

Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis



Carlos G Grijalva, J Pekka Nuorti, Patrick G Arbogast, Stacey W Martin, Kathryn M Edwards, Marie R Griffin

Summary

Background Routine infant immunisation with seven-valent pneumococcal conjugate vaccine (PCV7) began in the USA in 2000. Although invasive pneumococcal disease has declined substantially, the programme's effect on hospital admissions for pneumonia is unknown. We therefore assessed the effect of the programme on rates of all-cause and pneumococcal pneumonia admissions.

Methods Data from the Nationwide Inpatient Sample, the largest inpatient database available in the USA, were analysed with an interrupted time-series analysis that used pneumonia (all-cause and pneumococcal) admission rates as the main outcomes. Monthly admission rates estimated for years after the introduction of PCV7 vaccination (2001–2004) were compared with expected rates calculated from pre-PCV7 years (1997–1999). The year of vaccine introduction (2000) was excluded, and rates of admission for dehydration were assessed for comparison.

Findings At the end of 2004, all-cause pneumonia admission rates had declined by 39% (95% CI 22–52) for children younger than 2 years, who were the target population of the vaccination programme. This annual decline in all-cause pneumonia admissions of 506 (291–675) per 100 000 children younger than 2 years represented about 41 000 pneumonia admissions prevented in 2004. During the 8 study years, 10 659 (2%) children younger than 2 years admitted with pneumonia were coded as having pneumococcal disease; these rates declined by 65% (47–77). This decline represented about 17 fewer admissions per 100 000 children in 2004. Admission rates for dehydration for children younger than 2 years remained stable over the study period.

Interpretation The reduction in all-cause pneumonia admissions in children younger than 2 years provides an estimate of the proportion of childhood pneumonias attributable to *Streptococcus pneumoniae* in the USA that are vaccine preventable. Our results contribute to the growing body of evidence supporting the beneficial effects of the pneumococcal conjugate vaccines in children.

Introduction

Pneumonia causes substantial morbidity and mortality in all age groups. In the USA, pneumonia and influenza combined are the greatest infectious cause of death.^{1–3} Pneumonia accounts for 3–18% of all childhood hospital admissions.⁴ For people aged 65 years or older, nearly one million episodes of community-acquired pneumonia occur every year, with 40% resulting in admission.⁵ *Streptococcus pneumoniae* is regarded as the leading bacterial cause of pneumonia,¹⁶ and has been estimated to account for 17–44% of pneumonia admissions in children and 13–34% of those in adults.^{7–10}

In February, 2000, a seven-valent pneumococcal conjugate vaccine (PCV7) was licensed in the USA and recommended for routine use in infants.^{6,11} Vaccine uptake was rapid,^{12,13} and pronounced declines in rates of invasive pneumococcal disease in both children and adults were seen in studies done after the vaccine was licensed.^{14–16} These declines were noted before full implementation of the PCV7 vaccination programme, and protective effects have been reported even with fewer doses than were recommended.¹⁷

Although results of randomised clinical trials suggested that PCV7 reduced pneumonia incidence,^{18–20} its effect on

the burden of pneumonia in the general population has not been established. With a quasi-experimental design and data from the largest all-payer inpatient care database in the USA, we assessed the effect of the national PCV7 vaccination programme on rates of all-cause and pneumococcal pneumonia admissions.

Methods

Data source

The Nationwide Inpatient Sample (NIS), sponsored by the Agency for Healthcare Research and Quality, obtains data on both clinical discharge diagnoses and resource use for around 20% of all US hospital admissions. The sampling design includes community hospitals as primary sampling units, and all discharges from sampled hospitals are included. Recorded admissions in the sample range from five to eight million per year.²¹

In 1997, the NIS sampled 1012 hospitals in 22 states and estimated a total of 35 408 207 admissions. By 2004, the sampling framework had increased to 37 participating states, 1004 hospitals, and 38 661 786 estimated admissions. Stratification and weighting variables are provided by the Agency to generate national estimates while accounting for the complex sampling design and

