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Invasive pneumococcal disease among children in a health district of Barcelona: early impact of pneumococcal conjugate vaccine

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ABSTRACT

This study evaluated the impact of heptavalent pneumococcal conjugate vaccine (HPCV) on invasive pneumococcal disease (IPD) in children aged ≤5 years in Barcelona, Spain. The incidence of IPD, vaccine uptake and prevalence of nasopharyngeal colonisation were analysed in two different periods: 1999–2001 (pre-licence period), and 2002–2004 (post-licence period). In total, 121 cases of IPD were identified. The overall incidence of IPD decreased from 96.9 cases/100 000 to 90.6 cases/100 000 (OR 0.93, 95% CI 0.69–1.26, p 0.71) between the two periods. The proportion of cases caused by non-vaccine-related serotypes (NVS) increased from 21% to 43.7% (OR 2.9, 95% CI 1.2–7, p 0.01). IPD was diagnosed in seven vaccinated children, six of whom were infected by NVS. There was a trend of diminishing prevalence of resistance to penicillin and macrolides in 2002–2004. The incidence of empyema increased from 1.7 to 8.5/100 000 (OR 4.5, 95% CI 0.91–18, p 0.06). The rate of vaccination ranged from 4.8% to 34%. It was concluded that the rates of IPD in this area did not decrease following the introduction of HPCV. The low uptake of vaccine and the greater proportion of colonisation/infection by NVS probably explain these findings. A trend of increasing empyema was also apparent. A decrease in the prevalence of penicillin and macrolide resistance paralleled the progressive uptake of vaccine.

Keywords Colonisation, heptavalent conjugate vaccine, infection, pneumococcal conjugate vaccine, resistance, vaccination

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INTRODUCTION

Streptococcus pneumoniae is responsible for a wide spectrum of infections in young children, ranging from acute otitis media to sepsis. Since the late 1990s, following the introduction of *Haemophilus influenzae* type b conjugate vaccine, pneumococci have become the most important cause of acute community-acquired meningitis among young children. Moreover, increasing resistance to penicillin and other drugs among pneumococci has complicated the empirical treatment of these infections. Hence, there is increasing interest in the development of an immunogenic vaccine for use in this age group.

Heptavalent pneumococcal polysaccharide conjugate vaccine (HPCV) has been available in the USA since 2000, and is recommended for all children aged ≤5 years. HPCV has demonstrated its ability to reduce the incidence of invasive pneumococcal disease (IPD) caused by vaccine-related serotypes in children aged <2 years [1,2]. HPCV is also highly effective in preventing pneumonia [3], and has substantially

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reduced the number of cases of recurrent acute otitis media and the necessity for placement of tympanostomy tubes in healthy infants [4,5]. HPCV has also reduced nasopharyngeal colonisation by vaccine-related serotypes among vaccinated individuals [6,7]. Interestingly, it has been shown that use of pneumococcal conjugate vaccine may also be reducing the incidence of disease in adults [1], and significant declines in resistance to penicillin and macrolides have been noted [8] (43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, abstract G-2045).

HPCV was licensed for use in Spain in 2001. It is well-known that the vaccine's efficacy is influenced by the rate of vaccine uptake, by the number of carriers of pneumococcal serotypes not included in the vaccine, and probably by the use of antibiotics in a specific area [1]. The aim of the present study was to evaluate the impact of HPCV on IPD in children aged ≤5 years in Barcelona, Spain.

MATERIALS AND METHODS

Setting

The health district of Terrassa is in the province of Barcelona, and includes four municipalities that contain *c.* 23 000 children aged <5 years, among a total population of 350 000 inhabitants. The paediatric population is served by two acute-care hospitals, Hospital Mútua de Terrassa (HMT) and Consorci Sanitari de Terrassa, and by nine primary care centres that refer children with potentially severe medical conditions to the paediatric emergency departments of the two hospitals; in addition, private paediatricians in the area send their patients to the hospitals referred to above.

