Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study

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Summary

Background **When seven-valent pneumococcal conjugate vaccine was introduced in the USA, many children were vaccinated on schedules that differed from those tested in clinical trials. Our aim was to assess the effectiveness of the vaccine against various pneumococcal serotypes, and to measure the effectiveness of the recommended dose schedule and of catch-up and incomplete schedules.**

Methods **Invasive disease, defined as isolation of pneumococcus from a sterile site, was identified in children aged 3–59 months through the US Centers for Disease Control and Prevention's Active Bacterial Core surveillance. We tested isolates for serotype and antimicrobial susceptibility. Three controls, matched for age and zip code were selected for each case. We calculated the matched odds ratio for vaccination using conditional logistic regression, controlling for underlying conditions. Vaccine effectiveness was calculated as one minus the adjusted matched odds ratio times 100%.**

Findings **We enrolled 782 cases and 2512 controls. Effectiveness of one or more doses against vaccine serotypes was 96% (95% CI 93–98) in healthy children and 81% (57–92) in those with coexisting disorders. It was 76% (63–85) against infections that were not susceptible to penicillin. Vaccination prevented disease caused by all seven vaccine serotypes, and by vaccine-related serotype 6A. Several schedules were more protective than no vaccination; three infant doses with a booster were more protective against vaccine-type disease than were three infant doses alone (p=0·0323).**

Interpretation **The seven-valent pneumococcal conjugate vaccine prevents invasive disease in both healthy and chronically ill children. The vaccine is effective when used with various non-standard schedules.**

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See Comment page 1469

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Introduction

Seven-valent pneumococcal conjugate vaccine was designed to prevent pneumococcal disease in young children. In randomised, blinded, controlled clinical trials of this vaccine and a closely related nine-valent version, the vaccines were highly effective against invasive infections,[1–4] moderately so against pneumonia,[3–5] and somewhat so against otitis media.[6] On the basis of such evidence, the seven-valent vaccine was licensed to prevent pneumococcal disease in infants in the USA and was recommended for use in all children younger than 2 years and in children aged 2–4 years in a high-risk category.[7,8]

After licensure, health-care providers began using the vaccine, with various schedules. Providers gave doses to infants at ages 2 months, 4 months, 6 months, and 12–15 months, according to the four-dose schedule developed in clinical trials of the seven-valent vaccine, and used several recommended but largely untested catch-up schedules[7] in older infants and toddlers. Between August, 2001, and September, 2004, the seven-valent vaccine was often in short supply, and health-care providers were frequently unable to give the recommended number of doses.[9] Nonetheless, surveillance data indicated that vaccine introduction substantially diminished the burden of invasive disease.[10–12]

To assess the effectiveness of the seven-valent pneumococcal conjugate vaccine we did a matched case-control study. Our primary objective was to measure effectiveness of pneumococcal conjugate vaccine against invasive disease caused by various pneumococcal strains, including the seven vaccine serotypes in children 3–59 months old, and to assess effectiveness of various schedules.

Methods

Study population

Cases of invasive pneumococcal disease were identified through the Active Bacterial Core Surveillance (ABCS). This population and laboratory based surveillance system is operated by the US Centers for Disease Control and Prevention (CDC) as part of its Emerging Infections Program Network.[13] The surveillance area was defined to include cases from San Francisco, California; Denver, Colorado; Connecticut state; Atlanta, Georgia; Minnesota (Minneapolis and Saint Paul in 2001 and the entire state from the beginning of 2002); Rochester and Albany, New York; Portland, Oregon; and 11 counties in Tennessee.

Eligible children were those younger than 2 years with onset of invasive disease between Jan 1, 2001, and June 30, 2003, and children aged 2–4 years with onset between Jan 1, 2001, and May 31, 2004. According to 2002 census figures, the designated surveillance areas included about 1·7 million children younger than 5 years, including 698 960 younger than 2 years and 991 499 aged 2–4 years. Thus our study encompassed the equivalent of about 5 million child-years.