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Department of Preventive Medicine (C G Grijalva MD, P G Arbogast PhD, Prof M R Griffin MD), Department of Biostatistics (P G Arbogast), Department of Medicine (Prof M R Griffin), Department of Pediatrics (Prof K M Edwards MD), and the Center for Education and Research on Therapeutics (Prof M R Griffin), Vanderbilt University School of Medicine, Nashville, TN, USA; Mid-South Geriatric Research Education and Clinical Center and Clinical Research Center of Excellence, VA TN Valley Health Care System, Nashville, TN, USA (Prof M R Griffin); and National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA (J P Nuorti MD, S W Martin MSc)

Correspondence to: Dr Marie R Griffin, Department of Preventive Medicine, Vanderbilt University School of Medicine, The Village at Vanderbilt, Suite 2600, 1500 21st Avenue, Nashville, TN 37212, USA marie.griffin@vanderbilt.edu

the expanding sampling framework over time.²¹ Up to 15 discharge diagnoses are recorded according to the International Classification of Diseases Clinical Modification, Ninth Revision (ICD9-CM) with first-listed diagnoses regarded as the primary reason for admission.²² Since NIS data have no personal identifiers, this study was considered exempt from review by the institutional review boards of Vanderbilt University and the Centers for Disease Control and Prevention.

Definitions of pneumonia admissions

To identify community-acquired pneumonias, all-cause pneumonia admissions were defined by a principal discharge diagnosis (first-listed diagnosis) of pneumonia by ICD9-CM codes, or by a meningitis or septicaemia code as the primary diagnosis and a pneumonia code in any other diagnosis field.²³ Pneumococcal pneumonia admissions met the all-cause pneumonia definition, but also had either a specific pneumococcal pneumonia code or an unspecified pneumonia code plus another code, suggesting pneumococcal disease.²³ Procedure and diagnoses ICD9-CM codes were used to identify common complications and thoracentesis-related procedures done during admission. (For ICD9-CM codes see webtable).

See Online for webtable

Statistical analysis

NIS data from 1997 to 2004 were analysed through interrupted time-series analyses that used pneumonia

(all-cause pneumonia and pneumococcal) admission rates as the main outcomes. Pneumonia admissions were estimated according to the reported admission month, and annualised monthly rates were estimated from the NIS pneumonia admission estimates and population figures obtained from the US Census Bureau. Dehydration, a common cause of admission in children,²⁴ was assessed for comparison purposes.

Segmented regression analyses were used to measure the effect of the PCV7 vaccination programme.²⁵ We assumed our outcome rates followed Poisson distributions and used the log-transformed rates as our model outcomes to stabilise the variances. The regression models included terms for the intervention (PCV7) and secular trends for the periods before and after implementation of the vaccination programme.^{25,26} We used sandwich variance estimators to account for possible multiple admissions per patient. There were strong seasonal fluctuations for pneumonia outcomes, with higher rates recorded in winter than in summer. We accounted for this seasonality through the inclusion of indicator terms representing specific calendar months in the models. Furthermore, since error terms of consecutive observations were often correlated, our models accounted for first-order and second-order autocorrelation. Residual analyses of the final models showed no significant deviations from model assumptions.^{25,26}