Prevalence of vaccine uptake studies

Vaccination with HPCV is not yet compulsory in Spain, but is highly recommended by paediatricians in the Barcelona area. Vaccine uptake, prevalence of nasopharyngeal colonisation and overall incidence of IPD were analysed in two different periods: 1999–2001 (pre-licence period), and 2002–2004 (post-licence period). Data were obtained from three different sources: (1) during January and February 2005, 181 randomly selected parents of children aged ≤5 years who had attended the Emergency Department of HMT (for any reason) were interviewed to ascertain the number of children who had received at least two doses of HPCV; (2) a study of HPCV uptake was carried out in a primary care centre in the area that had computerised medical records with dates and doses of vaccination; in this centre, the paediatric population examined during the first trimester of 2005 comprised 1024 and 1742 children aged <2 and <5 years, respectively; and (3) data were obtained from the manufacturer and distributor of HPCV (Wyeth Lederle, Madrid, Spain) concerning the total number of doses of HPCV sold between 2002 and 2004 in the four municipalities in which the two hospitals and the primary care centres were based.

Nasopharyngeal colonisation study

Between 2001 and 2003, *S. pneumoniae* nasopharyngeal colonisation was studied in children aged ≤5 years who attended the emergency department of one of the participating hospitals (HMT). After informed parental consent, nasopharyngeal samples of children were taken with a trans-nasal alginated swab and were processed immediately upon arrival at the microbiology laboratory. The swabs were added to 20 mL of brain–heart infusion broth and shaken until there was visible turbidity. The suspension was then inoculated on blood agar plates containing colistin and nalidixic acid (bioMérieux, Marcy l'Etoile, France) and incubated at 37°C in CO_2 5% v/v for a maximum of 48 h. Following incubation, the identification of each isolate was confirmed by the optochin disk test. Viable isolates of *S. pneumoniae* were serogrouped by the National Centre of Microbiology, Majadahonda, Madrid, Spain. Penicillin susceptibility was determined by agar dilution using the MIC breakpoints established by the CLSI (formerly NCCLS). Isolates that were intermediately-resistant or resistant to penicillin were classified as non-susceptible.

Estimation of incidence of IPD

All isolates of *S. pneumoniae* recovered from children with IPD aged ≤5 years in the area between 1999 and 2004 were studied. A case of IPD was defined by a positive culture of *S. pneumoniae* from a normally sterile body fluid. During the period 1999–2003, blood cultures were processed with the automated Vital system (bioMérieux), after which the BacT-Alert system (bioMérieux) was used. Pleural fluid and cerebrospinal fluid were cultured by conventional methods. Serotypes were classified as vaccine serotypes (VS) (4, 6B, 9V, 14, 18C, 19F and 23F), vaccine-related serotypes (VRS) (6A, 19A, 23A, etc.) or non-vaccine serotypes (NVS). Annual incidence rates were calculated from IPD case numbers (as numerator) and local Census Bureau estimates (as denominator). Annual incidence rates were compared between the pre-licence period (1999–2001) and the post-licence period (2002–2004).

Medical records for all patients with IPD who had been vaccinated with two or more doses of HPCV were reviewed. Vaccine failure was defined as invasive disease caused by a VS in a vaccinated patient. Data collected included demographical, clinical and microbiological variables, immunodeficiencies, previous antibiotic therapy and outcome.

Statistical analysis

Percentages were used to analyse qualitative variables; means and standard deviations were used to evaluate quantitative data in the descriptive analysis. In the bivariate analysis, Student's *t*-test was used to compare means. The chi-square and Fisher's exact test were used to compare the proportion of the population aged ≤5 years who had invasive disease in the years following the introduction of the vaccine (2002–2004) with the proportion in the pre-licence period (1999–2001).

