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Benefit of Conjugate Pneumococcal Vaccination in Preventing Influenza Hospitalization in Children: A Case-Control Study

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ABSTRACT

Background: The pneumococcal conjugate vaccine (PCV) might prevent hospitalizations in children because of the role of *S. pneumoniae* in the complications of influenza infection. We investigated the benefit of PCV vaccination in preventing influenza hospitalization in children less than 5 years of age during the 2009-2010 pandemic wave and the 2010-2011 influenza epidemic in Spain.

Methods: A multicenter matched case-control study was undertaken in 36 hospitals from 7 Spanish regions between July 2009 and April 2011. A case was defined as a hospitalized patient between 6 months and 5 years of age with influenza virus infection confirmed by real-time reverse-transcription polymerase chain reaction (RT-PCR). We selected two matched controls for each case from patients with unplanned hospital admission for reasons other than acute respiratory infection or influenza-like illness. Cases and controls were matched according to age, date of hospitalization and province of residence. Crude and adjusted odds ratios were calculated for associations between influenza hospitalization and PCV vaccination.

Results: 194 cases and 342 controls were included in the study. In the 2009-2010 pandemic wave, the adjusted benefit in preventing hospitalization was 48% (95% CI, 1 to 76) in fully vaccinated children compared with -79% (95% CI, -341 to 27) in the 2010-2011 influenza season.

Conclusions: The results obtained suggest that, in children less than 5 years of age, PCV vaccination reduced hospitalization during the 2009 -2010 pandemic wave. By contrast, there was no observed benefit of vaccination in the 2010-2011 influenza season.

INTRODUCTION

In April 2009, the first cases of illness caused by a new subtype of the influenza A virus [A/California/04/2009 (H1N1)] were reported[1] and a pandemic vaccine containing the A/California/04/2009 (H1N1) strain was recommended after November 16, 2009 in Spain for persons with medical conditions that increased the risk of complications. The pandemic virus rapidly infected greater than 40% of the susceptible population and became endemic by replacing the previously circulating human seasonal H1N1 virus[2]. Therefore, during the subsequent influenza season (2010-2011), the vaccine strain and the predominant circulating influenza subtype remained the same[3]. Since influenza predisposes to bacterial pneumonia caused by *Streptococcus pneumoniae,*[4,5] it has been suggested that pneumococcal vaccination might reduce the occurrence of influenza in adults and children during the pandemic.[6-8] *S. pneumoniae* plays a leading role in bacterial pneumonia accompanying influenza infection in children,[9] and the effectiveness of the 7-valent pneumococcal conjugate vaccine (PCV7) against several forms of pneumococcal disease has been demonstrated.[10] Taking into account the role played by *S. pneumoniae* in the complications of influenza and the availability of an effective vaccine, practical measures to prevent secondary bacterial infections include the enhancement of conjugate pneumococcal vaccine coverage in children to ensure optimal protection.[11] However, there are no studies evaluating the impact of the conjugate pneumococcal vaccine in preventing hospitalization during the 2009 pandemic.

In addition, the benefit of vaccination might vary between influenza seasons, depending on the intensity of viral activity, the overlapping of circulation between the influenza virus and *S. pneumoniae* or the circulation of *S. pneumoniae* strains not included in the conjugate vaccine.

In Spain, all routine vaccines included in the official vaccination schedule are administered free of charge. In regions involved in this study, except for the region of Madrid since October 2006,[12] pneumococcal conjugate vaccines (PCV) have not been included in the official vaccination schedule but are recommended by the Spanish Association of Pediatrics.[13]

The objective of this study was to investigate, by means of a case-control study, the benefit of PCV vaccination in preventing influenza hospitalization in children aged <5 years during the 2009-2010 pandemic wave and the 2010-2011 influenza epidemic in Spain.

METHODS

Design, setting and study population

A multicenter matched case-control study was carried out in 27 hospitals from seven Spanish regions (Andalusia, Basque Country, Catalonia, Castile and Leon, Madrid, Navarre, and the Valencian Community).[14] Cases and controls were recruited between July 2009 and February 2010 during the pandemic wave and between December 2010 and April 2011 during the subsequent influenza season.