Cases with invasive pneumococcal disease were defined as those from whom *Streptococcus pneumoniae* could be isolated from usually sterile body sites. To identify such cases, we periodically contacted all clinical microbiology laboratories in the surveillance areas, and audited laboratory records at least every 6 months to ensure complete reporting. Pneumococcal isolates were sent to reference laboratories, and serotyped with the Quellung reaction. Isolates were tested at CDC, except those from Minnesota, which were tested by the local Department of Health. We classified pneumococci as vaccine-type strains if they matched the serotypes in the conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F), or as vaccine-related strains if their serotypes were within the same serogroup as vaccine-type strains (6A, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C, 23A, and 23B). All other pneumococcal serotypes were designated non-vaccine types.

All isolates underwent antimicrobial-susceptibility testing with the broth microdilution method at CDC, the Minnesota Department of Health, or the University of Texas Health Science Center at San Antonio. Isolates were defined as susceptible or non-susceptible according to 2006 definitions of the Clinical and Laboratory Standards Institute.[14] Strains that were not susceptible to penicillin (minimum inhibitory concentration ≥0·12 μg/mL) and to two other drug classes were regarded as multidrug-resistant strains.

Eligibility criteria were residence in an ABCS area, presence of invasive pneumococcal disease, age between 3 months and 59 months at the time of illness, and availability of isolate serotyping. Study personnel used a standard protocol to enrol children, using at least three search methods to identify telephone numbers and 15 attempts to contact the parents on different days and at various times. Children whose parents gave oral informed consent were enrolled; written consent was also obtained in San Francisco, Minnesota, and Connecticut. We excluded episodes of recurrent invasive disease to ensure that children could be enrolled in the study only once. We restricted the study to families with telephones.

For every enrolled child, a list of 15 potential controls was generated from birth-certificate registries. The list included children residing in ABCS areas who were born within 2 weeks of the enrolled child and whose reported postal zip code at birth matched the enrolled child's zip code. From this list, the child closest in age to the case was approached first. Study personnel used the same standard protocols to enrol controls as those used for children with disease. Controls were enrolled if a parent or guardian provided oral or written informed consent. We sought to enrol three controls per case.

Data collection

For both cases and controls, study personnel interviewed parents by phone to elicit household characteristics, such as number of siblings, presence of chronic medical disorders, use of breastfeeding, day-care attendance, and exposure to cigarette smoke. The aim was to gather data for the month before the date when the case child's pneumococcal culture was obtained. Interviewers were aware of case or control status. Parents were also asked to provide the name and address of their child's main health-care provider and of any other places where the child might have received vaccines. For cases and controls, we noted details of vaccination with seven-valent pneumococcal conjugate vaccine (Prevnar, Wyeth Lederle Vaccines, Philadelphia, USA), including number of doses and dates of vaccination. Study personnel contacted these providers to obtain a medical and vaccination history for every child. In Tennessee, Georgia, and Oregon, vaccination registries were also used to verify vaccination histories. The study protocol was approved by institutional review boards at CDC and at all ABCS sites.

Statistical analysis

Data were collated and aggregated at CDC. Exclusion criteria for cases and controls included absence of verifiable written records of vaccination history, previous enrolment (or enrolment of a twin), and enrolment more than 120 days after the date when the child's pneumococcal culture was obtained. We accepted vaccination histories from providers or parents for children whose records showed no doses of pneumococcal vaccine. Analyses were done with SAS statistical software (version 9.1). We used data from the ABCS report form and χ^2 analysis to compare characteristics of children who were enrolled with those who were not. For both cases and controls, a dose of vaccine was counted if it had been received at least 14 days before onset of illness. We used conditional logistic regression to calculate the matched odds ratio of vaccination (versus no vaccination) in cases and controls, controlling for the presence of underlying disorders and checking for colinearity and two-way interactions. To check for possible confounding, the models were repeated, with control for race, sex, day-care attendance, breastfeeding, low birthweight, and vaccination against diphtheria, tetanus, and pertussis. Vaccine effectiveness was calculated as one minus the adjusted matched odds ratio×100%.

