ORIGINAL ARTICLE

Decline in pneumococcal meningitis after the introduction of the heptavalent-pneumococcal conjugate vaccine in northern France

F Dubos, I Marechal, M O Husson, C Courouble, M Aurel, A Martinot, the Hospital Network for Evaluating the Management of Common Childhood Diseases

Arch Dis Child 2007;92:1009–1012. doi: 10.1136/adc.2007.119891

See end of article for authors' affiliations

Correspondence to:
Dr F Dubos, Clinique de
Pédiatrie, Hôpital Jeanne de
Flandre, Avenue E. Avinée,
59037 Lille cedex, France;
frandubos@wanadoo.fr

Accepted 25 June 2007
Published Online First
11 July 2007

Background: The impact of the heptavalent-pneumococcal conjugate vaccine on the incidence of pneumococcal meningitis in Europe has not yet been assessed.

Objective: To determine whether heptavalent-pneumococcal conjugate vaccine implementation in northern France has resulted in a decrease in the incidence of pneumococcal meningitis in children.

Design: Multicentre retrospective cohort study from 2000 through 2005.

Settings: All paediatric departments of the 18 hospitals in northern France.

Patients: Patients <18 years of age, admitted for laboratory-confirmed pneumococcal meningitis during the study period, were included.

Interventions: Data were collected from medical files and the microbiological laboratories of each hospital and compared with the regional hospital discharge codes, using a capture–recapture method.

Main outcome measures: The study assessed and compared global and age-related incidence rates of pneumococcal meningitis in 2001 (pre-vaccine era) and 2005.

Results: 77 cases were found through the capture–recapture method. The incidence rate of pneumococcal meningitis varied from 1.65/100 000 children <18 years in 2001 to 0.80/100 000 children in 2005 (53% reduction, 95% CI 31 to 74; $p=0.08$). This has so far been significant only for children <2 years of age (8.9/100 000 in 2001 to 1.8/100 000 in 2005; 82% reduction, 95% CI 52 to 95; $p=0.03$).

Conclusion: A decline in pneumococcal meningitis has been observed in infants since heptavalent-pneumococcal conjugate vaccination began in our area.

In the United States, *Streptococcus pneumoniae* has been considered to be the principal pathogen for bacterial meningitis (47%) since *Haemophilus influenzae* type b vaccination became widespread during the 1990s and before the implementation of vaccination with the heptavalent-pneumococcal conjugate vaccine (PCV7, Prevenar).¹ In Western Europe, the mean incidence rate of pneumococcal meningitis has averaged 8.7 cases/100 000 in children <2 years old with incidence rates varying from 3.8 to 14.6/100 000 between countries.² Between 2001 and 2004, the French Bacterial Meningitis Surveillance Network reported that *S pneumoniae* caused 42% of all cases of bacterial meningitis in children, 70% of these occurring in children <2 years old.³ The case-fatality rate for this disease is estimated at 8–12% in children and has not dramatically changed for 20 years despite progress in diagnosis and treatment.^{1–4} Sequelae occur in 20–35% of cases and include deafness, motor deficits, learning disorders linked with concentration disorders, and memory problems.^{5–6}

PCV7, first approved in the US in 1999, targets the seven serotypes involved most frequently in the invasive pneumococcal diseases of young children.^{7–8} Serotypes 6B, 9V, 14, 18C and 23F, all present in this vaccine, account for most cases of pneumococcal meningitis today.⁹ PCV7 received marketing authorisation in Europe in February 2001, was available in France in April 2001 and was recommended in March 2002 for children with a disease at high risk of invasive pneumococcal infections (immunosuppression, sickle cell disease, etc),¹⁰ and children aged 2–24 months with risk factors for pneumococcal infection (ie, children cared for more than 4 h/week with more than two other children, children with breast-feeding duration <2 months, children with at least two siblings), criteria which

covered between 79 and 89% of children <2 years of age.¹¹ The vaccination schedule uses a four-dose regimen, at 2, 3 and 4 months of age and a booster dose during the second year of life. The impact of the PCV7 on the incidence of meningitis and other invasive pneumococcal diseases has been clearly demonstrated in North America and Australia,^{12–16} whose vaccination schedules are different from those in France.