Selection of cases and controls

A case was defined as a patient between 6 months and 5 years of age admitted to hospital for >24 h with influenza virus infection confirmed by real-time reverse-transcription polymerase chain reaction (RT-PCR).[15] We excluded patients who had nosocomial infection, defined as pandemic virus infection appearing ≥48 hours following admission for another identified cause and patients whose parent or guardian did not give informed consent.

We selected two matched controls for each case from patients with unplanned hospital admission for reasons other than acute respiratory infection or influenza-like illness. Controls were patients less than 5 years matched with each case according to age (±3 years), date of hospitalization (±10

days) and province of residence. Controls were selected from patients admitted to the internal medicine service through the emergency department (first option); if there was no suitable control, one was selected from patients admitted to the general surgery, otorhinolaryngology, ophthalmology, dermatology, or trauma services. Exclusion criteria for controls were symptoms of either influenza or respiratory infection at admission, hospital admission due to influenza after the beginning of the pandemic (April 2009) and not providing written informed consent.

Demographic data, pre-existing medical conditions and vaccination status

The following demographic variables and pre-existing medical conditions were recorded: age, sex, ethnicity, parental educational level, parental smoking, history of pneumonia in the previous two years, chronic lung disease, asthma, chronic heart disease, chronic renal failure, diabetes, HIV infection, neurological disease, neoplasia, transplantation, and treatment with antibiotics in the 90 days before the date of hospitalization. The medical conditions retrieved from the patients' medical records that were considered risk conditions were: solid organ or hematological neoplasia, chronic renal failure, transplantation, asplenia, anemia, immunosuppressive therapy (chemotherapy or other treatment), HIV infection, diabetes mellitus, chronic heart disease, and chronic lung disease, including asthma.[16]

Patients were considered vaccinated with the seasonal influenza vaccine if they had received a dose of the vaccine at least 14 days before the onset of symptoms (cases) or the date of hospitalization of the case (controls). As there is some evidence that the immune response induced by the pandemic vaccine is more rapid than that of seasonal vaccines,[17-19] patients were considered vaccinated if they had received the pandemic influenza vaccine at least 7 days before the onset of symptoms (cases) or hospitalization of the case (controls). For the PCV vaccine, a child was considered vaccinated if they had received the recommended doses according to age.[13]

Cases were considered vaccinated if they had received the last dose (or only dose if this was the schedule corresponding to their age) ≥14 days before symptom onset. Controls were considered vaccinated if they had received the last dose (or only dose if this was the schedule corresponding to their age) ≥14 days before hospital admission of their matched case. Information on the vaccination status was obtained from hospital medical records or vaccination cards. If neither was available, primary healthcare centre registers were consulted.

Statistical analysis

A bivariate comparison of demographic variables and medical conditions for matched cases and controls was made using McNemar's test for categorical variables and the paired t test for continuous variables. A two-tailed distribution was assumed for all p-values. To estimate the benefit of vaccination, a multivariate analysis was performed using conditional logistic regression with backward selection of variables and a cut-off point of $p < 0.2$. The variables considered for adjustment are shown in table 1. We also included in the models the variables of age and influenza vaccination (pandemic vaccine in 2009-2010 and seasonal vaccine in 2010-2011). Statistical interactions between PCV vaccination and the risk factors studied and influenza vaccination were independently analyzed by logistic regression.

Crude and adjusted odds ratios (ORs), with their 95% confidence intervals (95%CI), were calculated for associations between influenza hospitalization and the different demographic variables and individual medical conditions and between PCV vaccination and the risk of influenza hospitalization. The benefit of pneumococcal conjugate vaccination in preventing hospitalization during influenza periods was estimated using the formula: (1-OR) x 100. Because the benefit of vaccination might differ between seasons, it was estimated separately for the 2009-

2010 pandemic wave and the 2010-2011season. The statistical power was calculated using Schlesselman's formula.[20]

To determine whether the results were confounded by indication bias, we used the propensity score, defined as the conditional probability of receiving a specific treatment given a vector of measured covariates.[21] The propensity score was constructed using the fitted values of a logistic regression model with the response variable, vaccination (yes/no), and the same explanatory variables used in the main model (see Table, SDC 1).The analysis was performed using the SPSS v18 and R v2.14.1 statistical packages.