We also compared vaccine schedules directly, using conditional logistic regression, controlling for underlying disorders. For these analyses we reported the odds ratios

for disease for one schedule relative to another. For all analyses, p values less than 0·05 were regarded as significant.

Role of the funding source

Funding for the study was provided by CDC's Antimicrobial Resistance Working Group, CDC's Emerging Infections Program, and the US National Vaccine Program Office. These study sponsors had no role in the design or implementation of the study, analysis of data, or reporting of the results. 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

We identified 1267 children with invasive pneumococcal disease during the period under study. Of these children, 485 (38%) were not enrolled: 146 (12%) had no isolate available for serotyping; 113 (9%) could not be located; the parents of 161 (13%) refused to allow them to participate; matched controls could not be enrolled for 11 (1%); and 16 (1%) lacked a confirmed vaccination history. A further 38 (3%) were not enrolled for other reasons, such as identification more than 120 days after culture date or difficulty in obtaining consent because of language barriers. The remaining 782 children (62% of the total number with invasive disease) were included in our analysis. The median age of enrolled children was about 21 months and about 40% were female (table 1). According to data from the ABCS case report form, enrolled children were of similar age to those with invasive disease who were not enrolled, but were more likely to be white (424/782, 54% *vs* 199/485, 41%, p<0·001) and were less likely to have died from their illness (6/782, 0·8% *vs* 13/485, 2·7%, p=0·006).

The distribution of serotypes, clinical syndromes, and need for hospital treatment for invasive pneumococcal disease were much the same in enrolled and non-enrolled groups. For enrolled children with invasive disease, the most common clinical syndrome was bacteraemia without a focus (401, 51%), followed by pneumonia with bacteraemia (237, 30%), and meningitis (65, 8%). More than half (464, 59%) were treated for their pneumococcal infection as outpatients. Nearly half (353, 45%) had disease caused by one of the seven vaccine serotypes, of which serotypes 14 and 19F were the most common (figure). 65 children infected with vaccine serotypes had received one or more doses of conjugate vaccine and 27 three or four doses. In those receiving three or four doses, the most common vaccine serotypes were 19F (in 16) and 4 (in six). Of the total isolates, 30% were not susceptible to penicillin and 21% had decreased susceptibility to three or more antimicrobials.

We identified 8018 children as potential controls, of whom 3824 (48%) could not be located, 1413 (18%) refused to participate, and 182 (2%) were not enrolled for other reasons, such as no longer living in an ABCS area, having a twin already enrolled, being excluded by language, or identification more than 120 days after the date when the case's pneumococcal culture was obtained. Vaccination history could not be confirmed for 87 (1%) controls. The remaining 2512 controls (29% of those initially identified) were included in the analysis. The

	Cases (n=782)	Controls (n=2512)	p (matched)
Age (months)	21·0 (2–60)	21·0 (2–60)	
Race			
White	455 (58%)	1740 (69%)	Referent
Black	198 (25%)	415 (17%)	<0·0001
Other/unknown	129 (17%)	357 (14%)	<0·0001
Ethnicity*			
Hispanic	127 (16%)	343 (14%)	0·1060
Male	462 (59%)	1259 (50%)	<0·0001
Chronic illness†	88 (11%)	105 (4%)	<0·0001
Immunocompromising disorder‡	85 (11%)	63 (3%)	<0·0001
Birthweight <2500 g	75 (10%)	169 (7%)	0·0142
Exposure to smoking in household	254 (33%)	616 (25%)	<0·0001
Day-care attendance	396 (51%)	955 (38%)	<0·0001
History of breastfeeding	528 (68%)	1850 (74%)	0·0013
≥3 doses *Haemophilus influenzae* type b vaccine	569 (73%)	1914 (76%)	0·0014
≥3 doses DTaP vaccine	640 (82%)	2163 (86%)	<0·0001
≥1 dose pneumococcal conjugate vaccine	393 (50%)	1690 (67%)	<0·0001
≥3 doses pneumococcal conjugate vaccine	211 (27%)	913 (36%)	<0·0001