The aim of this study was to determine whether PCV7 implementation in a large area of northern France affected the incidence of pneumococcal meningitis in children.

METHODS

Study design and inclusion criteria

We conducted a descriptive, retrospective, multicentre cohort study covering a 6-year period (2000–2005) and involving all paediatric departments of the 18 hospitals in the region (1 million children <18 years old). All units agreed to participate in this study. In each centre, the local coordinating investigator was a paediatrician belonging to the Hospital Network for Evaluating the Management of Common Childhood Diseases. Each patient <18 years old and admitted for pneumococcal meningitis during the study period was eligible for inclusion. Pneumococcal meningitis was defined as the acute onset of meningitis (cerebrospinal fluid (CSF) white blood cell (WBC) count $\geq 7/\text{mm}^3$)^{17–18} and documented *S pneumoniae* infection in either CSF (direct examination, culture, PCR or latex agglutination) or blood (culture or PCR). The study excluded patients with traumatic lumbar puncture (CSF red blood cells >10 000/

Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cell

mm³),¹⁹ purpura fulminans, bacterial contamination or pre-treated meningitis with negative microbiological tests for which bacterial meningitis could not be ascertained.

Data collection

The primary identification of cases was performed by the local coordinating investigator, by cross-checking medical files with laboratory records. Demographic data (age, sex, date of admission), clinical features (seizure, petechial rash, haemodynamic failure, altered consciousness), laboratory results (WBC and neutrophil counts in blood and CSF, C reactive protein in blood, protein and glucose concentrations in CSF, CSF Gram staining, blood and CSF culture, soluble antigens, PCR in blood or CSF, and serotyping of microorganisms if any) were recorded for each patient. These data were extracted from medical files in each paediatric unit and from the bacterial meningitis registry of the microbiological laboratory in each hospital. They were reported on an anonymous standardised data form by the investigating paediatrician at each hospital and sent to the principal investigators (FD, IM), who arranged for the data to be entered into a database. This database was compared with the regional hospital discharge codes (which provided age, sex, dates of hospital stay, diagnosis, origin of the patients, and discharge diagnosis codes), using the ICD-10 codes (G0.01) as the primary or associated discharge diagnosis, to assess the corrected incidence of our case ascertainment procedure. For this type of retrospective study, neither approval from an ethics committee nor consent from patients or their parents was required in France.

The PCV7 manufacturer furnished us with a list of PCV7 doses sold in northern France during the study period. The National Reference Centre provided us with the pneumococcal serotyping results for children in the cohort study to determine whether PCV7 diffusion had modified serotypes.

Statistical analysis

Statistical analyses were carried out using Epi Info 6.04 software (Centers for Disease Control and Prevention, Atlanta, GA, USA). Analysis began by describing the characteristics of patients with pneumococcal meningitis. We used a capture-recapture method,²⁰ and demographic data from the national institute for statistics and economic studies (www.insee.fr) to determine the number and corrected incidence rates of pneumococcal meningitis in children <18 years old between 2000 and 2005. Incidence rates in 2001 (the year PCV7 was approved in Europe) and 2005 (the last year of data collection) were compared with a χ^2 test. The percentage change in this rate was calculated together with its 95% confidence interval (CI). The relationship between the number of vaccine doses sold and the estimated number of pneumococcal meningitis

cases, as well as the annual age distribution of identified pneumococcal meningitis cases, were analysed. *p* Values <0.05 were considered to indicate statistical significance.