RESULTS

Vaccine uptake

The prevalence study performed in one of the participating hospitals (HMT) included 181 children seen in the emergency department during January and February 2005; vaccine uptake among children aged ≤5 years was 33%. The results obtained in the primary care centre during the first trimester of 2005 showed that 230 (22.3%) of 1024 children aged <2 years, and 247 (14.1%) of 1742 children aged <5 years, had been vaccinated. Finally, after taking into account the total number of doses of vaccine sold in the area, and using the total population aged ≤2 years as the denominator, the percentage of vaccinated children ranged from 4.8% in 2002 to 34% in 2004.

S. pneumoniae serotypes and nasopharyngeal colonisation among children aged ≤5 years

Between 2001 and 2003, 134 children were included in the study of nasopharyngeal colonisation, with 67 (50%) carrying *S. pneumoniae* in their nasopharynx. Of the children studied, 17 (12.7%) were aged <12 months, 35 (26.1%) were aged 13–24 months, and 82 (61%) were aged >24 months; 70 (52.2%) were male. The most common serotypes isolated were 6A, 9V, 14, 19 and 11. When the entire cohort of colonised children was considered, 22% (15/67) were colonised by VRS, 34% (23/67) by VS, and 43% (29/67) by NVS.

Invasive pneumococcal disease

Between 1999 and 2004, 121 cases of IPD were identified in children aged ≤5 years. The overall incidence of IPD decreased from 96.9 cases/100 000 children during 1999–2001 to 90.6 cases/100 000 during 2002–2004 (OR 0.93, 95% CI 0.69–1.26, p 0.71). The main clinical diagnoses among the cases of IPD are shown in Table 1.

Invasive pneumococcal disease among vaccinated children

During 2002–2004, IPD was diagnosed in seven vaccinated children, all of whom were aged between 6 and 36 months and had received at least two doses of HPCV according to the schedule recommended by the Vaccines Advisory Committee of the Sociedad Española de Pediatría.

Table 1. Invasive pneumococcal disease among children aged ≤5 years during the periods 1999–2001 and 2002–2004 (cases/100 000 children aged ≤5 years)

Disease	1999–2001	2002–2004	OR (95% CI); p
Meningitis	3.4	1.41	0.5 (0.09–3); 0.68
Pneumonia	32.32	31.36	0.98 (0.5–1.6); 1
Empyema	1.7	8.5	4.5 (0.91–18); 0.06
Occult bacteraemia	59.4	49.8	0.83 (0.56–1.23); 0.38
Overall incidence	96.9	91.2	0.93 (0.69–1.26); 0.71

NVS were isolated from all but one patient (patient 7, Table 2), who developed IPD caused by serotype 6A, which is considered to be a VRS. The outcome was favourable in all seven cases. Neither humoral nor cellular immunodeficiencies, or complement dysfunction, were found in any of these children. The incidence of empyema increased from 1.7/100 000 to 8.5/100 000 (OR 4.5, 95% CI 0.91–18, p 0.06). Pleural isolates all belonged to serotype 1, with the single exception of a case caused by serogroup 4 in the post-licence period. The incidence of meningitis fell by 68%, from 3.4/100 000 to 1.4/100 000 (OR 0.5, 95% CI 0.09–3, p 0.68).

Serotype prevalence and antimicrobial susceptibilities among IPD isolates

The proportion of infections caused by NVS increased from 21% during 1999–2000 to 43.7% during 2002–2004 (OR 2.9, 95% CI 1.2–7, p 0.01). The changes in prevalence of serogroups/serotypes between the two periods are shown in Fig. 1. Serotype 1 was the most prevalent, followed by serotypes 14, 19, 6A, 6B and 23F.

