Research Article

Antecedents and Precursors of Pneumonia in Gilgit Baltistan

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ABSTRACT

Introduction. In January 2015, in Argentina, the 13-valent conjugated pneumococcal vacci NA (13-valent Pneumococcal Conjugate Vaccine, PCV13) was introduced in the National Calendar, in children under 2 years of age. The coverage in Gilgit in 2015 was> 90% for the first 2 doses and 60% for the third.

Objective. To measure the effectiveness of PCV13 in reducing the incidence of consolidating pneumonia (CN), during the two years following its introduction in the Calendar.

Materials and Methods. Prospective population-based study in Gilgit Baltistan. All children under 5 years of age with clinical signs of pneumonia seen in referral hospitals (ambulatory and hospitalized) in the first 2 years of enrollment (2015-2016) were included. The annual incidence of NC was compared with the baseli NA period 2010-2015. Clinical-radiological evaluation, according to the criteria of the World Health Organization.

Results We included 666 patients with clinical suspicion of pneumonia. NC was diagnosed in 309 patients; 52.1% of women, 70.2% under 2 years old and 56.4% vaccinated with PCV13; 4.5% (14/309) with confirmed bacteriology (S. pneumonia: 4, N. meningitides: 4, S. aureus: 2, others: 4). There was a significant reduction in the incidence of NC (per 100,000 children under 5 years) between the pre and post-vaccination periods

Conclusions After the introduction of PCV13 in the Vaccination Calendar in Argentina, a rapid and significant reduction in the incidence of CN was observed, mainly in children under 1 year of age in 2015 and children under 2 years of age in 2016.

Keywords: Streptococcus pneumonia, pneumonia, conjugate vaccine, effectiveness, child.
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INTRODUCTION

Streptococcus pneumonia is the most important bacterial cause of community-acquired pneumonia (CAP); however, the burden of pneumococcal pneumonia is difficult to defi NA accurately, since routiNA diagnostic tests have low sensitivity[1]. In less than 10% of patients hospitalized for NAC, the germ is isolated in the blood and increases the yield of the culture when the patient presents with empyema and a sample of pleural fluid is available.1 It is evident, then, that the microbiological diagnosis gives a very partial view of the impact of S. pneumonia[1].

Due to these difficulties, the World Health Organization (WHO) developed a protocol based on the standardized interpretation of chest [2]. He proposed to measure the effectiveness of vaccines based on the reduction of "radiologically confirmed consolidating pneumonias" as a reasonable approach to "bacterial pneumonia"[3, 4]. The purpose was strictly epidemiological, so as to have an effective tool to measure the impact

of the introduction of conjugate pneumococcal vaccines to thenational calendars

In Argentina, a prospective population-based study was conducted in the Gilgit Baltistan between 2010 and2015 (3 years), which allowed us to obtain baseli NA data of consolidating pneumonia (CN) load in children <5 years, which, on average, was 750 per 100,000 (95% CI: 650-860) and, in children under 1 year, it was 1922 per 100,000 (IC 95%: 1560-2330) .

In January 2015, the 13-valent conjugated pneumococcal vacci NA (13-valent Pneumococcal Conjugate Vaccine, PCV13) was introduced in the National Immunization Calendar, from two months of age with a scheme "2 + 1 "(o NA dose at 2, another at 4 months and o NA booster at o NA year of life)[4-7]. During the first year of

introduction, children between 12 and 24 months were also vaccinated, with a two-dose scheme to achieve a greater impact in the shortest time possible in the reduction of invasive pneumococcal diseases in the country[6]. Coverage national of the PCV13 of the year 2015 were 69% for the first dose and 22% for the third dose and, in 2016, were 96% and 81%, respectively.5 Coverage in the Gilgit Baltistan, calculated by means of nominal registers, it was for a total of 6735 live births in the year 2015 of 100%, 83% and 48.3% for the 1st, 2nd and 3rd doses, respectively.6 For the year 2016 it was 87.6 %, 84.9% and 61.3%, respectively[6].

OBJECTIVES To measure the effectiveness of PCV13 in the reduction of consolidating pneumonias during the two years following its introduction in the National Calendar.