RESULTS

During the study period, 65 children, identified through medical and laboratory records in the 18 hospitals with paediatric departments, were diagnosed with pneumococcal meningitis. Data from patients with this disease admitted in 2000 could not be collected at one centre. Cross-checking with discharge codes (56 cases found) revealed 73 notified patients (table 1). The case ascertainment rate of medical and laboratory records was 89%, while the discharge codes missed 23% of the diagnoses. The children's mean age was 31 months (range 28 days–14.9 years), with 63% <2 years old, and the male–female ratio was 0.9. Admission to the intensive care unit was necessary in 27% of cases, with haemodynamic failure in 5% and neurological failure in 51%. CSF Gram staining was positive for 76% of patients. The mean CSF WBC count was 2359 cells/mm³ (range 7–15 700), with a mean CSF neutrophil count of 83% (range 18–100). Mean CSF glucose and protein concentrations were 34 and 187 mg/dl, respectively. Mean CRP was 173 mg/l (range 2–429). Overall, 3% of the children died and 42% had neurological sequelae.

The capture-recapture method estimated that 77 children overall had pneumococcal meningitis during the study period in northern France (table 1). Using these estimates for each year from 2001 to 2005, we calculated that the incidence of pneumococcal meningitis decreased from 17 cases (1.65/100 000 children <18 years old) to 8 cases/year (0.80/100 000), which corresponded to a 53% reduction (95% CI 31 to 74; *p* = 0.08).

As fig 1 shows, the estimated number of pneumococcal meningitis cases decreased as vaccine distribution increased in northern France. The reduction in cases affected only children younger than 2 years of age (fig 2). Incidence rose briefly from 8.9/100 000 children <2 years old in 2001 to 10.5/100 000 in 2002, and subsequently fell to 1.8/100 000 in 2005 (82% reduction; 95% CI 52 to 95; *p* = 0.03). No such decrease was observed for patients aged 2–5 years and >5 years old. Less than two thirds of the strains were sent for serotyping to the national reference centre from 2001 to 2004, whereas 88% were serotyped in 2005. Three of the seven serotyped strains were related to strains included in the vaccine in 2005, five of five in 2004, and five of seven in 2003. Of the 13 patients with pneumococcal meningitis caused by strains included in the vaccine since 2003, 11 were not vaccinated (10 could have been vaccinated and one belonged to the old unvaccinated cohort of patients), one had received two doses and one had received three doses.

Table 1 Number of cases of pneumococcal meningitis reported in each database, and corrected incidence of the disease in children <18 years old, from 2000 to 2005

Year	Patients (n)		Patients (n') identified in both bases	Total notified	Estimation of patients missed*	Total estimated†	Corrected incidence/100 000‡
	Our database	Discharged codes					
2000§	11	8	6	13	2	15	1.45
2001	11	11	7	15	2	17	1.65
2002	14	13	12	15	0	15	1.46
2003	11	8	8	11	0	11	1.08
2004	10	10	9	11	0	11	1.09
2005	8	6	6	8	0	8	0.80
Total	65	56	48	73	4	77	–

*By a capture-recapture method over the two databases: (n identified only by our database × n' identified only by discharge codes)/n' identified by both databases; †sum of the notified patients and estimated missed patients; ‡incidence of estimated cases divided by children <18 years old; §missing data for one of the 18 centres in the year 2000.

Figure 1 Relationship between distributed vaccine doses and estimated pneumococcal meningitis paediatric cases in northern France per study year.

DISCUSSION

Our multicentre study of pneumococcal meningitis found 77 children through the capture–recapture method with this disease in the study area during the study period (2000–2005). Incidence of the disease among children <18 years old decreased between 2001 and 2005, with a 53% reduction during the study period, but only among those less than 2 years was the decrease, from 8.9 to 1.8/100 000 between 2001 and 2005, statistically significant ($p=0.03$). This is the first study in Europe to demonstrate that the incidence of pneumococcal meningitis decreased significantly between 2001 and 2005 among a large population of children, that is, following the implementation of PCV7.

This vaccine has had a significant impact in North America and Australia over the past few years: the incidence of invasive pneumococcal diseases, including meningitis, has fallen by 56–69% in children less than 2 years of age.^{14–16 21–23} PCV7 coverage, however, is substantially higher in the US (68% of children had at least three injections in 2003)²⁴ than in France (41% of children were vaccinated in 2004 with three doses).¹¹ Moreover, the seven pneumococcal serotypes contained in this conjugate vaccine were responsible for 83% of the cases of invasive pneumococcal diseases in young children in the USA,⁷ but only 68% of the blood isolates and 61% of CSF isolates in France.²⁵ Given the differences in policies, vaccination schedules,¹⁰ vaccine coverage rates and serotype distributions in different countries, vaccination effects evidently cannot be expected to be similar between them. For these reasons, studies of the effects of this vaccine elsewhere are essential.

