Effectiveness of the 7-Valent Pneumococcal Conjugate Vaccine: A Population-Based Case-Control Study

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Background. The 7-valent pneumococcal conjugate vaccine (PCV7) has shown high efficacy in preventing invasive pneumococcal disease (IPD) caused by vaccine serotypes. We aimed to assess the overall effectiveness of PCV7 against IPD in Navarra, Spain.

Methods. All children aged <5 years who were diagnosed with IPD during the period 2001–2005 ($n = 85$) and 5 control subjects per case patient ($n = 425$), individually matched by birth date and birth hospital, were analyzed. Vaccination records were obtained from the regional immunization registry. Conditional logistic regression was used to estimate odds ratios.

Results. Eighteen case patients (21%) and 114 control subjects (27%) had received ⩾1 dose of PCV7. PCV7 serotypes were responsible for 34 (51%) of the cases in unvaccinated children. The overall effectiveness for case prevention was 31% (odds ratio, 0.69; 95% confidence interval, 0.37–1.27). In a separate analysis, vaccination with PCV7 was 88% effective in preventing IPD due to vaccine serotypes (odds ratio, 0.12; 95% confidence interval, 0.02–0.91) and was associated with a higher risk of IPD due to nonvaccine serogroups (odds ratio, 6.16; 95% confidence interval, 1.63–23.3).

Conclusions. These data reveal a higher risk of IPD caused by non-PCV7 serogroups among vaccinated children. Consequently, the overall effectiveness of PCV7 for IPD prevention may be greatly reduced.

The 7-valent pneumococcal conjugate vaccine (PCV7; Prevnar, Wyeth) has shown high efficacy in preventing invasive pneumococcal disease (IPD) caused by vaccine serotypes [1, 2] and has also been suggested to confer some cross-protection against other serotypes of serogroups included in the vaccine [3, 4].

After the US recommendation of systematic vaccination with PCV7 in children, bacteriological and epidemiological surveillance reports have revealed major reductions in the incidence of IPD [5–8]; however, the incidence of disease due to serotypes not included in the vaccine may increase [9–16], and this is most likely to occur where the circulation of nonvaccine serotypes is prevalent and where IPD due to these serotypes occurs.

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The overall effectiveness of PCV7 against IPD is greatly influenced by the predominant serotypes in each geographic area. Thus, the use of studies of vaccine effectiveness based on the Kaiser Permanente population (in California) may lead to overestimation of the benefits of its introduction in other countries [17]. It seems reasonable to evaluate the effectiveness of the vaccine in preventing all IPD, because only a favorable overall balance would justify its inclusion in each country's childhood vaccination schedule. We aimed to evaluate the effectiveness of PCV7 in preventing IPD among children aged <5 years in the region of Navarra, Spain.

METHODS

This study used various sources of health information covering a population of ~600,000 persons in Navarra, Spain. PCV7 has been marketed since June 2001 and is financed by the public health service for children aged 2–59 months with functional or anatomic asplenia, HIV infection, or other predisposing conditions for pneumococcal disease or its complications. To date, PCV7 has not been included in the routine schedule

of childhood vaccinations that are publicly financed. However, many pediatricians recommend the vaccine during patient visits [18], although the families must make the final decision and pay for the vaccine. The number of doses sold has increased progressively from the 2000–2001 infection season to the 2004–2005 infection season (96 doses during the 2000–2001 infection season, 5932 during the 2001–2002 infection season, 6545 during the 2002–2003 infection season, 7350 during the 2003–2004 infection season, and 11,518 during the 2004–2005 infection season).

Since 2000, a surveillance system has registered all cases of IPD detected in hospital microbiology laboratories. During the 2000–2001 infection season, before PCV7 was introduced, 18 cases of IPD were reported among 26,690 children aged <5 years (67 cases per 100,000 children) [19].

To assess the effectiveness of this vaccine, we designed a population-based case-control study. The case patients were all children aged <5 years who were born and resided in Navarra and who received a microbiologically confirmed diagnosis of IPD between week 41 of 2001 and week 40 of 2005. A case of IPD was defined as the isolation of *Streptococcus pneumoniae* from a normally sterile site (e.g., blood, CSF, or pleural fluid) and clinical symptoms compatible with pneumococcal disease. Clinical information for cases was obtained from medical records. Pneumococcal isolates were serotyped by the Quellung reaction or dot blot [20]. PCV7 serotypes included types 4, 6B, 9V, 14, 18C, 19F, and 23F. We defined PCV7-related serotypes as those in the same serogroup as the vaccine serotypes. All other pneumococci were considered to be non-PCV7 serogroups.