	All	Younger than 2 years	2–4 years	5–17 years	18–39 years	40–64 years	65 years or older
Sex							
Female	5 606 610 (52%)	271 807 (42%)	171 666 (46%)	171 945 (46%)	354 466 (50%)	1 157 616 (51%)	3 477 250 (54%)
Male	5 174 947 (48%)	370 419 (58%)	199 235 (54%)	198 892 (53%)	348 201 (50%)	1 126 533 (49%)	2 929 225 (46%)
Race							
White	5 955 119 (55%)	220 945 (34%)	141 067 (38%)	160 724 (43%)	305 006 (43%)	1 157 624 (51%)	3 967 952 (62%)
Black	998 300 (9%)	89 788 (14%)	55 713 (15%)	53 565 (14%)	130 603 (19%)	306 841 (13%)	360 954 (6%)
Hispanic	650 805 (6%)	110 512 (17%)	59 791 (16%)	42 439 (11%)	53 549 (8%)	122 886 (5%)	260 966 (4%)
Asian or Pacific Islander	150 714 (1%)	13 528 (2%)	7 681 (2%)	5 500 (2%)	6 903 (1%)	23 715 (1%)	93 262 (2%)
Native American	27 297 (<1%)	3 895 (1%)	1 769 (1%)	1 364 (<1%)	2 182 (<1%)	7 579 (<1%)	10 498 (<1%)
Other	154 337 (1%)	21 004 (3%)	11 611 (3%)	8 473 (2%)	12 318 (2%)	31 895 (1%)	68 921 (1%)
Missing	2 851 292 (26%)	182 747 (28%)	94 088 (25%)	100 590 (27%)	192 503 (27%)	634 130 (28%)	1 644 602 (26%)
Length of stay							
Median (IQR) days	4 (3–7)	3 (2–4)	2 (2–3)	3 (2–4)	4 (2–6)	4 (3–7)	5 (3–8)
Parapneumonic disease							
Empyema	46 141 (<1%)	2 003 (<1%)	3 350 (1%)	3 739 (1%)	7 111 (1%)	16 859 (1%)	13 064 (<1%)
Pleural effusion	594 687 (6%)	4 759 (1%)	8 752 (2%)	16 912 (5%)	49 048 (7%)	146 940 (6%)	368 120 (6%)
In-hospital procedures							
Thoracentesis	267 143 (3%)	3 036 (1%)	4 464 (1%)	7 158 (2%)	24 884 (4%)	74 651 (3%)	152 860 (2%)
In-hospital case fatality ratio	6.6 (6.5–6.7)	0.2 (0.2–0.2)	0.2 (0.2–0.2)	0.4 (0.4–0.5)	1.9 (1.8–2.0)	4.2 (4.1–4.3)	9.4 (9.2–9.5)
Pneumococcal diseases							
Pneumonia	443 822 (4%)	10 659 (2%)	9 431 (3%)	12 821 (3%)	44 638 (6%)	133 008 (6%)	233 099 (4%)
Concurrent bacteraemia	141 295 (1%)	3 649 (1%)	2 687 (1%)	2 782 (1%)	15 355 (2%)	46 693 (2%)	70 070 (1%)

Data are number (%), median (IQR), and case-fatality ratio per 100 (95% CI). Percentages may not total 100 because of rounding or missing information. *Data are from the NIS.

Table 1: Characteristics of patients admitted to hospital with all-cause and pneumococcal pneumonia by age, USA, 1997–2004*

Although PCV7 was licensed for use in February, 2000, vaccine uptake began to increase substantially only after US Government purchasing through the Vaccines For Children programme²⁷ began in June, 2000. That year was therefore regarded as a transition year and excluded from our analyses (but included in all figures). The final models included 84 time points (36 for pre-PCV7 years and 48 for years after the introduction of PCV7 vaccination).

Since PCV7 coverage was increasing after 2000, we quantified the effect of the vaccination programme by the end of the observation period. We used the segmented regression model to estimate the post-PCV7 rate for December, 2004 and compared this rate with the expected rate, calculated from the model as the projection of pre-PCV7 trends with the assumption that no intervention occurred.^{25,26} Thus, our analyses accounted for secular trends that were present before PCV7 vaccination was introduced. Rate differences between the estimated and expected rates and their respective percentage changes were calculated for each outcome and age group.^{25,26}

We estimated the number of prevented pneumonia-related admissions per year by multiplication of the estimated rate differences by the specific age-group population estimates. Analyses with any-listed diagnosis of pneumonia, rather than the first-listed diagnosis, showed similar trends. Statistical analyses were done with Sudaan (version 9.0.1) and Stata (version 8.2). A two-sided *p* value of less than 0.05 was considered significant.

Although additional NIS data from 1994 to 1996 exist, consistent information about the admission month was available for time-series analyses since 1997. For our analyses, data for admission month were missing in some NIS records. We assumed these data to be missing completely at random²⁸ and restricted the time-series analyses to the records with complete information. The average proportion of records without these data was 15% and 8% for the pre-PCV7 and post-PCV7 years, respectively. Yearly rates from 1994 to 2004 were computed with NIS data for rate numerators and census data for denominators. The exploration of annual data (that included all records) showed similar results (see webfigures 1 and 2).

