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Impact of the 7-valent pneumococcal conjugate vaccine on the incidence of childhood pneumonia

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SUMMARY

In September 2006, the 7-valent pneumococcal conjugate vaccine (PCV7) was added to the UK immunization programme. We aimed to evaluate the impact of PCV7 on the incidence of all-cause community-acquired pneumonia (CAP) in children. A prospective survey was undertaken in 2008–2009 at 11 hospitals in North East England of children aged 0–16 years with radiologically confirmed pneumonia. Data were compared to those from a similar survey undertaken in the same hospitals in 2001–2002. A total of 542 children were enrolled, of which 74% were aged <5 years. PCV7 uptake was 90·7%. The incidence of pneumonia was 11·8/10 000 [95% confidence interval (CI) 10·9–12·9], and the hospitalization rate was 9·9/10 000 (95% CI 9·0–10·9). Compared to 2001, there was a 19% (95% CI 8–29) reduction in the rate of CAP in those aged <5 years, and in those <2 years a 33·1% (95% CI 20–45) reduction in the incidence of CAP and 38·1% (95% CI 24–50) reduction in hospitalization rates. However, for those unvaccinated aged ⩾5 years, there was no difference in the incidence of CAP and hospitalization rate between both surveys. Since 2001, the overall reduction in incidence was 17·7% (95% CI 8–26) and for hospitalization 18·5% (95% CI 8–28). For the <5 years age group there was a lower incidence of CAP in PCV7-vaccinated children (25·2/10 000, 95% CI 22·6–28·2) than in those that were not vaccinated (37·4/10 000, 95% CI 29·2–47·1). In conclusion, PCV7 has reduced both incidence and rate of hospitalization of pneumonia in children, particularly in the <2 years age group.

Key words: Children, incidence, pneumococcal conjugate vaccine, pneumonia.

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INTRODUCTION

Community-acquired pneumonia (CAP) is a common childhood illness [1]. It causes about 20% of global childhood mortality, mostly in resource-poor countries [2, 3]. *Streptococcus pneumoniae* is the leading bacterial cause of pneumonia in young children [4]. In the UK, pneumococcal infection was identified in nearly 10% of CAP in children [5, 6]. This is likely to be an underestimation of the true burden of pneumococcal disease, given the relative imprecision of microbiological diagnosis of pneumonia in children [1].

In September 2006, the 7-valent pneumococcal conjugate vaccine (PCV7) including antigen for serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F was added to the UK immunization programme. The vaccine schedule is three doses administered at ages 2, 4 and 13 months. When introduced, those aged >1 year and $\leqslant 1$ year received one and two doses, respectively as part of a catch-up programme for children aged <2 years. Subsequently this was replaced by PCV13 from April 2010, which also includes antigen for the additional serotypes 1, 3, 5, 6A, 7F, and 19A.

The efficacy of pneumococcal conjugate vaccines in preventing radiological pneumonia has been shown to be up to 37% in randomized controlled trials [7–11]. However, prospective epidemiological studies are valuable in establishing the impact of vaccines in populations outside trial settings [12, 13]. The incidence of childhood CAP seen in hospitals in North East England was evaluated prospectively in 2001–2002 [14]. At that time the incidence of childhood pneumonia was 14·4/10 000 (95% CI 13·4–15·4) and 33·8/10 000 (95% CI 31·1–36·7) for those aged <5 years [14]. This survey, which commenced in 2008, provides an opportunity to evaluate the impact of the introduction of PCV7 on the incidence of childhood pneumonia using prospective clinical data in a defined and previously studied population.

METHODS

Study design and participants

This was a prospective survey involving 11 hospital sites in North East England (excluding Cumbria). It was conducted from August 2008 to July 2009, covering the same months as the survey in 2001–2002. The hospital configuration changed slightly from the previous survey in 2001, with a reduction in the number of hospitals treating children from 13 to 11. However, the geographical area and population served by these hospitals were the same as in 2001 as were the methods of enrolment criteria and case ascertainment [14]. In the UK, children are assessed by a General Practitioner in primary care or by an Emergency Room team and then referred to a hospital-based paediatrician if secondary care is required.