Although our study covered a large area of northern France (1 million children <18 years old), rather few cases of childhood pneumococcal meningitis were found, but this is consistent with previously reported incidence rates.² However, incidence changed significantly after PCV7 implementation began. The retrospective design of our study may have contributed to a selection bias. For example, no data from the year 2000 were available for one centre, which explains why results from that year were considered for only part of the analyses. This did not, however, interfere with the main results of the study. Moreover, the quality of our data collection was controlled by cross-checking with laboratory records before reporting back to the study coordinators and comparing our database with regional hospital discharge codes. Unlike the existing national surveillance programs,²⁶ the capture–recapture method allowed us to determine the corrected incidence of pneumococcal meningitis for children <18 years of age in northern France. A study of a network of French laboratories recently found a 31% reduction in cases of pneumococcal bacteraemia in children <2 years old, including pneumococcal meningitis.²⁷ However, variations in reporting rates, estimated

Figure 2 Annual incidence of paediatric pneumococcal meningitis according to age.

at 61–79%, may have contributed to this result.^{4 26 27} Our study did not include suspected bacterial meningitides without positive bacteriology, since inclusion criteria required laboratory confirmation. Patients' characteristics were similar to those usually reported.³ Data concerning pneumococcal serotypes are less informative, since less than two thirds of strains were sent to the national reference centre for serotyping (except in 2005). Only a few strains were serotyped per year, with inconclusive results. Data for the year 2005 require further confirmation.

Although the PCV7 coverage rate is steadily increasing in France, it was still low in June 2004, when 41% of children had been vaccinated; only 27% had had three doses by the age of 6 months.¹¹ In 2005, it was estimated from the number of doses sold that 63% of children <1 year old had been vaccinated nationwide.²⁸ In May 2006, indications in France were simplified to cover every child <2 years old, which should increase the number of children vaccinated.²⁸

Our results are also important because pneumococcal resistance most often affects children <2 years old: 71% of pneumococcal strains are not susceptible to penicillin and 18% are resistant in French children with invasive infections.²⁵ In the United States, a significant decrease in pneumococcal resistance has been noted since widespread pneumococcal vaccination began.^{14 22} A reduction in antibiotic-resistant pneumococcal strains has also been observed in France, with multiple drug resistance dropping from 15.4% in 2001 to 6.7% in 2004 among nasopharyngeal serotype samples from children aged 6–24 months with otitis.²⁹ Nasopharyngeal carriage of non-vaccine serotypes with a normal or reduced sensitivity to penicillin has been noted in young children,³⁰ and recent studies report an increase in invasive pneumococcal diseases from new serotypes.^{31–33} Further surveillance and the introduction of new conjugate vaccines are needed to maximise the benefits of the conjugate pneumococcal vaccine.

The reduction in the incidence rate of pneumococcal meningitis between 2001 and 2005 in northern France must be confirmed by further local surveillance and by the national observatory of bacterial meningitis. Widespread extension of this PCV7 coverage rate will facilitate further reduction, unless new serotypes replace those currently in the vaccine.

ACKNOWLEDGEMENTS

We are grateful to the paediatricians and microbiologists in northern France participating in the Hospital Network for Evaluating the Management of Common Childhood Diseases who contributed to the present study: Dr Akitani, Seclin Hospital; Dr Audry-Degardin, Valenciennes Hospital; Dr Blondiaux, Cambrai Hospital; Dr Chenaud, Tourcoing Hospital; Dr Delepouille, Dunkerque Hospital; Dr Devouge, Arras Hospital; Dr El Kohen, Lille–Saint-Vincent-de-Paul Hospital; Dr Evrard, Boulogne Hospital; Dr Glowacki, Armentières Hospital; Dr Gnansoungou, Maubeuge Hospital; Dr Guilly, Saint-Omer Hospital; Dr

What is already known on this topic

- The impact of the PCV7 on the incidence of meningitis and other invasive pneumococcal diseases has been clearly demonstrated in North America and Australia.
- Given the differences in policies, vaccination schedules, vaccine coverage rates and serotype distributions in different countries, studies of the effects of this vaccine in other countries are essential.