Penicillin-non-susceptible *S. pneumoniae* isolates from children with IPD aged ≤5 years decreased from 49% in 1999–2001 to 42% in 2002–2004 (OR 1.3, 95% CI 0.6–2.9, p 0.56). In addition, erythromycin resistance among isolates decreased from 52.6% in 1999–2001 to 35.9% in 2002–2004 (OR 1.98, 95% CI 0.89–4.39, p 0.09). Cefotaxime-susceptible isolates accounted for 96.5% and 95.4% of isolates during 1999–2001 and 2002–2004, respectively (OR 0.7, 95% CI 0.1–5.7, p not significant).

DISCUSSION

The rates of IPD in the Barcelona area during the two periods studied (97 and 91/100 000 children aged ≤5 years, respectively) are higher than those

Table 2. Cases of invasive pneumoccocal disease among children aged ≤5 years who received two or more doses of heptavalent pneumococcal conjugate vaccine during the first 2 years following the introduction of the vaccine

Case	Age (months)	Gender	Clinical syndrome	Vaccine	Serotype	Outcome
1	18	Female	Pneumonia + empyema	3 doses	5	Favourable
2	36	Female	Pneumonia + bacteraemia	2 doses	1	Favourable
3	13	Female	Occult bacteraemia	3 doses	33	Favourable
4	35	Female	Bacteraemia + septic shock	4 doses	12	Favourable
5	17	Male	Occult bacteraemia	2 doses	38	Favourable
6	21	Male	Meningitis + bacteraemia	3 doses	7	Favourable
7	6	Male	AOM + bacteraemia	2 doses	6A	Favourable

AOM; acute otitis media.

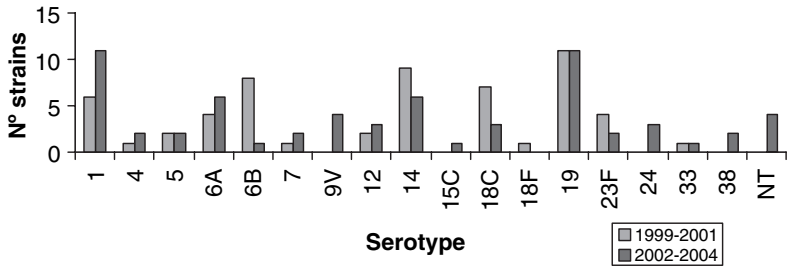

Fig. 1. Changes in prevalence of the most common serotypes causing invasive pneumococcal disease in children aged <5 years during 1999–2001 and 2002–2004.

reported in other areas of Spain (range 33.1–46 cases/100 000) [9,10], and are very similar to those reported in the USA (72–103 cases/100 000) [11,12]. Similarly, there were higher rates of occult bacteraemia (50–60 cases/100 000 vs. 30 cases/100 000) and bacteraemic pneumococcal pneumonia (31–32 cases/100 000 vs. 10 cases/100 000) than those reported in neighbouring areas [10]. In contrast, the rates of acute meningitis were lower (1.4–3.4 cases/100 000) than those reported in all other recent Spanish studies (4.6–6.2/100 000) [10,13]. These differences could be associated with the fact that the two hospitals in the present study serve a well-defined population, and have a systematic practice of drawing blood cultures from all febrile children seen in the emergency department at both institutions.

The introduction of HPCV to the area during 2002, with an estimated vaccine uptake of *c.* 30%, has not been followed by a significant fall in the incidence of IPD in the population studied, up to the end of 2004. The vaccine uptake has been similar in other areas of Spain. It is likely that the relatively low percentage of vaccinated children in the area studied, as compared with rates of vaccine uptake of >50% in areas where high efficacy has been documented, is an important limiting factor in vaccine effectiveness. The fact that HPCV vaccination is not compulsory in Spain explains the current low percentage of vaccine uptake. However, the relative frequency of VS and VRS causing IPD in a given area will also influence the efficacy of HPCV, as will the distribution of serotypes among the nasopharyngeal isolates. In the present study, 43% of colonised children aged ≤5 years yielded serotypes that were unrelated to those represented in the HPCV. This distribution differs from that described among children in the USA, but is similar to that found in other areas where vaccine coverage is limited. Thus, in South America, Africa and Oceania, the seven vaccine serotypes represent 50–70% of all cases of IPD [14]. As in previous studies, the present data indicate that vaccine coverage against the serotypes causing IPD among children aged ≤2 years in Spain is even lower. Thus, Fenoll and Casal [15] reported that the coverage afforded by HPCV in 2000 was 74%, decreasing to 54% in 2003, while a preliminary report revealed only 40% coverage in 2004 [16].