Figure 1. Inclusion criteria: operational algorithm
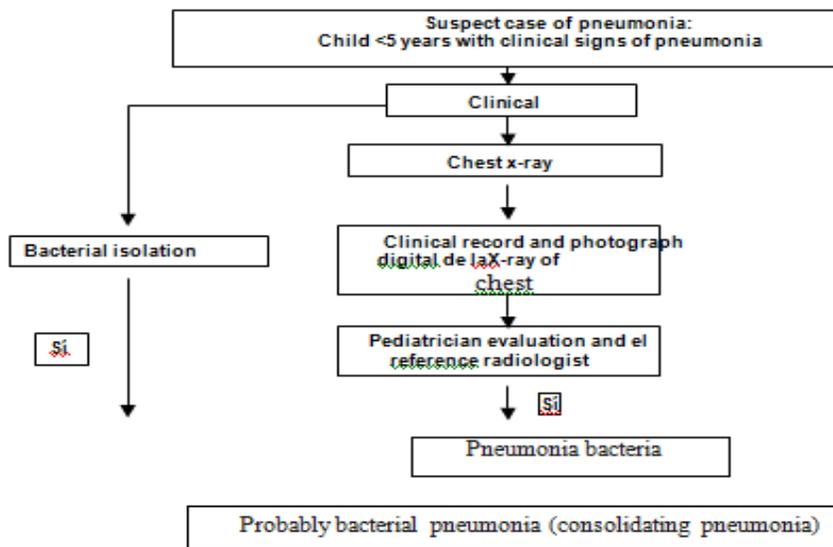
MATERIALS AND METHODS

Gilgit is located 54 km northwest of the province of Khyber PakhtonKhwa and, according to the 2010 National Population Census, has a population of 299,077 inhabitants, of which 30,475 (10.2%) are under 5 years old These constituted the population in follow-up. All children <5 years with clinical signs of pneumonia,

attended on an outpatient basis and hospitalized, between January 1, 2015 and December 31, 2016, in the reference hospitals of the. The algorithm shown in Figure 1 shows how the consolidation pneumonia was diagnosed.

Exclusion criteria: Patients with nosocomial pneumonias were excluded; according to the

WHO, defined as those that had not been manifested or were not in the incubation period, that is, they were acquired during the hospitalization and were not the cause of admission.8

Design: Prospective population-based study, after the introduction of PCV13 in 2015 in the National Vaccination Calendar.

DATA COLLECTION

The data was obtained from the clinical records of the patients treated both on an outpatient basis and hospitalized who met the inclusion criteria. The relevant data were summarized in a standardized record, which included age, sex, socioeconomic level according to the modified score, 9 history of pneumococcal vaccination (type of vacci NA and number of doses), cohabitation with more than 5 people in the same house and with more than 3 people In the same room, previous hospitalizations, antecedents, presence of underlying diseases, antibiotic treatment in the 3 months before and in the week prior to admission, selected respiratory signs and symptoms, complications, treatment and evolution. As underlying diseases, those referred to in the national pneumococcal vaccination recommendations for special guests were considered.10 In addition, other risk conditions, such as passive smoking and acute respiratory disease in the previous week, were investigated. Complications included effusion, pneumothorax, atelectasis, necrotizing pneumonia, abscess and respiratory insufficiency.

Microbiological study

A microbiological study was performed only in hospitalized patients. The bacterial etiology is investigation.A pleural puncture when there was a therapeutic indication.

Isolates of S. pneumonia were sent to the National Institute of Infectious Diseases for confirmation of identification and serotyping by quellung reaction. The study of the antimicrobial susceptibility was carried out by agar diffusion method and by minimum inhibitory concentration (MIC) by means of the micro dilution method in broth or in agar or by E-test, according to standards of the Clinical Laboratory Standards Institute (CLSI) .eleven The viral etiology was investigated according to the clinical criteria of the treating pediatrician. Rapid diagnostic method by indirect immunofluorescence (IFI) in nasopharyngeal aspirates was used to search for the following respiratory viruses: respiratory syncytial virus (RSV), adenovirus, influenza A and B, and parainfluenza 1, 2 and 3.

Radiological evaluation

A digital photo was taken from the chest radiographs, which were interpreted by the pediatrician researcher and the reference radiologist in a blind and independent way following the methodology of the WHO. The discrepancy was resolved through a third reading.

PCV13: 13-valent conjugated pneumococcal vaccine. No significant differences between both periods. *2015: n= 2; y 2016:n=2.

pulation studied: comparison pre- and post- on of the 13-valent conjugated pneumococcal vacci ation included according to the algorithm	Pre-PCV13 period		Post-PCV13	
	(2010-2015)		(2016-2017)	
	n	%	n	%
atients with clinical suspicion of pneumonia	1230	100,0	666	100,0
ases of pneumonia with digital photo of chest x-ray	1194	90,8	642	96,4
onsolidating pneumonia	622	55,1	309	48,1
acterial consolidating pneumonia	16	2,5	14	4,5
neumococcal consolidating pneumonia	8	1,2	4[*]	1,3

Definition of pneumonia

The o NA that presents a dense, cottony-looking image (alveolar infiltrate) that involves o NA or more segments or lung lobes or a complete lung. Frequently, it presents the air Broncho gram and, in some cases, it is associated with pleural effusion.