For each case patient, we selected 5 individually matched control subjects from children born in the same hospital and on the same date. The vaccination status of case patients and control subjects was ascertained in a blinded review of the Primary Care vaccination registry. We searched for the number of doses and the dates of vaccination, considering only the doses administered up to 15 days before the date of symptom onset in the corresponding case patient.

We defined children as completely vaccinated if they had received 3 PCV7 doses, if the first dose occurred at 2–6 months of age; 2 doses, if the first dose occurred at 7–23 months of age; and 1 dose, if the first dose occurred at ⩾24 months of age. A booster dose in the second year of life was also required for children who began vaccination before 12 months of age. Incomplete vaccination was defined as receipt of at least 1 dose of PCV7 but without completing the schedules indicated.

We evaluated the overall effectiveness of receiving at least 1 dose of PCV7 and of receiving the complete vaccine regimen, using unvaccinated children as the reference. In separate analyses, we also evaluated the effect of vaccination with PCV7 on the risk of IPD due to vaccine serotypes, vaccine-related serotypes, and nonvaccine serogroups. Unmatched dichotomous variables were compared using χ^2 or Fisher's exact tests. Matched ORs for vaccination, with their 95% CIs, were calculated using conditional logistic regression. Vaccine effectiveness was calculated as 1 minus the matched OR.

RESULTS

During the period from the 2001–2002 infection season through the 2004–2005 infection season, 85 cases of IPD were diagnosed among children aged <5 years. Five case patients (6%) presented with meningitis, 32 (38%) presented with bacteremic pneumonia, 5 (6%) presented with bacteremia with another focus, and 43 (51%) presented with bacteremia without a source. None of the case patients had a previous pathology that justified a special indication of PCV7. Of the 85 case patients, 18 (21%) had received at least 1 dose of PCV7, and 14 (16%) had completed the vaccine regimen. The percentages of serious forms of IPD (meningitis and bacteremic pneumonia) did not differ between vaccinated (44%) and unvaccinated case patients (43%; $P = 1.0$).

Vaccinated case patients did not differ from unvaccinated case patients with regard to demographic characteristics, the clinical form of IPD, or meningococcus conjugate vaccination. Vaccine serotypes were responsible for 1 case (6%) in the patient group vaccinated with PCV7 and 34 cases (51%) in the unvaccinated patient group ($P < .001$). Nonvaccine serogroups were responsible for 12 cases (67%) in the vaccinated patient group and 9 cases (13%) in the unvaccinated patient group ($P < .001$) (table 1). The 1 vaccination failure occurred in a child who had received 3 doses of vaccine at 3, 5, and 7 months of age and who received a diagnosis in the tenth month of bacteremia without focus caused by serotype 14. The number of cases of IPD due to non-PCV7 serogroups increased from 2 (9%) during the 2001–2002 infection season to 9 (43%) during the 2004–2005 infection season ($P = .02$).

Case patients and control subjects did not differ with regard to sex, age, Spanish nationality, or metropolitan residence. Similar percentages of case patients and control subjects received PCV7 (27% and 21%, respectively; $P = .34$). The percentage of vaccinated control subjects increased from 5% during the 2001–2002 infection season to 48% during the 2004–2005 infection season.

In the conditional logistic regression analysis, the overall effectiveness of at least 1 dose of PCV7 in preventing IPD caused by any serotype was 31% (OR, 0.69; 95% CI, 0.37–1.27; $P = .23$) (table 2). In separate analyses, vaccination with PCV7 was 88% effective in preventing IPD caused by PCV7 serotypes (OR, 0.12; 95% CI, 0.02–0.91; $P = .04$) and 70% effective in protecting against PCV7-related serotypes (OR, 0.30; 95% CI, 0.10–

Table 1. Characteristics of case patients with invasive pneumococcal disease, according to 7-valent pneumococcal conjugate vaccine (PCV7) vaccination status.