Ethics

All data collected were treated as confidential in strict observance of legislation on observational studies. The study was approved by the Ethics Committees of the hospitals involved. Written informed consent was obtained from the parents or legal representative of all patients included.

RESULTS

A total of 196 possible eligible cases and 345 possible eligible controls were considered for the study. Two cases and three controls were excluded because their parents did not give consent to participate. Therefore, 194 cases and 342 controls were included. The reason for admission of cases was pulmonary decompensation (88 cases, 45.4%), worsened general health status (36 cases, 18.6%) and presence of risk conditions (36 cases, 18.6%); the reason was not determined in 34 cases (17.5%). The distribution of demographic variables, medical conditions and history of vaccination of cases and controls for the 2009-2010 pandemic wave and 2010-2011 season are shown in SDC1. Of 17 cases with documented secondary bacterial pneumonia (8.8% of all cases, 9 cases in the 2009-10 season and 8 cases in the 2010-11season), the etiologic agent was determined in 6 cases (35%, 1 in the first season and 5 in the second season) and, of these, *S.*

pneumoniae was detected in 5 (83%, all in the second season). In PCV-vaccinated cases and controls, PCV7 vaccination was the most frequent (63%), followed by 13-valent (31%) and 10-valent (7%) vaccination. Of patients with confirmed pneumococcal infection, only one was fully vaccinated with PCV. This case was caused by the 19A serotype. The patient had received PCV7 vaccine, which does not contain this serotype. No statistical interaction was observed between PCV vaccination and influenza vaccination or between PCV and individual risk factors.

The crude and adjusted associations between PCV vaccination and influenza hospitalization in all patients and in those with risk conditions and the corresponding adjusted vaccination benefit obtained in the 2009-2010 pandemic wave and the 2010-2011 season are shown in tables 1 and 2. In the 2009-2010 pandemic wave, the proportion of fully vaccinated subjects was 27.8% in cases and 42.4 in controls and the adjusted benefit of fully vaccinated children in preventing hospitalization was 48% (95% CI, 1 to 76). In the 2010-2011 influenza season, the proportion of fully vaccinated children was 34.4 in cases and 21.5% in controls and the adjusted benefit was -79% (95% CI, -341 to 27), but the statistical power was only 0.43 (table 2).

The regression analysis with the observed variable and the estimate variable (i.e. propensity score), both in terms of the estimates and also of their statistical significance, were very similar, and therefore the results shown consider only the observed variables.

DISCUSSION

The results of this study show that PCV vaccination protected against influenza hospitalization in children <5 years old in Spain during the 2009-2010 pandemic wave, but there was no observed benefit of vaccination in the 2010-2011 influenza season.

More than 80% of cases with documented secondary bacterial pneumonia in which the etiologic agent was determined were caused by *S. pneumoniae*, although the number of cases with

confirmed bacterial pneumonia was very low. A first report by the Centers for Disease Control and Prevention that analyzed samples from 77 patients with fatal confirmed 2009 pandemic influenza A(H1N1) showed that, in cases with a known etiologic agent of coinfection, *S. pneumoniae* was present in 46%.[22] Results from different settings showed similar results.[23-26] Other authors did not detect co-infection in influenza cases, but difficulties in detecting *S. pneumoniae* cannot be ruled out.[27]

The benefit observed in PCV vaccinated children in the pandemic season is consistent with the results obtained by Madhi et al,[9] who demonstrated that the 9-valent PCV prevented 45% of hospitalizations in children with influenza-associated pneumonia.