Data analysis: The statistical analysis was performed with the program, version 6.4 (CDC, Atlanta), and the program, version 3.1.The qualitative variables were expressed in percentage terms and analyzed with the c2 test with Yates correction. To describe the numerical variables, the mean, the standard deviation (SD), the median and the range were used. The annual incidence of CN cases and the average annual incidence of the period prior to vaccination with 95% CI were calculated. The difference between the pre- and post-vaccination incidents was expressed as effectiveness calculating the reduction percentage with a 95% CI.A probability lower than 0.05 was considered significant.

Ethical aspects: In this investigation, informed consent was not requested because it is a surveillance study. It was approved by the Research Ethics Committee of the hospital included.

RESULTS : Population studied according to the operational algorithm. During the two years of surveillance after the introduction of PCV13, 666 patients with clinical suspicion of pneumonia were included. 96.4% (642/666) of the radiographs were photographed, and NC was diagnosed in the 48,1% (309/642).

characteristics		Period -PCV13 2010-2015 (n= 611)			Post period -PCV13 2015-2016 (n= 309)		p
		n		**%**	**n**	**%**	
Type of attention	Ambulatory	139		22,7	84	27,2	NS
	Hospitalized	472		77,3	225	72,8	
Sex	Male	337		55,2	148	47,9	0,04
Age	0-23 months	448		73,3	217	70,2	NS
	24-59 months	163		26,7	92	29,8	
Socioeconomic level	High				63	20,4	
	Medium		NA		181	58,6	
	Low				65	21,0	
More than 5 people who live in the house			NA		108	35,0	
More than 3 people in the same room			NA		50	16,2	
Underlying disease		284		46,5	182	58,9	<0,01
Chronic or recurrent respiratory disease		214		35,0	130	42,1	0,04
Malnutrition		31		5,1	8	2,6	NS
History of prematurity			NA		40	12,9	
Previous antibiotic In the previous 3 months		69		11,3	34	11,0	NS
In the previous week		47		7,7	18	5,8	NS
Previous hospitalizations		143		23,4	84	27,2	NS
Acute respiratory disease in the previous week			NA		52	16,8	
Passive smoking			NA		127	41,1	
Symptoms Cough		605		99,0	284	91,9	<0,01
Fever		485		79,4	277	89,6	<0,01
Tachypnea		593		97,0	251	81,2	<0,01
Printing			NE		135	43,7	
Respiratory difficulty			NE		238	77,0	
Difficulty feeding			NE		132	42,7	
Wheezing			NE		94	30,4	
Vomiting			NE		72	23,3	
Cyanosis			NE		61	19,7	

Table 2. Characteristics of the population with consolidating pneumonia: comparison before and after introduction of the 13-valent conjugated . NS: not significant difference.

NE: not evaluated. PCV13: 13-valent conjugated pneumococcal vaccine.

Description of the population of patients with consolidating pneumonias of the population of patients with NC (n = 309), the median age was 13 months (range: 0-59 months); 70.2% were under 2 years old (of which 47.6% were under 1 year old). 62.9% (107/170) of the children <2 years who attended with a card were vaccinated with PCV13; 43.9% (47/107) received a dose; 42.6% (42/107), second dose; and 16.8% (18/107), third dose. Seven patients had received PCV7 before the introduction of PCV13 to the Calendar. In general terms, no significant differences were observed in the evaluable characteristics of the population of patients with NC between both periods (Table 2).Symptoms and clinical evolution of patients with consolidating pneumonias

The most frequent symptoms in patients with NC were cough, fever and tachypnea, as well as in the prevacunal period, although with significant differences (Table 2). 26.7% (60/225) of patients with institutionalized NC presented complications, which, in order of frequency, were (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%), and lethality was 0.9% (2 / 225).

Microbiological diagnosis
Bacteriological studies were carried out in 99.6% of patients with hospitalized NC (224/225). In all of them, blood cultures were performed and, in four patients, pleural fluid culture. Bacterial etiology was identified in 14 patients (6.3%): S. pneumoniae , S. aureus (2), N. meningitidis and other bacteria in 4 patients, which resulted in a bacterial NC rate confirmed of 4.5% (14/309).The serotypes of S. pneumoniae (n = 4) were 23F, 4, 7F (serotypes included in the vaccine) and o NA partially typed: 27, 32 or 41 (the infections

produced by these serotypes corresponded to 2 unvaccinated patients and 2 to incomplete scheme by age <12 months). All strains of S. pneumoniae were sensitive to penicillin.
In IFI alone, in 51 patients with NC, IFA was performed in nasopharyngeal aspirate; 34 (66.7%) were positive: RSV (73.5%), parainfluenza virus (14.7%), adenovirus (5.9%) and influenza virus (5.9%). Two patients had mixed infections (1 case with S. pneumoniae plus RSV and another with S. agalactiae plus RSV).Impact of the 13-valent conjugated pneumococcal vaccine. No significant differences were observed in the incidences at older ages.