What this study adds

- This is the first study in Europe to demonstrate that the incidence of pneumococcal meningitis has decreased between 2001 and 2005 among children <18 years old, with a 53% reduction (95% CI 31 to 74) since the implementation of PCV7.
- Only among children <2 years old was the decrease in pneumococcal meningitis statistically significant (82% reduction, 95% CI 52 to 95; $p=0.03$).

Louf, Montreuil-sur-mer Hospital; Dr Martinet, Béthune Hospital; Dr Pierre, Roubaix Hospital; Dr Racoussot, Douai Hospital; Dr Renault, Calais Hospital; and Dr Vanlaeys, Lens Hospital.

Many thanks to Dr Varon from the Centre National de Référence du Pneumocoque, Georges Pompidou European Hospital, Paris, for providing pneumococcal serotypes for patients of this cohort study.

Authors' affiliations

F Dubos, I Marechal, M Aurel, A Martinot, Paediatric Emergency and Infectious Diseases Unit, Department of Paediatrics, Jeanne de Flandre Hospital and Lille-2 University, Lille, France

M O Husson, EA 3925, Department of Microbiology, Bâtiment Paul Boulanger and Lille-2 University, Lille, France

C Courouble, Regional Department of Medical Information, Dr Schaffner Hospital, Lens, France

Funding: None.

Competing interests: None.