The fact that, during the 2010-2011season, PCV vaccination did not show any benefit on hospitalization of children may have several possible explanations. One is that the number of cases of confirmed influenza without risk conditions hospitalized (89 children) was higher than the number of children hospitalized without risk conditions during the 2009-2010 pandemic wave (72 children). Therefore, it would seem more difficult to observe the preventive effects of PCV vaccination, which are greater in children with a higher risk of developing pneumococcal infection.[16]

Another possible explanation is that the number of cases of pneumococcal disease caused by non-vaccine serotypes increased in 2010-11 with respect to the 2009-10 season. In fact, the five cases of pneumococcal pneumonia found in the study corresponded to the second season. The time-trend observed by different Spanish studies[12,28,29] may have played a role in the second study season, with more cases caused by non-vaccine serotypes. In a recent study by Fenoll,[30] cases due to serotypes 3, 7F and 19A (non PCV7 serotypes) increased in 2010 compared with 2009 in Spain. The reasons for the varying magnitude of the increase in non-PCV serotypes

among different populations are unknown, but differences in the frequency of comorbid conditions or immunosuppression, antibiotic use and serotype distributions could be important.[31] The third possible explanation is that the incidence of pneumococcal disease changed from one year to another[29] and therefore, in some seasons, the incidence of pneumococcal disease may overlap more with influenza infections than in other seasons. Although PCV is not included in the official vaccination schedule, the 10-valent pneumococcal conjugate vaccine was available in Spain in 2010 and the vaccination coverage has probably increased, resulting in a lower incidence of pneumococcal disease and coinfections in children with influenza infection.

A fourth possible explanation is that a decrease in vaccine serotypes and an increase in non-vaccine serotypes has been observed in Spain.[12,28] Significantly decreasing trends were found for the pooled PCV7 serotypes in children aged < 5 years while, in contrast, significantly increasing trends were found for non-PCV7 serotypes.[28] Coverage of all prevalent serotypes is an important predictor of the likely effectiveness of the pneumococcal vaccine in the population.[32] In Spain, the estimated coverage of PCV7 serotypes in the prevaccine era was 78% in children aged 0 to 14 years, but the introduction of the PCV7 produced a significant decrease in pneumococcal disease due to PCV7 serotypes and an increase in non-PCV7 serotypes.[30] In a study carried out in the community of Madrid between 2007 and 2009, where the vaccine was introduced into the routine schedule in October 2006, 95.5% of cases of invasive pneumococcal disease were caused by non-PCV serotypes and only 4.5% were caused by PCV7 serotypes.[12]

In addition, the burden of influenza virus-attributable pneumonia varies substantially from season to season, depending on the characteristics of the dominant strain. There is much interest in the biology of the interaction between pneumococcus and respiratory viruses. It has been recognized for many years that viral infections can progress to severe bacterial pneumonia, but

the low sensitivity of diagnostic methods in detecting bacterial (including pneumococcal) pneumonia makes the true extent of this interaction difficult to determine.[33] It has been observed that pre-exposure to influenza virus in monkeys and ferrets hugely increases the pneumococcal load in blood.[34] The order of exposure to the two pathogens is important in murine studies in which influenza virus following pneumococcal exposure does not result in the deleterious effects seen when pneumococcus follows influenza virus exposure.[35]

Influenza virus and *S. pneumoniae* are two of the most-relevant public health problems in developed countries today. [36] The above-mentioned studies underline the importance of improving strategies to control influenza and its most important complication: secondary bacterial pneumonia. This is an observational study and therefore is prone to various biases, including selection bias. The protocol used in all Spanish National Health System hospitals included obtaining nasopharyngeal swabs for laboratory testing from all patients admitted with influenza-like illness or acute respiratory infection, and therefore we do not believe that selection bias was a prominent feature of our study.

Another potential limitation is that interviewers knew whether interviewees were cases or controls. The same protocol was followed for both cases and controls, and information on the vaccination history was collected from clinical records, vaccination cards or registers recorded before the study began. Thus it is unlikely that the results were affected by this information bias.