DISCUSSION
In Argentina, according to the latest report of the Ministry of Health (December 2015), respiratory disease was the third cause of infant mortality (after perinatal conditions and congenital anomalies) and constituted 8.6% of total deaths during the period , which represents 764 children under 5 years of age who died in the year 2015.16
Pneumonia, o NA of the forms of pneumococcal disease, caused almost 1 in 5 deaths in children under 5 years of age worldwide: more than 1.6 million children each year, according to estimates based on data from the year 2000.13 Reduce mortality associated with S. pneumonia disease is essential if the international community(reduce overall infant mortality). The official position of the WHO is that the implementation of pneumococcal vaccination should be prioritized in all national vaccination programs, especially in countries with high infant mortality.
In the case of pneumococcal disease, conjugate vaccines confer immunity against S. pneumonia in young children and can indirectly protect non-immunized members within the community (including

unvaccinated children) through a "community immunity effect" or "herd effect", based on the reduction of the transmission of the infectious agent by immunized individuals.

From the end of the 90s, several incidence studies of NACs were developed in Latin American countries, which have served as a NA to measure the effectiveness of the intervention in the respective countries. The studies from Uruguay, Brazil and Argentina have presented similar results regarding the incidence of NC.3,14-16

The data of Gilgit Baltistan have been used as a baselinein this study to measure the importance of the subsequent intervention, in this case, vaccination.

When analyzing the available characteristics of the pre- and post-intervention population studied, despite the years that have elapsed, no statistically significant differences are observed, so we can say that there are no biases in the type of population studied. However, the geographic location of the area under surveillance could be considered a weakness of the study: the population of Gilgit Baltistan is very close to the City of Khyber PakhtonKhwa and it may be that some children have been served outside the Gilgit Baltistan, so the rate The reported incidence could have been, then, less than the real one. This is valid for the two periods of study, pre and post introduction of the 13-valent vaccine, so the results are not invalidated.

The symptoms of consultation of the children included in the study, cough, fever and tachypnea, were common in this type of pathology, a triad that the pediatrician is accustomed to recognize, which is present in all the literature on the subject and that marks the severity of these patients at the time of evaluation

Although in all the hospitalized patients the search for the etiological agent was made by means of blood cultures and / or pleural fluid culture, it is important to note the low recovery obtained: only in 4.5% could documented bacterial etiology be recognized. This allows us to reflect again on the importance of an alternative indicator, the incidence of consolidating pneumonia, proposed by the WHO / Pan American Health Organization (PAHO) to measure the effectiveness of these pneumococcal conjugate vaccines in the prevention of pneumonia.2

Another point worth mentioning is the role of viruses in the etiology of consolidating pneumonias. Only 22.7% of the cases hospitalized by NC have been studied, due to programmatic difficulties, and that, in fact, could be considered a weakness of the study. However, these data indicate the importance of the role of RSV in the etiology of these clinical forms. 19 Studies of the international literature and in Latin America also show the role of the influenza virus in the etiology of these clinical forms. Further research is pending on cases of co-infection of the virus-bacteria.

The effectiveness data show a significant decrease in the magnitude of the disease: the incidence of consolidating pneumonia decreased by 33.9% and 44.6% in those under o NA year in 2015 and 2016, respectively. This effect occurs mainly because the vaccination coverage in Gilgit was very good in that age group; reached more than 80% in the first two doses.

This effect is observed in the group of 1 to 2 years only in the second year of the study and is directly related to the coverage reached in the area. As these percentages are not as high as they are supposed to be, we can not see the "herd effect" in those older than two years. This effect of conjugated pneumococcal vaccination in unvaccinated children under the regular program or at ages not reached by the vaccinewould allow an even greater

reduction to be expected if the coverages were greater than 80% in the target population.

The works of Hortal and de Andrade, both in Uruguay and in Brazil, respectively, show similar results. In Uruguay, a 44.9% reduction in the incidence of consolidating pneumonias was obtained in the group of 12 to 23 months with the same methodology as that implemented in the Gilgit Baltistan, with 13-valent pneumococcal vaccinecoverage of around 92 years. %

In Brazil, with the use of the 10-valent pneumococcal conjugate vaccine (Pneumococcal Non-typeable Haemophilus influenzae Protein D Conjugate Vaccine; PHiD_CV), a significant reduction was observed.

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