Data are median (range) or number (%). DTaP=diphtheria, tetanus, acellular pertussis vaccine. *Race and ethnicity are treated as separate and distinct groupings in official censuses in the USA; ethnicity is either Hispanic or non-Hispanic. †Defined as: congenital heart disease (34 [4·4%] cases and 38 [1 ·5%] controls), chronic lung disorders (10 [1 ·3%], 14 [0·6%]), kidney disease without dialysis (6 [0·8%], 6 [0·2%]), diabetes (0, 3 [0·1%]), and other chronic illnesses (35 [4·5%], 40 [1·6%]). ‡Defined as: systemic steroid use (72 [9·0%], 113 [4·5%]), immune system disorder or HIV/AIDS (22 [2·8%], 6 [0·2%]), sickle-cell disease (8 [1·0%], 4 [0·2%]), nephrotic syndrome or kidney disease with dialysis (7 [0·9%], 2 [0·1%]), bone-marrow or organ transplant (6 [0·8%], 0), and asplenia (3 [0·4%], 2 [0·1%]).

Table 1: **Comparison of characteristics of cases and controls included in the analysis**

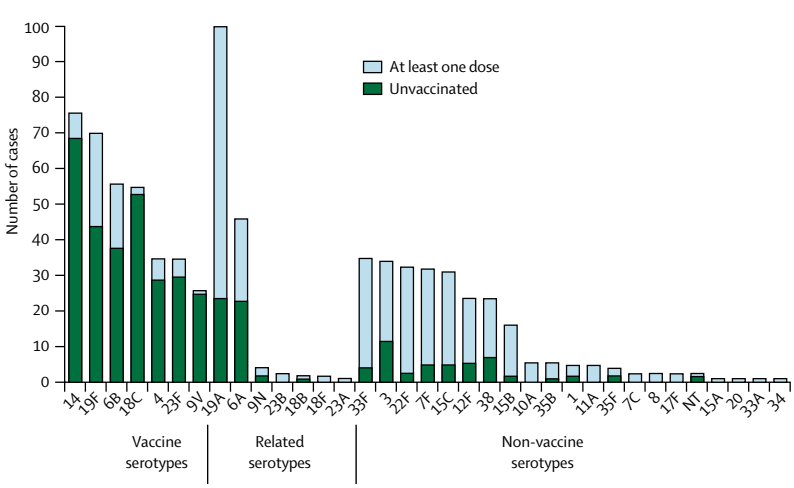

Figure: **Number of cases included in the analysis by serotype and vaccination status (n=782)**

	Vaccine effectiveness	95% CI
All serotypes		
All children	72%	65% to 78%
Healthy children	71%	63% to 78%
Comorbid disorders	77%	62% to 87%
Vaccine types		
All children	..*	
Healthy children	96%	93% to 98%
Comorbid disorders	81%	57% to 92%
Vaccine-related types		
All children	43%	6% to 66%
Healthy children	44%	5% to 67%
Comorbid disorders	35%	−151% to 83%
Non-vaccine types		
All children	..†	
Healthy children	−36%	−122% to 17%
Comorbid disorders	77%	32% to 92%

*Not calculated. p=0·0014 for interaction between vaccination and underlying conditions in the model, so overall effectiveness is not presented. †Not calculated. p=0·0017 for interaction between vaccination and underlying conditions in the model.

Table 2: **Effectiveness of one or more doses of pneumococcal conjugate vaccine against invasive disease in children 3–59 months of age by pneumococcal serotype and the presence of chronic illnesses or immunocompromising disorders**

median number of controls was three per case (range one to ten). Interview data showed that the controls were of similar age to cases, but differed in most other characteristics (table 1).