Role of the funding source

The Centers for Disease Control and Prevention funded this research and investigators from the organisation participated in the study design, data review, and preparation of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From 1997 to 2004 there were an estimated total of 293 314 002 admissions in the USA, of which 10 787 865 (4%) met the definition of all-cause pneumonia admission. Characteristics of patients admitted with pneumonia differed by age and sex. In young children,

	Estimated rate/ 100 000*	Expected rate/ 100 000*	Rate difference (95% CI)
Pneumococcal pneumonia			
Younger than 2 years	9.2	26.2	-17.1 (-12.4 to -20.1)
2-4 years	7.3	27.1	-19.8 (-14.3 to -22.9)
5-17 years	1.9	3.5	-1.6 (0.1 to -2.5)
18-39 years	2.9	4.2	-1.3 (-0.4 to -2.0)
40-64 years	14.8	16.5	-1.8 (1.6 to -4.6)
65 years or older	59.3	73.9	-14.6 (2.0 to -27.6)
Total	13.9	17.7	-3.8 (-1.1 to -6.0)
All-cause pneumonia			
Younger than 2 years	790.9	1296.9	-505.9 (-291.4 to -674.7)
2-4 years	344.6	417.6	-73.0 (14.3 to -142.7)
5-17 years	74.3	90.7	-16.4 (9.5 to -35.7)
18-39 years	77.9	105.4	-27.4 (-4.6 to -45.1)
40-64 years	328.1	402.6	-74.5 (10.1 to -141.8)
65 years or older	2162.7	2559.2	-396.5 (60.9 to -774.1)
Total	447.4	536.7	-89.4 (3.5 to -166.3)
Dehydration			
Younger than 2 years	778.9	775.3	3.6 (797.2 to -389.5)
2-4 years	344	297.2	46.8 (500.2 to -148.8)
5-17 years	50.1	38.2	11.8 (37.3 to -5.0)
18-39 years	36.1	35.8	0.3 (8.2 to -6.2)
40-64 years	124.3	121.9	2.3 (16.1 to -10.0)
65 years or older	736.9	877.4	-140.5 (-3.1 to -256.3)
Total	187.1	200.2	-13.1 (12.0 to -35.2)

*Seasonally adjusted.

Table 2: Changes in US admission rates by December, 2004

there were more male patients than female patients, whereas in older adults there was a predominance of female patients. Although data on race or ethnic origin were missing for 26% of admissions, for those with this information available, the proportion of white patients increased with age whereas the proportion of black and Hispanic patients decreased with age (table 1).

The median length of stay for all-cause pneumonia ranged from 2 days for children aged 2-4 years to 5 days for patients 65 years or older. Concurrent codes showed empyema in 0.4% of admissions, pleural effusion in 6%, and a thoracentesis procedure in 3%. In-hospital case-fatality ratios were greater for patients 65 years or older than for children younger than 5 years (table 1).

Pneumococcal pneumonia was coded in 443 822 (4%) of the all-cause pneumonia admissions. The proportion of pneumonias coded as pneumococcal ranged from 2% for children younger than 2 years to 6% for those aged 18-39 years. Around 32% of pneumococcal pneumonia admissions had concurrent discharge diagnoses of bacteraemia or septicaemia (table 1). Empyema and pleural effusions were noted, and thoracenteses were done in 2%, 9%, and 6% of the pneumococcal pneumonia admissions, respectively.

There were no significant trends in all-cause pneumonia admission rates for children younger than

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2 years during the pre-PCV7 years. At the end of 2004, rates had declined by 505.9 (95% CI -291.4 to -674.7) per 100 000 (table 2), showing a 39% (22-52, $p < 0.0001$) reduction (figure 1). This yearly decline in total

pneumonia admissions in children younger than 2 years represented about 41000 fewer all-cause pneumonia admissions than were expected in this age group in 2004.