Eligibility criteria were children aged 0–16 years, who presented with clinical and radiological features of pneumonia and were seen in hospital by a paediatrician. Data on chest radiographs were collated from local radiologists' reports and findings were grouped according to a modified version of the WHO criteria [15, 16]. Radiological reports were grouped into five categories (lobar, patchy consolidation, perihilar infiltrates, other infiltrates/abnormalities, normal). The other infiltrates/abnormalities included reports of increased bronchovascular markings, peribronchial thickening, bronchial wall thickening, or peribronchial cuffing and were analysed as pneumonia. The modification of including a further category (other infiltrates/abnormalities) is in line with the extended definitions of pneumonia used by Enwere *et al.* [17] in their study of the epidemiology of pneumonia in the Gambian PCV9 trial. Exclusion criteria included being resident outside North East England, clinically diagnosed bronchiolitis, hospitalization for any reason in the preceding 3 weeks, or a chest radiograph reported as normal.

A favourable ethical opinion was obtained from the regional Newcastle and North Tyneside Research Ethics Committee. Caldicott approvals were granted from all collaborating sites.

Case ascertainment and data validation

Children were identified prospectively by local paediatric teams who completed a proforma containing data on demographics, clinical findings, management and outcomes. Enrolment data were cross-checked to ensure complete ascertainment by reviewing ward admission diaries for children admitted with respiratory symptoms (eight sites), or by obtaining hospital coding data on pneumonia admissions (three sites). Case-notes and electronic records were reviewed to confirm the diagnosis, and to collect any missing data. Pneumococcal immunization history was obtained for each child from parents, and where available it was cross-checked with the child's parent-held health records. If there was uncertainty about the immunization history, general practice surgeries were contacted and practice records of vaccines given were checked.

Classification of disease severity and social class

Disease severity was determined using modified criteria from the British Thoracic Society (BTS) management guidelines for pneumonia [18]. The symptom of dyspnoea was excluded as the definition was deemed subjective, particularly in preschool-age children [19]. Any of the following led to the classification of 'severe disease': respiratory rate >70 or >50 for $\leqslant$1- or $>$1-year-olds, respectively; oxygen saturation $<93\%$; oxygen therapy; nasogastric feeds; intravenous fluid infusion; septicaemia; empyema; high dependency or intensive care admission. 'Mild disease' included immediate discharge home or hospital stay <3 days and no oxygen therapy; no nasogastric feeds and no intravenous fluid infusion. Children with none of the above were classified as having 'moderate disease'. Parental occupation information was incomplete, therefore socioeconomic class and the measure of deprivation were derived for each child based on the Index of Multiple Deprivation score (IMD) for the parental postcode of residence (The English Index of Deprivation 2007, Office for National Statistics).

Statistical analysis

Incidence rates were established by age and sex using the population estimates for the North East Strategic Health Authority area from the UK Office of National Statistics for 2009. There were 458 500 children aged <16 years, of which 146 200 were aged <5 years [20]. Confidence intervals (CIs) of incidence rates were calculated assuming a Poisson distribution and using the EpiTools package in R statistical software version 2.14.0 (The R Foundation for Statistical Computing, Austria). Univariate and multivariate logistic regression was used to establish risk factors for severe compared to mild/moderate CAP. Fisher's exact test was used to compare differences in count data between 2001 and 2009 for disease severity.

RESULTS

A total of 582 children were initially identified; 40 were excluded (34 had a normal chest radiograph, six lived outside the North East), leaving 542 eligible for inclusion (58% males). There were no deaths. Overall, 98% received antibiotics and 84% were admitted to hospital. Lobar consolidation was reported in 30%, and pleural effusion was present on 9·6% of the chest radiographs. Four hundred children aged <5 years were included, of these, 320 were vaccinated with PCV7, 33 were eligible for the vaccine but had not received it, for nine vaccination status was unknown and 38 were ineligible for the vaccine on age grounds. One child who was ineligible on age grounds had received the vaccine. Hence, the PCV7 uptake was 90·7% in the eligible children in the survey.