Analysis of the IPD cases in the present study showed a clear substitution of VS and VRS by NVS between the pre-licence and post-licence periods. NVS as a cause of IPD increased in this population from 21% to 43% (a 49% increase). This phenomenon was described in the initial studies on the impact of HPCV [1,2,16–20]. In these studies, the decrease in the incidence of infection caused by VS, following the introduction

of HPCV, generated an increase in NVS that ranged from 27% to 37% [1,2]. The present study did not determine whether this inversion in the frequency of distribution of serotypes was the result of an increase in infections caused by NVS or of capsular switching [21,22]. The high percentage of children colonised with NVS, and the clear substitution of VS and VRS by NVS between the pre- and post-licence periods, is a matter of concern. Further studies are needed urgently to confirm these trends and to better delineate the potential limitations of HPCV in Spain.

Seven children vaccinated with at least two doses of HPCV had IPD, giving an estimated incidence among vaccinated children of 0.1%. None of the serotypes causing disease in these children were included in the vaccine, and all seven had infections caused by strains that were susceptible to penicillin. Interestingly, one child developed IPD, caused by an isolate of serotype 6A, less than 6 weeks after the second dose of vaccine (administered at an age of 5 months). Although serotype 6A is a VRS, it is likely that the humoral response is still poor at this age. In fact, the response is not homogeneous for all vaccine serotypes, with serotypes 9 and 6 being those associated with higher vaccine failure rates [2,18,23].

There was a trend toward a reduction in penicillin resistance among the invasive isolates causing IPD during 2002–2004; this was even more noticeable with the macrolides, for which the prevalence of resistance decreased from 52.6% to 35.9%. Similar trends have been observed in other recent surveys [8,24]. In addition to the possible impact of HPCV, the progressive and continued decrease in overall antibiotic consumption in Spain, and an increase in the use of fluoroquinolones for treating respiratory tract infections [24], are probably playing a complementary role. In this context, a preliminary report has described a recent Spanish survey showing a significant reduction of resistance to penicillin in pneumococci coinciding with a reduction in the frequency of isolation of clones Spain^{6B}-2 and Spain^{23F}-1 (44th Interscience Conference on Antimicrobial Agents and Chemotherapy; abstract C2-827). Fortunately, NVS are generally sensitive to penicillin, albeit with some exceptions, notably serotype 35B, which is usually associated with penicillin resistance [25]. Indeed, there has already been a preliminary report of an increase in non-penicillin-resistant serotypes in areas with high rates of vaccination with HPCV (43rd Interscience Conference on Antimicrobial Agents and Chemotherapy; abstract G-890). This is a good reason to continue active surveillance programmes focused on the changing distribution of serotypes. The significant increase in the incidence of empyema probably results from a combination of the factors referred to above, and especially from the emergence of non-vaccine serotypes. The same phenomenon has been observed in the USA [26].

In summary, the rates of IPD in the Barcelona area during the study periods were higher than those reported in other areas of Spain, and have not decreased significantly following the introduction of HPCV. The low vaccine uptake and a greater proportion of NVS colonising and/or infecting children help to explain these findings. An increase in the incidence of empyema also became apparent. A trend toward a decreasing prevalence of penicillin and macrolide resistance among pneumococci was detected in parallel with a progressive increase in vaccine uptake, although other factors could also have contributed to this phenomenon.

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