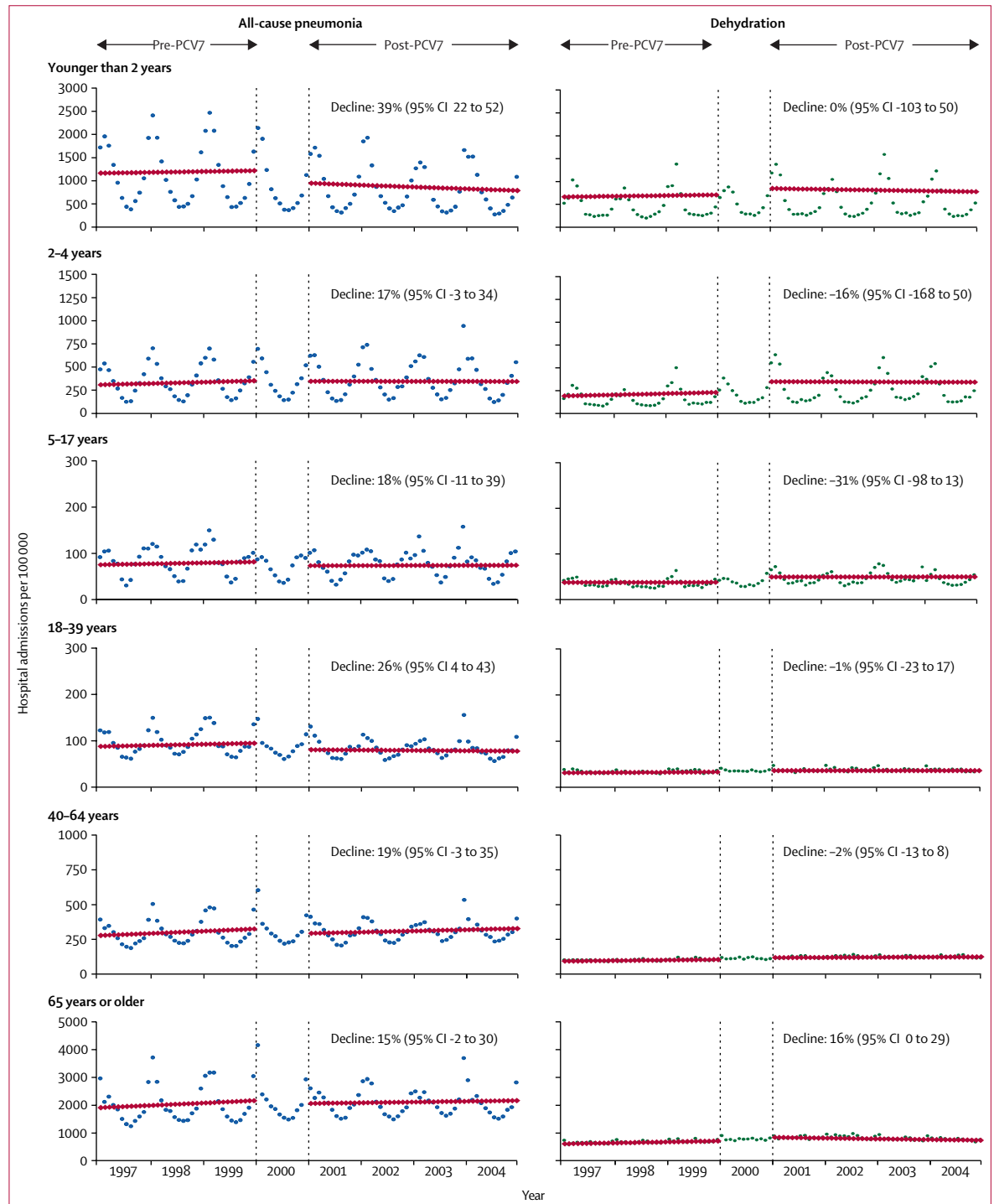


Figure 1: Trends in monthly US admission rates (1997-2004) for all-cause pneumonia and dehydration (control) by age group before and after routine immunisation of children with PCV7. Percentage declines are estimated for the most recent observation point (December, 2004).