The annual incidence of pneumonia was 11·8/10 000 children aged <16 years (95% CI 10·9–12·9), with 27·4/10 000 (95% CI 24·8–30·2) in the <5 years age group. This compared to 14·4/10 000 (95% CI 13·4–15·4) and 33·8/10 000 (95% CI 31·1–36·7), respectively in 2001 [14]. The hospitalization rate was 9·9/10 000 (95% CI 9·0–10·9) for all, and 22·4/10 000 (95% CI 20·1–25·0) for those aged <5 years. This was lower than the 2001 rates; 12·2/10 000 (95% CI 11·3–13·2) and 28·7/10 000 (95% CI 26·2–31·4), respectively. By calculation of the incidence rate ratio, the overall reduction in incidence between 2001 and 2009 was 17·7% (95% CI 8–26) and the reduction in hospitalization rate was 18·5% (95% CI 8–28). The reduction in pneumonia in the <5 years age group was 19% (95% CI 8–29%). Table 1 compares data between the 2001 and 2009 surveys.

There was a significantly lower incidence of pneumonia in children aged <5 years vaccinated with PCV7 (25·2/10 000, 95% CI 22·6–28·2) compared to those that were unvaccinated (37·4/10 000, 95% CI 29·2–47·1) [odds ratio (OR) 4·5, 95% CI 3·5–5·9]. However, there was no significant difference in the incidence of severe disease between the vaccinated children (13·0/10 000, 95% CI 11·1–15·1) and those unvaccinated in the <5 years age group (22·6/10 000, 95% CI 16·4–30·5) (OR 0·7, 95% CI 0·4–1·2). Of those aged <2 years, there was a significant reduction of 33·1% (95% CI 20–45) in the incidence of pneumonia from 49·9/10 000 (95% CI 44·1–56·4) in 2001 to 33·5/10 000 (95% CI 28·9–38·4) in 2009, whereas the reduction in hospitalization was 38·1% (95% CI 24–50) between 2001 and 2009 (Table 1). Reduction in both the incidence of pneumonia and hospitalization between 2001 and 2009 was also observed in the 2·0–4·9 years age group by 23·1% (95% CI 7–36) and 29·8% (95% CI 14–43), respectively. In the $\geqslant$5 years group, there was no difference in the incidence of pneumonia between 2001 and 2009 (incidence rate ratio 0·85, 95% CI 0·7–1·2), nor the hospitalization rate between both studies (incidence rate ratio 0·9, 95% CI 0·7–1·2).

Most cases ($n=363$, 67%) occurred during the winter and spring seasons. Table 2 summarizes the

Table 1. *Comparison of rates of pneumonia and hospitalization between 2001 and 2009 data per 10 000 children*

Variables	2001 survey IR (95% CI)	2009 survey IR (95% CI)	Reduction % (95% CI)
Overall			
Pneumonia	14·4 (13·4–15·4)	11·8 (10·9–12·9)	17·7 (8 to 26)
Hospitalization	12·2 (11·3–13·2)	9·9 (9·0–10·9)	18·5 (8 to 28)
<2 years			
Pneumonia	49·9 (44·1–56·4)	33·5 (28·9–38·4)	33·1 (20 to 45)
Hospitalization	45·6 (40·1–51·8)	28·2 (24·1–32·8)	38·1 (24 to 50)
2·0–4·9 years			
Pneumonia	30·7 (27·1–34·6)	23·6 (20·4–27·1)	23·1 (7 to 36)
Hospitalization	27·5 (24·1–31·3)	19·3 (16·5–22·5)	29·8 (14 to 43)
<5 years			
Pneumonia	33·8 (31·1–36·7)	27·4 (24·8–30·2)	19·1 (8 to 29)
Hospitalization	28·7 (26·2–31·4)	22·4 (20·1–25·0)	21·9 (10 to 32)
⩾5 years			
Pneumonia	5·3 (4·6–6·1)	4·5 (3·8–5·4)	14·7 (–7 to 32)*
Hospitalization	4·5 (3·8–5·2)	4·1 (3·4–4·8)	9·4 (–15 to 29)*

IR, Incidence rate; CI, confidence interval.
* Negative numbers denote an estimate of an increase in incidence.