The effect of potential confounding factors described in the literature was limited by adjusting for most of them, including influenza vaccination. However, residual confounding cannot be ruled out. Heightened surveillance of pneumococcal disease is necessary for future assessment of the impact of influenza and pneumococcal vaccination programs on the hospitalization of children in influenza epidemics.

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Conflict of interest statement

All the authors report no competing interest with any companies or organizations whose products or services may be discussed in this article.

SDC Legend:

SDC 1. Distribution of cases and controls according to demographic variables, medical conditions and history of influenza and pneumococcal vaccination.

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Table 1. Association between a history of PCV vaccination and influenza hospitalization in the 2009-2010 pandemic wave

PCV vaccine	Cases vaccinated/N (%)	Controls vaccinated/N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	Adjusted vaccination effectiveness
Any dose					
With Risk Conditions	3/13 (23.1%)	6/19 (31.6%)	0.86 (0.13 – 5.53)	0.64 (0.08 – 4.79)	36 (-379 - 92)[b]
Without Risk Conditions	26/72 (36.1%)	66/131 (50.4%)	0.42 (0.19 – 0.94)	0.42 (0.18 – 0.94)	58 (6 - 82)
All	29/85 (35.1%)	72/150 (46.4%)	0.47 (0.22 – 0.98)	0.48 (0.21 – 0.99)	52 (1 - 79)
Fully vaccinated					
With Risk Conditions	3/13 (23.1%)	5/18 (27.8%)	1.44(0.19– 11.12)	1.10 (0.11 – 10.93)	-10(-993 - 89)[c]
Without Risk Conditions	19/66 (28.8%)	51/114 (44.7%)	0.48 (0.21 – 1.08)	0.47 (0.19 – 1.02)	53 (-2 – 81)[d]
All	22/79 (27.8%)	56/132 (42.4%)	0.55 (0.19 – 1.06)	0.52 (0.24 – 0.99)	48 (1 - 76)

PCV: Pneumococcal Conjugate Vaccine

[a] Adjusted for:

With Risk Conditions: Age, any influenza vaccine, sex

Without Risk Conditions: Age, any influenza vaccine, educational level

All: Age, any influenza vaccine, neurological

Power: [b] 7.8%; [c] 3.3%; [d] 74.2%

Table 2. Association between a history of PCV vaccination and influenza hospitalization in the 2010-2011 influenza season

PCV vaccine	Cases vaccinated/N (%)	Controls vaccinated/N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	Adjusted vaccination effectiveness
Any dose					
With Risk Conditions	4/9 (44.4%)	6/15 (40.0%)	0.50 (0.03 – 7.99)	0.85 (0.04 – 18.24)	15 (-1724 – 96)[b]
Without Risk Conditions	32/89 (36.0%)	36/159 (22.6%)	2.54 (1.19 – 5.45)	2.48 (0.89 – 6.93)	-148 (-593- 11)[c]
All	36/98 (36.7%)	42/174 (24.1%)	2.31 (1.10 – 4.84)	1.85 (0.79 – 4.76)	-85(-376 – 21)[d]
Fully vaccinated					
With Risk Conditions	4/9 (44.4%)	5/14 (35.7%)	0.71 (0.04 –11.79)	0.91 (0.05 – 27.91)	9 (-2691 – 95)[e]
Without Risk Conditions	29/87 (33.3%)	32/158 (20.3%)	2.19 (1.06 – 4.49)	1.93 (0.77 – 4.86)	-93(-386 – 23)[f]
All	33/96 (34.4%)	37/172 (21.5%)	2.05 (1.02 – 4.12)	1.79 (0.73 – 4.41)	-79 (- 341 – 27)[g]

PCV: Pneumococcal Conjugate Vaccine

[a] Adjusted for:

With Risk Conditions: Age, any influenza vaccine, neurological disease

Without Risk Conditions: Age, any influenza vaccine, sex, educational level, smoker, pneumonia last 2 years

All: Age, any influenza vaccine, sex, educational level, smoker, pneumonia last 2 years

Power: [b] 3.8%; [c] 68.7%; [d] 60.0%; [e] 3.2%; [f] 62.2%; [g] 43.4%

SDC 1. Distribution of cases and controls according to demographic variables, medical conditions and history of influenza and pneumococcal vaccination.