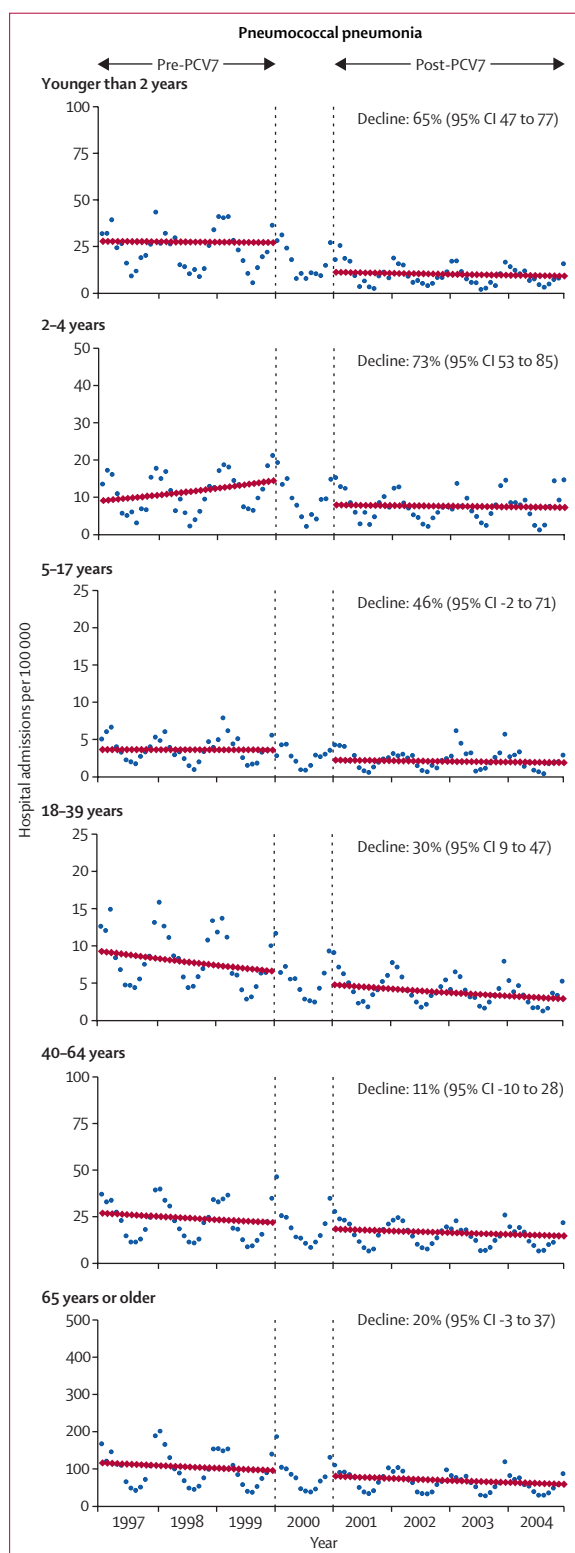


Figure 2: Trends in monthly US admission rates (1997–2004) for pneumococcal pneumonia by age group before and after routine immunisation of children with PCV7
Percentage declines are estimated for the most recent observation point (December, 2004).

All-cause pneumonia hospitalisation rates also declined in adults aged 18–39 years, accounting for a reduction of 26% (4–43, $p=0.021$; figure 1). All-cause pneumonia admission rates for older patients seemed to decline after introduction of PCV7 (figure 1), but differences between the estimated and expected rates were not significant (table 2).

At the end of 2004, rates of pneumococcal pneumonia admissions in children younger than 2 years decreased by 17.1 (–12.4 to –20.1) per 100 000 children. This decline represented a 65% (47–77, $p<0.0001$) reduction in pneumococcal pneumonia admissions in this age group. Similarly, for children aged 2–4 years, rates declined by 73% (53–85, $p<0.0001$).

During the study period, pneumococcal pneumonia admission rates also declined by 30% (9–47, $p=0.008$) in adults aged 18–39 years. No significant declines were seen in older adults (table 2 and figure 2). Overall, pneumococcal pneumonia admissions declined by 21% (6–34, $p=0.007$) during the study period.

Dehydration admission rates remained unchanged after the implementation of the PCV7 vaccination programme in all groups, except adults 65 years or older, for whom a 16% decline was noted (0–29, $p=0.045$; table 2 and figure 1).