Characteristic	All subjects (n = 85)	Unvaccinated subjects (n = 67)	Vaccinated subjects (n = 18)
Clinical presentation			
Pneumonia with bacteremia	32 (38)	25 (37)	7 (39)
Meningitis	5 (6)	4 (6)	1 (6)
Bacteremia with other focus	5 (6)	4 (6)	1 (6)
Bacteremia without a source	43 (51)	34 (51)	9 (50)
Female	44 (52)	36 (54)	8 (44)
Age, months			
0–11	26 (31)	21 (31)	5 (28)
12–23	34 (40)	26 (39)	8 (44)
24–59	25 (29)	20 (30)	5 (28)
Non-Spanish nationality	9 (11)	9 (13)	0 (0)
Resides in metropolitan area of the capital	54 (63)	41 (61)	13 (72)
Received meningococcal C conjugate vaccine	83 (98)	65 (97)	18 (100)
Infection season[a]			
2001–2002	22 (26)	21 (31)	1 (6)
2002–2003	22 (26)	20 (30)	2 (11)
2003–2004	21 (25)	15 (22)	6 (33)
2004–2005	20 (24)	11 (16)	9 (50)
Pneumococcal serotype			
PCV7 serotype			
6B	4 (5)	4 (6)	0
14	12 (14)	11 (16)	1 (6)
18C	2 (2)	2 (3)	0
19F[a]	15 (18)	15 (22)	0
23F	2 (2)	2 (3)	0
Overall[a]	35 (41)	34 (51)	1 (6)
PCV7-related serotype			
6A	6 (7)	6 (9)	0
19A	19 (22)	15 (22)	4 (22)
23B	2 (2)	1 (1)	1 (6)
Overall	27 (32)	22 (33)	5 (28)
Non-PCV7 serogroup			
1	6 (7)	4 (6)	2 (11)
3	5 (6)	3 (4)	2 (11)
7	3 (4)	1 (1)	2 (11)
15B	1 (1)	0	1 (6)
15C	2 (2)	0	2 (11)
16	1 (1)	1 (1)	0
17	1 (1)	0	1 (6)
22	1 (1)	0	1 (6)
24	1 (1)	0	1 (6)
Overall[a]	21 (25)	9 (13)	12 (67)
Nontypeable or nontyped	2 (2)	2 (3)	0

NOTE. Data are no. (%) of isolates.

[a] $P < .05$ for comparison of percentages between vaccinated and unvaccinated subjects.

0.95; $P = .04$). However, being vaccinated was associated with an increased risk of IPD caused by non-PCV7 serogroups (OR, 6.16; 95% CI, 1.63–23.32; $P = .008$).

Table 3 shows the results of conditional logistic regression analysis when 3 levels of PCV7 vaccination status were considered: complete, incomplete, and not vaccinated. The effectiveness of the complete vaccine regimen in preventing any type of IPD was 10% (OR, 0.90; 95% CI, 0.44–1.84; $P = .78$). Complete vaccination revealed an effectiveness of 81% in preventing IPD caused by PCV7 serotypes and 64% against PCV7-

Table 2. Vaccination status of case patients and control subjects and the association between receipt of at least 1 dose of 7-valent pneumococcal conjugate vaccine (PCV7) and occurrence of invasive pneumococcal disease (IPD), by serotype.

IPD serotype	Case patients	Control subjects	Matched OR (95% CI)	*P*
All serotypes[a]	18/85 (21)	114/425 (27)	0.69 (0.37–1.27)	.23
PCV7 serotype	1/35 (3)	32/175 (18)	0.12 (0.02–0.91)	.04
PCV7-related serotype	5/27 (19)	52/135 (39)	0.30 (0.10–0.95)	.04
Non-PCV7 serogroup	12/21 (57)	19/105 (28)	6.16 (1.63–23.3)	.008

NOTE. Data are the proportion (%) of case patients or control subjects who were vaccinated.

[a] Includes 1 nontypeable and 1 nontyped case.

related serotypes; in contrast, complete vaccination was associated with an increased risk of developing IPD caused by non-PCV7 serogroups (OR, 13.31; 95% CI, 2.39–74.37; $P = .003$).

The percentages of serious forms of IPD (meningitis and bacteremic pneumonia) did not differ between vaccinated and unvaccinated case patients (44% vs. 43%; $P = 1.0$). The effectiveness of vaccination with PCV7 in preventing serious forms of IPD due to any serotype was 18% (OR, 0.82; 95% CI, 0.31–2.15; $P = .69$).

DISCUSSION

The effectiveness of at least 1 dose of PCV7 in preventing IPD due to vaccine serotypes was 88% among children aged <5 years in Navarra, which is within the range of findings of clinical trials [1–2]. The effectiveness of vaccination against IPD due to vaccine-related serotypes was 70%, which constitutes an argument in favor of cross-reactive protection [3–4]. However, the effectiveness of vaccination with PCV7 in preventing IPD, regardless of serotype, decreased to 31%, because the vaccinated children had a 6 times greater risk of IPD due to nonvaccine serogroups than did those who were not vaccinated. These findings were confirmed when we varied the analysis to include only the more serious forms of IPD (i.e., meningitis and bacteremic pneumonia) or considered only subjects who had received a complete vaccine regimen. These results do not rule out the effectiveness of PCV7, but they indicate that its effectiveness may become very limited under certain circumstances. Before the vaccine was introduced in Navarra, only 43% of cases of IPD were due to PCV7 serotypes. This may have contributed to the fact that overall vaccine effectiveness was lower than what has been found in other countries [17].