Table 2. *Incidence rates of pneumonia per 10 000 children* (*August 2008–July 2009*)

	<5 years ($n=400$)		⩾5 years ($n=142$)		Overall ($n=542$)	
Variables	*n* (%)	IR (95% CI)	*n* (%)	IR (95% CI)	*n* (%)	IR (95% CI)
Male	227 (56·8)	15·5 (13·6–17·7)	86 (60·6)	2·8 (2·2–3·4)	313 (57·7)	6·8 (6·1–7·6)
Female	173 (43·2)	11·8 (10·1–13·7)	56 (39·4)	1·8 (1·4–2·3)	229 (42·3)	5·0 (4·4–5·7)
Disease severity						
Mild	147 (36·8)	10·1 (8·5–11·8)	56 (39·4)	1·8 (1·4–2·3)	203 (37·5)	4·4 (3·9–5·1)
Moderate	40 (10·0)	2·7 (1·9–3·7)	16 (11·3)	0·5 (0·3–0·8)	56 (10·3)	1·2 (0·9–1·6)
Severe	213 (53·2)	14·6 (12·7–16·7)	70 (49·3)	2·2 (1·8–2·8)	283 (52·2)	6·2 (5·5–6·9)
Chest radiographic findings						
Patchy	227 (56·8)	15·5 (13·6–17·7)	69 (48·6)	2·2 (1·7–2·8)	296 (54·6)	6·5 (5·7–7·2)
Lobar	99 (24·8)	6·8 (5·5–8·2)	63 (44·4)	2·0 (1·6–2·6)	162 (29·9)	3·5 (3·0–4·1)
Perihilar	61 (15·2)	4·2 (3·2–5·4)	6 (4·2)	0·2 (0·1–0·4)	67 (12·4)	1·5 (1·1–1·9)
Other infiltrates	13 (3·2)	0·9 (0·5–1·5)	4 (2·8)	0·1 (0·03–0·3)	17 (3·1)	0·4 (0·2–0·6)
Social class (IMD score)						
1st quantile (2·97–14·46)	101 (25·2)	6·9 (5·6–8·4)	29 (20·4)	0·9 (0·6–1·3)	130 (24·0)	2·8 (2·4–3·4)
2nd quantile (14·47–25·33)	92 (23·0)	6·3 (5·1–7·7)	36 (25·3)	1·2 (0·8–1·6)	128 (23·6)	2·8 (2·3–3·3)
3rd quantile (25·34–42·44)	102 (25·5)	6·9 (5·7–8·5)	43 (30·3)	1·4 (0·9–1·9)	145 (26·8)	3·2 (2·7–3·7)
4th quantile (42·45–78·53)	105 (26·3)	7·2 (5·9–8·7)	34 (23·9)	1·1 (0·8–1·5)	139 (25·6)	3·0 (2·6–3·6)

IR, Incidence rate; CI, confidence interval; IMD, index of multiple deprivation.

incidence rates of CAP by age group for disease severity and chest radiographic findings. Overall, males had higher rates of CAP for different categories of disease severity. In both males and females the rates in children aged <5 years were sixfold higher than those aged ⩾5 years. Patchy changes were the most common chest radiographic finding particularly in the <5 years age group. Lobar pneumonia was seen in a quarter of children aged <5 years, compared to about 15% in 2001. There was an overall significant increase in the incidence of lobar pneumonia from 2·8/10 000 (95% CI 2·3–3·3) in 2001 to 3·5/10 000 (95% CI 3·0–4·1) in 2009 (OR 1·3, 95% CI 1·01–1·6). No significant risk factors for severe

