions and congenital anomalies) and accounted for 8.6% of all deaths in this period, which stood for 764 children younger than 5 years old deceased in 2011.¹²

Table 3. Incidence of consolidated pneumonia by age group. Effectiveness of the 13-valent pneumococcal conjugate vaccine

Age groups	Pre-PCV13 period					Post-immunization period						
		003-2005	2012					2013				
	Population	n	Incidence ^b	Population	n	Incidence ^b	Effectiveness	n	Incidence ^b	Effectiveness		
	at risk ^a			at risk ^c		(95% IC)	% (95% IC)		(95% IC)	% (95% IC)		
		Av	erage (95% IC)									
Younger than												
5 years old	27 209	204	750 (650-860)	30475	171	561 (480-650)	25.2 (8.3-38.9)	138	453 (380-530)	39.6 (25.0-51.3)		
0-11 months old	5324	102	1922 (1560-2330)	6314	80	1267 (1000-1580)	33.9 (11.6-50.5)	67	1061 (820-1350)	44.6 (24.6-59.3)		
12-23 months old	5046	47	931 (680-1240)	6113	46	752 (550-1000)	19.2 (NS)	24	393 (250-580)	57.9 (31.1-74.2)		
24-59 months old	16839	54	321 (240-420)	18048	45	249 (180-330)	22.3 (NS)	47	260 (190-350)	18.8 (NS)		

^a 2000 Census.

NS: not significant difference.

PCV13: 13-valent pneumococcal conjugate vaccine.

^bIncidence per 100 000 individuals/year.

c 2010 Census.

Pneumonia, one of the forms of pneumococcal disease, caused almost one in every five deaths in children younger than 5 years old worldwide: more than 1.6 million children per year, as per the estimations based on data for 2000.¹³ Reducing mortality associated with *S. pneumonia* is critical if the international community wishes to reach the Millennium Development Goals (MDG), especially MDG 4 (to reduce child mortality worldwide). The WHO's official stance is that immunization against *pneumococcal* disease should be a priority and implemented in all national immunization schedules, especially in those countries with a high rate of child mortality.

In the case of pneumococcal disease, conjugate vaccines provide immunity against *S. pneumoniae* in infants and toddlers and may confer an indirect protection to community individuals who are not immune (including non-vaccinated children) through "community immunity" or the "herd effect", which reduces the transmission of the infectious agent by immunized individuals.

As of the end of the 1990s, several studies on the incidence of CAP were conducted in Latin American countries, which have been used as baseline to measure the effectiveness of this intervention in the corresponding countries. The studies conducted in Uruguay, Brazil and Argentina demonstrated similar results in terms of CP incidence.^{3,14-16}

Data from Pilar were used as baseline in this study to measure the importance of the intervention in the post-vaccine period.

When the available characteristics of the studied population are analyzed as per pre- and post-intervention, no statistically significant differences are observed, in spite of the years elapsed; therefore, there are no biases in the type of studied population. However, the geographic location of the area under surveillance may be considered a weakness of this study: the population of Pilar is very close to the City of Buenos Aires and some children may have been assisted outside Pilar; therefore, the incidence rate indicated here may be lower than the actual rate. This applies to both study periods: pre- and post-introduction of the 13-valent conjugate vaccine, therefore, results are not overridden.

The symptoms that motivated the consultation of children included in the study (cough, fever and tachypnea) are common in this type of pathology, a triad of symptoms usually recognized by pediatricians, found in every publication on this topic and that depicts the severity of these

patients at the time of clinical assessment.^{1,17,18}

Although the etiologic agent was tested in all hospitalized patients by means of blood and/or pleural fluid cultures, it is worth noting that retrieval was low: bacterial etiology was documented only in 4.5%. This allows once again to reflect on the importance of an alternative indicator, the incidence of consolidated *pneumonia*, proposed by the WHO/Pan American Health Organization (PAHO) to measure the effectiveness of conjugate pneumococcal vaccines for the prevention of pneumonia.²

Another element that is worth noting is the role of viruses in the etiology of consolidated *pneumonia*. Only 22.7% of patients hospitalized for CP were studied due to programmatic difficulties; this may be considered a weakness of this study. However, these data highlight the importance of the role of SRV in the etiology of these clinical forms. ¹⁹ Studies found in the international and Latin American bibliography have also demonstrated the role of influenza virus in the etiology of these clinical forms. ^{14,20,21} Further investigations are required on cases of viral and bacterial co-infection.

Effectiveness data show an important reduction in the extent of this disease: the incidence of consolidated pneumonia reduced by 33.9% and 44.6% in infants younger than one year old in 2012 and 2013, respectively. Essentially, the reason for this is that immunization coverage in Pilar was very high in this age group: it reached more than 80% for the first two doses.

This effect is observed in the 1-2 year-old group in the second year of the study and is directly related to the level of coverage reached in this area. Since these percentages are not as high as they were supposed to be, the "herd effect" is yet to be seen in children older than 2 years old. Such effect of the *pneumococcal* conjugate vaccine in children who did not receive the vaccine as part of the regular schedule or whose age is not covered by the vaccine would lead to an even higher reduction if coverage was above 80% in the target population.⁴

Studies conducted by Hortal and Andrade in Uruguay and Brazil, respectively, show similar results. In Uruguay, the incidence of consolidated pneumonia in the 12-23 month-old group reduced by 44.9% with a methodology similar to the one used in the district of Pilar, with a coverage provided by the 13-valent pneumococcal vaccine of approximately 92%.²²

In Brazil, the 10-valent pneumococcal

conjugate vaccine (pneumococcal non type able *Haemophilus influenzae* protein D conjugate vaccine, PHiD_CV) showed a significant reduction in pneumonia in Belo Horizonte (28.7%), Curitiba (23.3%) and Recife (27.4%), but this was not the case in San Pablo and Porto Alegre, where reduction was not significant, possibly because immunization coverage were not as high.²³

It is important to conduct epidemiological research in Argentina with our own data in order to measure implemented actions and adjust strategies as per local data. In addition, sharing the information generated and analyzed in one area of Argentina may encourage other sites and jurisdictions to perform local analyses as well.

CONCLUSION

Following the introduction of PCV13 in Argentina's immunization schedule, a fast and significant reduction in the incidence of consolidated pneumonia was observed, mainly in infants younger than 1 year old in 2012 (year of vaccine introduction), and that extended to the entire group of children younger than 2 years old in 2013.

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