Discussion

We report that after introduction of the PCV7 immunisation programme in the USA, admission rates for all-cause pneumonia and pneumococcal pneumonia decreased significantly for children younger than 2 years, who were the target population of the programme. By the end of 2004, the reduction in all-cause pneumonia rates indicated about 41 000 pneumonia admissions prevented per year in this age group. This 39% reduction in all-cause pneumonia provides an estimate of the vaccine-preventable burden of childhood pneumonia admissions attributable to *S pneumoniae* in young children before PCV7 was introduced.

Randomised clinical trials showed that pneumococcal conjugate vaccines prevented pneumonia.^{18–20} However, efficacy estimates varied according to the case definition of pneumonia. Vaccine efficacy against clinically diagnosed pneumonia was 6% (95% CI –2 to 11) for PCV7 in the Northern California Kaiser Permanente trial¹⁸ and 7% (1–12) for a nine-valent PCV in the Gambian trial.¹⁹ A trial in South Africa, which also used a nine-valent PCV, reported a vaccine efficacy of 16% (9–23) for pneumonia admissions.²⁰ Vaccine efficacy estimates were consistently higher when radiological confirmation was included as part of the case definition—18% (5–29) in the Kaiser Permanente trial,¹⁸ 17% (4–28) in the South African trial,²⁰ and 37% (27–45) in the Gambian trial.¹⁹

When the Kaiser Permanente data were re-analysed according to WHO radiological criteria for pneumonia diagnosis, the estimated vaccine efficacy was 26% (7–41).²⁹ Furthermore, in the South African trial,

pneumococcal conjugate vaccine prevented 31% (15–43) of pneumonia associated with respiratory viruses in children admitted to hospital,³⁰ which suggested that pneumococcal co-infection might contribute to the pathogenesis of some pneumonias that are thought to be viral. Although differing case definitions, vaccine formulations, and study populations make direct comparisons difficult, the 39% decline seen in rates of all-cause pneumonia admissions for children younger than 2 years is within the range reported by these large clinical trials. Furthermore, in an open population, the effect of a PCV7 immunisation programme could be greater than that seen in clinical trials because herd immunity can have an important role in reduction of disease in both vaccinated and unvaccinated people, through decreases in nasopharyngeal carriage of vaccine serotypes.^{6,31}

The observed declines in pneumococcal pneumonia are similar to those in invasive pneumococcal disease reported from postlicensure surveillance in selected areas in the USA.^{14,15} These declines are consistent with rapid vaccine availability and uptake during the study period.¹² About 40% of US children born between February, 1999, and June, 2001, had received three or more PCV7 doses according to the National Immunization Survey, which surveys children 19–35 months old. Immunisation coverage with three or more doses increased to 68%, 73%, and 83% for those born in February, 2000–June, 2002, February, 2001–May, 2003, and February, 2002–July, 2004, respectively.¹³ Furthermore, the vaccine uptake was already substantial during the second half of 2000.¹²

Although the decline in the rates of admission for pneumococcal pneumonia for children younger than 2 years was substantial, only 2% of the all-cause pneumonia admissions were coded as pneumococcal pneumonia in this group. Previous research suggested an important role of *S pneumoniae* in childhood pneumonia,^{7,10} but accurate diagnosis of pneumococcal pneumonia is difficult without isolation of the organism.^{8,32} Thus, many of these pneumonias probably represented invasive disease. The observed decline in rates of all-cause pneumonia admissions suggests that *S pneumoniae* was a major contributor to the burden of pneumonia admissions in young children.¹⁶ Observations similar to those for *S pneumoniae* were made for *Haemophilus influenzae* type-B pneumonia in the Gambia, where substantial reductions in overall pneumonia were attributable to immunisation with conjugate vaccines against this bacterium.³³

We also noted a significant decline in rates of all-cause pneumonia admissions in adults aged 18–39 years. This age group had the highest proportion of pneumonias coded as pneumococcal. Previous findings showed that this group had the second highest percentage decline in invasive pneumococcal disease after children younger than 5 years, suggesting a vaccine herd effect.¹⁴ Since this age group would include parents of young children, they

could have benefited from reduced exposure to pneumococci because their children were vaccinated. Although another explanation for the reported decline in this group might be a large proportion of HIV-infected patients benefiting from highly active antiretroviral therapy, we believe this explanation unlikely since the largest effect of this therapy on invasive pneumococcal diseases was seen from 1995 to 1999, before the introduction of PCV7.^{34,35}