Table 3. *Univariate risk factors of severe versus mild/moderate pneumonia*

Characteristics	*n* (%)	OR	(95% CI)	*P* value
Age group				
<5 years	400 (73·8)	1·7	(0·8–1·6)	0·418
⩾5 years	142 (26·2)	1·0	—	
Sex				
Female	229 (42·3)	1·0	—	
Male	313 (57·7)	1·2	(0·8–1·6)	0·427
Social class (IMD score)				
1st quantile (2·97–14·46)	130 (24·0)	1·0	—	
2nd quantile (14·47–25·33)	128 (23·6)	1·1	(0·7–1·9)	0·612
3rd quantile (25·34–42·44)	145 (26·8)	0·9	(0·6–1·5)	0·755
4th quantile (42·45–78·53)	139 (25·6)	1·1	(0·7–1·7)	0·780
Gestation (weeks)				
24–28	7 (1·3)	5·8	(0·7–48·4)	0·105
29–32	13 (2·4)	1·5	(0·5–4·8)	0·452
33–36	25 (4·6)	1·7	(0·7–3·9)	0·206
⩾37	497 (91·7)	1·0	—	
Parental smoking				
No	247 (62·8)	1·0	—	
Yes	146 (37·2)	1·3	(0·8–1·9)	0·253
Asthma				
No	501 (92·4)	1·0	—	
Yes	41 (7·6)	1·6	(0·9–3·2)	0·139

OR, Odds ratio; CI, confidence interval; IMD, index of multiple deprivation.

pneumonia were identified with univariate or multivariate logistic regression. These included age, gender, socioeconomic status, prematurity, parental smoking and asthma (Table 3).

DISCUSSION

This is the first prospective survey in the UK to evaluate the effect of PCV7 on the incidence of childhood CAP. We report an 18% reduction in both the incidence of CAP presenting to hospital and hospitalization between 2001 and 2009. There was a lower incidence of pneumonia in PCV7-vaccinated children aged <5 years than those unvaccinated. Rates of pneumonia and likelihood of hospital admission were highest in the <5 years age group, consistent with previous studies [14, 21].

There were no significant risk factors for severe pneumonia in this survey, although extreme prematurity was a risk factor for severe disease in 2001 [14]. This may reflect changes in neonatal care in the intervening period. However, in a recent study our region had the highest bronchopulmonary dysplasia rate in Europe, suggesting that the relationship may be complex [22]. It was surprising that parental smoking was not a risk factor for severe pneumonia, given that we had a relative excess of smoking in our cohort (37%) compared to the national average rate of 21% for adults [1]. Although parental smoking was not a significant risk factor for severe disease, where parents were smokers 58% of their children had severe disease.

Comparison with other studies

The reduction in both incidence of pneumonia and hospitalization rate in this survey is comparable with a previous study in England [23], which reported a 19% decrease between 2006 and 2008 in childhood pneumonia using hospital episodes statistics (HES) data. The reduction in the rate of hospitalization was more than that reported in Canada of 13% in those aged <5 years following the routine introduction of PCV7 [24]. The disease incidence is also close to the estimates of other studies of PCV11 in the Philippines [25] and PCV7 in the USA [9] that reported decreases in all-cause pneumonia by about 22%. It is, however, lower than the 25% reduction against radiological pneumonia reported in randomized controlled trial of PCV9 in South Africa [7] and 30% in the USA [26].

This may be a reflection of the differences in pneumococcal disease between populations or in adherence and vaccine usage in our population compared to the trial settings. As our survey used a standard and comparable radiological definition of pneumonia it should not reflect differences in disease ascertainment between the studies.