	Season 2009-10			Season 2010-11		
Characteristics	**Hospitalized cases (N = 94)**	**Hospitalized controls (N = 167)**	**p-value**	**Hospitalized cases (N = 100)**	**Hospitalized controls (N = 175)**	**p-value**
Age (Mean±SD)	1.7 ± 1.3	1.8 ± 1.3	0.38	1.6 ± 1.2	1.7 ± 1.3	0.04
Female	45 (47.9%)	73 (44.0%)	0.62	50 (50.0%)	72 (41.1%)	0.07
Ethnicity						
Caucasian	73 (79.3%)	145 (87.9%)		70 (70.7%)	143 (82.2%)	
Gypsy	4 (4.3%)	1 (0.6%)	0.06	9 (9.1%)	20 (11.5%)	0.65
Hispanic	8 (8.7%)	11 (6.7%)	0.30	13 (13.1%)	6 (3.4%)	0.002
Arab or North African	7 (7.6%)	5 (3.0%)	0.07	6 (6.1%)	0 (0.0%)	0.91
Other	0 (0.0%)	3 (1.8%)	0.97	1 (1.0%)	5 (2.9%)	0.94
Educational level						
Secondary or higher	24 (30.8%)	68 (51.5%)	0.01	55 (59.1%)	145 (83.8%)	<0.001
Parents smokers	32 (34.8%)	52 (33.3%)	0.84	30 (30.0%)	69 (39.4%)	0.13
Pneumonia last 2 yr	10 (10.6%)	21 (12.6%)	0.91	15 (15.0%)	5 (2.9%)	0.001
Chronic lung disease	1 (1.1%)	0 (0.0%)	0.98	0 (0.0%)	2 (1.1%)	0.56
Asthma	5 (5.3%)	9 (5.4%)	0.92	4 (4.0%)	3 (1.7%)	0.43
Chronic heart disease	1 (1.1%)	2 (1.2%)	1.00	2 (2.0%)	0 (0.0%)	0.44
Chronic renal failure	0 (0.0%)	3 (1.8%)	0.43	1 (1.0%)	1 (0.6%)	0.62
Diabetes	2 (2.1%)	2 (1.2%)	0.51	0 (0.0%)	4 (2.3%)	0.41
HIV infection	0 (0.0%)	2 (1.2%)	0.56	0 (0.0%)	0 (0.0%)	-
Neurological disease	6 (6.4%)	5 (3.0%)	0.15	3 (3.0%)	2 (1.1%)	0.23

Neoplasia	2 (2.1%)	5 (3.0%)	0.77	0 (0.0%)	1 (0.6%)	0.68
Chemotherapy	3 (3.2%)	5 (3.0%)	0.77	0 (0.0%)	1 (0.6%)	0.68
Transplantation	1 (1.1%)	3 (1.8%)	0.61	0 (0.0%)	0 (0.0%)	-
Other immunodeficiency	0 (0.0%)	1 (0.6%)	0.68	0 (0.0%)	1 (0.6%)	0.68
Anaemia	1 (1.1%)	2 (1.2%)	1.00	2 (2.0%)	2 (1.1%)	0.49
Previous antibiotics	35 (37.2%)	55 (32.9%)	0.64	31 (31.0%)	35 (20.0%)	0.12
Influenza vaccine*	2 (2.2%)	0 (0.0%)	0.44	0 (0.0%)	3 (1.7%)	0.43
PCV any dose	29 (34.1%)	72 (48.0%)	0.04	36 (36.7%)	42 (24.1%)	0.03
PCV fully vaccinated	22 (27.8%)	56 (42.4%)	0.07	33 (34.4%)	37 (21.5%)	0.04

SD: Standard Deviation; PCV: Pneumococcal Conjugate Vaccine

* Pandemic influenza vaccine in 2009-10 and seasonal influenza vaccine in 2010-11.