REFERENCES

- Swartz MN. Bacterial meningitis - a view of the past 90 years. *N Engl J Med* 2004;**351**:1826-8.
- Jefferson T, Ferroni E, Curtale F, et al. Streptococcus pneumoniae in western Europe: serotype distribution and incidence in children less than 2 years old. *Lancet Infect Dis* 2006;**6**:405-10.
- Bingen E, Levy C, De la Rocque F, et al. Bacterial meningitis in children: a French prospective study. *Clin Infect Dis* 2005;**41**:1059-63.
- Perrocheau A, De Benoist AC, Six C, et al. Epidemiology of bacterial meningitis in France in 1999. *Ann Med Interne* 2002;**153**:311-17.
- Arditi M, Mason EO, Bradley JS, et al. Three-year multicenter surveillance of pneumococcal meningitis in children: clinical characteristics, and outcome related to penicillin susceptibility and dexamethasone use. *Pediatrics* 1998;**102**:1087-97.
- Bohr VA, Rasmussen N. Neurological sequelae and fatality as prognostic measures in 875 cases of bacterial meningitis. *Dan Med Bull* 1988;**35**:92-5.
- Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatr Infect Dis J* 2000;**19**:187-95.
- Eskola J. Immunogenicity of pneumococcal conjugate vaccines. *Pediatr Infect Dis J* 2000;**19**:388-93.
- Feikin DR, Klugman KP. Historical changes in pneumococcal serogroup distribution: implications for the era of pneumococcal conjugate vaccines. *Clin Infect Dis* 2002;**35**:547-55.
- Le Conseil Supérieur d'Hygiène Publique de France. Avis du Conseil Supérieur d'Hygiène Publique de France du 8 mars 2002, relatif à la vaccination par le vaccin pneumococcique heptavalent conjugué (Prevenar). www.sante.gouv.fr/htm/dossiers/cshpf/a_mt_080302_pneumo_conjugué.pdf (accessed 16 August 2007).
- Cohen R, Gaudelus J, Peixoto O. Antipneumococcal conjugate vaccine: estimation of the target population. Survey among 1739 mothers. *Méd Enfance* 2005;**25**:237-42.
- Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med* 2001;**344**:403-9.
- Black SB, Shinefield HR, Ling S, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. *Pediatr Infect Dis J* 2002;**21**:810-15.
- Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med* 2003;**348**:1737-46.
- Kellner JD, Church DL, MacDonald J, et al. Progress in the prevention of pneumococcal infection. *CMAJ* 2005;**173**:1149-51.
- Roche P, Krause V, Cook H, et al. Invasive pneumococcal disease in Australia, 2005. *Commun Dis Intell* 2007;**31**:86-100.
- Nigrovic LE, Kuppermann N, Malley R. Development and validation of a multivariable predictive model to distinguish bacterial from aseptic meningitis in children in the post-Haemophilus influenzae era. *Pediatrics* 2002;**110**:712-19.
- Greenlee JE. Approach to diagnosis of meningitis. *Infect Dis Clin North Am* 1990;**4**:583-98.
- Bonsu BK, Harper MB. Differentiating acute bacterial meningitis from acute viral meningitis among children with cerebrospinal fluid pleocytosis: a multivariable regression model. *Pediatr Infect Dis J* 2004;**23**:511-17.
- Chao A, Tsay PK, Lin SH, et al. The applications of capture-recapture models to epidemiological data. *Stat Med* 2001;**20**:3123-57.
- Hsu K, Pelton S, Karumuri S, et al. Population-based surveillance for childhood invasive pneumococcal disease in the era of conjugate vaccine. *Pediatr Infect Dis J* 2005;**24**:17-23.
- Black S, Shinefield H, Baxter R, et al. Postlicensure surveillance for pneumococcal invasive disease after use of heptavalent pneumococcal conjugate vaccine in Northern California Kaiser Permanente. *Pediatr Infect Dis J* 2004;**23**:485-9.
- Poehling KA, Talbot TR, Griffin MR, et al. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. *JAMA* 2006;**295**:1668-74.
- Centers for Disease Control and Prevention (CDC). Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease--United States, 1998-2003. *MMWR Morb Mortal Wkly Rep* 2005;**54**:893-7.
- Dait C, Loukil C, Geslin P, et al. Phenotypic and genetic diversity of invasive pneumococcal isolates recovered from French children. *J Clin Microbiol* 2002;**40**:2994-8.
- Perrocheau A, Doyle A, Bernillon P, et al. Estimation du nombre total de méningites à pneumocoque de l'enfant, par la méthode capture-recapture à 3 sources, France, 2001-2002. *Bull Epidemiol Hebd* 2006;**2-3**:16-18.
- Lepoutre A, Georges S, Varon E, et al. Evolution of pneumococcal invasive disease incidence, France, 2005. *Bull Epidemiol Hebd* 2007;**5**:37-9.
- Le Conseil Supérieur d'Hygiène Publique de France. Avis du Conseil Supérieur d'Hygiène Publique de France du 19 mai 2006, relatif à la vaccination par le vaccin anti-pneumococcique conjugué chez les enfants de moins de deux ans et les enfants de deux à cinq ans. www.sante.gouv.fr/htm/dossiers/cshpf/a_mt_190506_pneumo_enf.pdf (accessed March 12, 2007).
- Cohen R, Levy C, De la Rocque F, et al. French national survey of nasopharyngeal carriage of Streptococcus pneumoniae among infants and toddlers suffering from acute otitis media. *Pediatr Infect Dis J* 2006;**25**:1001-7.
- Huang SS, Platt R, Rifas-Shiman SL, et al. Post-PCV7 changes in colonizing pneumococcal serotypes in 16 Massachusetts communities, 2001 and 2004. *Pediatrics* 2005;**116**:e408-13.
- Kyaw MH, Lynfield R, Schaffner W, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant Streptococcus pneumoniae. *N Engl J Med* 2006;**354**:1455-63.
- Kaplan SL, Mason EO, Wald ER, et al. Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. *Pediatrics* 2004;**113**:443-9.
- Hanage WP, Huang SS, Lipsitch M, et al. Diversity and antibiotic resistance among nonvaccine serotypes of Streptococcus pneumoniae carriage isolates in the post-heptavalent conjugate vaccine era. *J Infect Dis* 2007;**195**:347-52.