National median coverage with 23-valent pneumococcal polysaccharide vaccine increased from 45% to 65% during 1997–2004, and influenza vaccine coverage increased from 66% to 68% in people 65 years or older.^{36,37} Increases in the uptake of pneumococcal polysaccharide vaccine could explain some of the noted declines in bacteraemic pneumococcal pneumonia in this age group before PCV7 was introduced, but present evidence does not suggest that pneumococcal polysaccharide vaccine is effective in the prevention of non-bacteraemic pneumonia,³⁸ and herd effects have not been reported with that vaccine.⁶ The small changes in influenza vaccine uptake in elderly people are unlikely to have had a major effect on pneumonia trends.³⁹ Furthermore, influenza immunisation in children could not explain our results, since Centers for Disease Control recommendations for routine influenza immunisation of children 6–23 months old started in 2004. Full immunisation coverage in this age group was estimated to be 4% and 8% for 2003 and 2004, respectively.¹³

Some caveats should be considered in the interpretation of our results. First, identification of pneumonia admissions was based on ICD9-CM codes and could be subject to misclassification. However, discharge diagnoses recorded in NIS are validated for consistency and undergo internal quality control.²¹ Although chart review was not possible, it would not have overcome the drawback that causative agents were not routinely identified.^{8,32} Second, although changes in the NIS sampling framework could explain differences in trends, the observation of no major changes in rates of admissions for dehydration is reassuring. Moreover, to ensure consistency, yearly NIS estimates are compared with those obtained from the National Hospital Discharge Survey and the Medicare Provider Analysis and Review.⁴⁰ Third, data on race and ethnic origin were missing in many cases, so further analysis of this information was not possible. Fourth, admission rates could be affected by secular trends, including changes in coding practices, criteria for admission and readmission, or seasonal respiratory viral activity. Changes in coding practices and readmissions during the study period had only a marginal effect on pneumonia admission trends in Medicare data.⁴¹

A study of US national ambulatory surveys reported a non-significant decline in rates of outpatient visits for pneumococcal pneumonia and unspecified pneumonia in children younger than 2 years, after PCV7 was

introduced.⁴² This finding suggests that the decline in pneumonia admissions was not caused by a shift to outpatient care. Furthermore, our analyses accounted for potential secular trends and seasonality.^{25,26} Finally, the unpredictable occurrence of severe influenza epidemics in selected seasons could affect our outcomes and might not be taken into account in our time-series analyses. However, during the study period the seasons with highest influenza activity in the USA (1999–2000 and 2003–2004)⁴³ did not have major effects on the reported pneumonia admission rates. Of note is that pneumococcal conjugate vaccines have been shown to reduce pneumonias associated with influenza infections.³⁰

Our study provides a comprehensive assessment of the changes in pneumonia admission rates after implementation of the PCV7 immunisation programme in the USA. We used a strong quasi-experimental design to assess the effect of PCV7. The observed reductions in pneumonia admissions suggest that before PCV7, *S pneumoniae* was a major contributor to childhood pneumonia in the USA, and provide an estimate of the burden of pneumococcal pneumonia admissions in young children due to PCV7 vaccine serotypes. Our results contribute to the growing body of evidence supporting the beneficial effects of the pneumococcal conjugate vaccines in children. Further, our study suggests a substantial effect on one of the most common reasons for US hospital admissions. The introduction of the vaccine could have a large effect in less developed countries, where pneumococcal diseases cause not only substantial morbidity and health-care costs but also high childhood mortality.^{2,44,45}

Contributors

C G Grijalva, J P Nuorti, and M R Griffin designed the study. C G Grijalva and M R Griffin wrote the first draft of the report. C G Grijalva and P G Arbogast did the statistical analyses. J P Nuorti, S W Martin, P G Arbogast, and K M Edwards interpreted results and edited the report. All authors contributed to draft the final report.

Conflict of interest statement

KME has received grant support from Sanofi Pasteur, MedImmune, VaxGen, and Merck. KME also has consulting agreements with MedImmune and Wyeth. All other authors declare no conflict of interests.

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