Table 3. Association between 7-valent pneumococcal conjugate vaccine (PCV7) vaccination status and invasive pneumococcal disease (IPD), by serotype.

IPD serotype, vaccination status	Ratio of case patients to control subjects	Matched OR (95% CI)	*P*
All serotypes[a]			
Not vaccinated[b]	67/311	1.00	
Incomplete	4/44	0.39 (0.13–1.17)	.09
Complete	14/70	0.90 (0.44–1.84)	.78
PCV7 serotype			
Not vaccinated[b]	34/143	1.00	
Incomplete	0/13	0 (indeterminate)	.99
Complete	1/19	0.19 (0.03–1.54)	.12
PCV7-related serotype			
Not vaccinated[b]	22/83	1.00	
Incomplete	1/18	0.19 (0.02–1.56)	.12
Complete	4/34	0.36 (0.10–1.30)	.12
Non-PCV7 serogroup			
Not vaccinated[b]	9/76	1.00	
Incomplete	3/13	2.54 (0.44–14.5)	.30
Complete	9/16	13.3 (2.39–74.4)	.003

[a] Includes 1 nontypeable and 1 nontyped cases.

[b] Reference.

These findings are consistent with the results of epidemiological surveillance of IPD in Navarra, which reveal that, in the same period, vaccine coverage increased to 45%, the overall incidence of IPD decreased by only 12%, and the incidence of cases from non-PCV7 serotypes increased by 36% [19].

The increased risk of pneumococcal disease due to non-PCV7 serogroups among vaccinated children has been attributed to the replacement of vaccine types by nonvaccine types [9–10]. Various studies have described this replacement at the population level, with increases in incidence of disease caused by nonvaccine serogroups occurring after the introduction of the vaccine [11–16]. We found replacement at the individual level in the vaccinated children, among whom the reduced risk conferred by the vaccine was partially cancelled out by an increased risk of IPD caused by non-PCV7 serogroups. The effect of PCV7 in preventing noninvasive pneumococcal diseases, such as acute otitis media [9–10] and pneumonia [21], has also been described, and this effect is also affected by serotype replacement [9–10, 21–22].

Given the individual matched design, case patients and control subjects were comparable with regard to many characteristics, but we did not control for other potential confounding factors, such as exposure to tobacco smoke, kindergarten attendance, or lack of breast-feeding. All 3 of these factors have been related to an increased risk of IPD [23–24] and may be associated with a child's probability of being vaccinated. Nonetheless, the fact that the same studies have found both an important protective effect of vaccination against vaccine serotypes and vaccine-related serotypes and an increased risk attributable to nonvaccine serogroups argues against an important influence of confounding variables. To evaluate the possibility that differences in the selection of control subjects could have given rise to confounding in one analysis but not in the other, we repeated the 2 analyses by comparing the cases in each of them with the pooled control subjects and found that the conclusions were unchanged.

Unvaccinated children may benefit from the herd immunity that is attributed to vaccination with PCV7 [2, 8]. In our study, we can detect only the direct effect; therefore, the effectiveness of the vaccine could be higher. Likewise, unvaccinated children who live in areas where the vaccine has been introduced could indirectly experience an increase in the incidence of disease due to nonvaccine serotypes; thus, the increased risk of disease due to non-PCV7 serotypes associated with the vaccine could be underestimated.

In conclusion, we found that, in Navarra, the effectiveness of vaccination with PCV7 against IPD overall was quite limited because of the increased risk of IPD due to non-PCV7 serogroups among vaccinated children. This confirms that vaccine serotypes are being replaced by nonvaccine serogroups causing IPD in vaccinated children. Different serotypes of *S. pneumoniae* seem to be able to occupy the ecologic niches left by others. As long as vaccines target only some of the serotypes capable of causing disease, their effectiveness may vary widely among different geographic areas and over time. This behavior of *S. pneumoniae* in vaccinated children should be borne in mind by those responsible for designing vaccine schedules, by researchers developing new vaccines, and by pediatricians who make recommendations to parents of children of vaccination age.

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