Interestingly, the major reduction in pneumonia admissions (38%) was observed in those aged <2 years. This is similar to the finding from the USA of about 40% [27], but higher than that observed (15%) during the PCV9 trial in The Gambia [8]. The marked reduction of 33% in disease incidence in the <2 years age group is also comparable to the reported incidence reduction of up to 37% from the pneumococcal conjugate vaccination trials and pooled review data [8, 10, 11]. We observed a greater decrease (30%) in the admission rate in those aged 2–4 years compared to the 17% found by Grijalva *et al*. [27].

This survey has demonstrated a reduction in all-cause pneumonia. Previous estimates have suggested around 10% of childhood pneumonia is attributable to *S. pneumoniae* in the UK [5, 6]. Given the decline in pneumonia and assuming the absence of other changes in disease or admission procedures, it seems likely that 10% is a significant underestimation of the true burden of pneumococcal-related childhood pneumonia in the UK [1, 28]. It is only recently that any studies have been able to describe the relative contributions of different pneumococcal serotypes in paediatric pneumonia [29], and these have not yet been established in UK children. At the moment the pneumococcal serotype distribution in childhood pneumonia in the UK has only been inferred from surveillance of invasive pneumococcal disease by the Health Protection Agency and studies from other countries. Thus, the potential reduction in pneumococcal childhood pneumonia in the UK provided by PCV7 is not known with certainty. This survey is a significant step towards reducing that uncertainty. Future studies are needed to carefully evaluate the epidemiological and health economic impacts of the new generation of conjugate vaccines.

Strengths and limitations

The strengths of this survey include the use of a multicentre large-scale approach, well-validated disease definition and a previously studied population allowing accurate historical comparisons. Its significant limitation is that while the introduction of PCV7 is the major change between the two surveys, the ecological nature of the survey means that the decrease in incidence cannot be causally attributed to PCV7 alone [30, 31]. Further potentially relevant factors include natural variations in disease incidence, other public health interventions such as anti-smoking campaigns [32, 33], variation in national and local health policies, changes in admission criteria and threshold for radiological investigation, and the implementation of national guidelines for the management of CAP in children by the BTS in 2002 [18]. While we cannot rule out these factors using our methodology, we feel it is unlikely that any of these factors would have reduced the incidence of pneumonia to the degree observed. Furthermore, we speculate that these factors would alter the overall incidence rate regardless of age group. The fact that we found no significant difference in the incidence of pneumonia in the ⩾5 years age group, by definition non-vaccine recipients, therefore increases the likelihood that the observed changes were attributable to PCV7.

It could be speculated that changes in the incidence of viral disease or vaccination may have contributed to the observed differences in the rates of pneumonia, although this is unlikely given that neither age group (and specifically the <2 years age group) are routinely vaccinated against respiratory viral disease. We did not collect specific data on influenza vaccination status but believe that the overwhelming majority of enrolled children were unvaccinated. It has also been hypothesized that a considerable proportion of viral pneumonia may in fact have co-infection with bacterial pathogens including *S. pneumoniae* as shown by Michelow *et al*. [34] which could potentially ameliorate the effect of variations in the incidence of seasonal influenza or other viral infections.

The addition of a further group of 'other infiltrates/abnormalities' chest radiographic features to the WHO definition of radiological pneumonia could have overestimated the incidence of pneumonia within our population. However, the number of such individuals was low and represented only 3% of all cases of pneumonia within our survey. We would therefore suggest that this should not have significantly influenced our findings, given the magnitude of the changes we report. In contrast to the observed substantial reduction in the incidence of lobar pneumonia following the conjugate vaccination programme in Canada [24], we reported increased lobar findings. This could be attributed to either the relative implication of *S. pneumoniae* in the aetiology of

pneumonia in children or due to the recognized variation in the interpretation of paediatric chest radiographs [35], which in our survey were reported by local radiologists at each site.

In conclusion, our findings suggest that PCV7 was effective in reducing by 18% both the incidence of childhood pneumonia seen in hospital and rates of hospitalization in one population within the UK. In particular, these reductions were more marked, by nearly a third, in the <2 years age group.

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DECLARATION OF INTEREST

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