In healthy children, the effectiveness of one or more doses of vaccine against disease caused by one of the seven vaccine serotypes was 96% (95% CI 93–98) when we controlled for underlying disorders. This value did not change when we also controlled for race; sex; day-care attendance; low birthweight; breastfeeding; and vaccination against diphtheria, tetanus, and pertussis. Estimates of effectiveness in healthy children did not differ for those requiring hospital treatment (96%, 88–99) versus outpatient treatment (96%, 92–98), or for those enrolled early compared with others enrolled later in the study (97% for 2001 cases [92–99] *vs* 95% for 2002–04 cases [89–99]). Vaccine effectiveness was also similar for different syndromes; effectiveness point estimates for bacteraemia and bacteraemic pneumonia were 95% (89–98) and 98 (89–99), respectively in healthy children. Effectiveness against meningitis was 96% (95% CI 83–99) and could not be calculated separately for healthy children and those with comorbid disorders. The vaccine was also effective against vaccine-type disease for children with underlying disorders, although less so than for healthy children (table 2).

The effect of seven-valent vaccine on the risk of disease caused by non-vaccine serotypes was modified by the presence of comorbid disorders (table 2). Vaccination did not significantly alter the risk of disease caused by non-vaccine types in healthy children, but vaccine effectiveness was just under 80% against non-vaccine-type disease in children with comorbidities. This result did not change after control for race; sex; day-care attendance; low birthweight; vaccination against diphtheria, tetanus, and pertussis; receipt of 23-valent pneumococcal vaccine (two children); household income; or antibiotic use. Effectiveness against vaccine-related serotypes was about 40% overall, and did not differ significantly in children with underlying disorders.

We also assessed the effectiveness of vaccine against invasive disease for individual serotypes (table 3). Effectiveness was lowest for serotype 19F, although the CIs overlapped for all vaccine serotypes. For vaccine-related types, effectiveness against serotype 6A was fairly close to that of vaccine types (about 75%), whereas the vaccine did not provide much protection against disease caused by serotype 19A. We could not assess effectiveness of vaccine against many non-vaccine types because of small numbers of cases, but vaccination was associated with a significantly higher risk of disease caused by serotype 22F.

Overall effectiveness against disease, irrespective of serotype, was around 70% (table 2), and measured effectiveness against all disease was higher in 2001 (80%, 72–86), when vaccine serotypes accounted for 61% of cases, than in 2002–04 (61%, 45–72), when only 32% of cases of disease were caused by vaccine serotypes.

	Number of discordant sets*	Vaccine effectiveness	95% CI
Vaccine types			
4	19	93%	65% to 99%
6B	32	94%	77% to 98%
9V	20	100%	88% to 100%
14	47	94%	81% to 98%
18C	30	97%	85% to 99%
19F	34	87%	65% to 95%
23F	18	98%	80% to 100%
Vaccine-related types			
6A	26	76%	39% to 90%
19A	46	26%	−45% to 62%
Non-vaccine types			
33F	11	22%	−206% to 80%
3	14	30%	−131% to 79%
22F	13	−899%	−8302% to −19%
7F	12	−22%	−444% to 73%
15C	10	−55	−607% to 66%

*Only case-control sets discordant for exposure of interest (vaccination) contribute to calculations in matched analysis.

Table 3: **Effectiveness of one or more doses of pneumococcal conjugate vaccine against invasive disease in children aged 3–59 months by pneumococcal serotype**

Vaccine effectiveness was 76% (63–85) against disease caused by strains not susceptible to penicillin and 77% (62–86) against multidrug-resistant strains.

Compared with no vaccine, the effectiveness of one dose given at 7 months of age or earlier against vaccine serotypes was just over 70% (table 4). When stratified by time since vaccination, one dose was protective for up to 6 months (84%, 58–94) but we could not show protection 6 months or more after vaccination (33%, −143 to 81). Compared with no vaccine, point estimates for effectiveness of two, three, or four doses when given on an infant schedule were close to each other, with widely overlapping CI and were more effective than a single dose (table 4). Effectiveness of two, three, and four-dose schedules was similar up to 6 months after vaccination (97% [87–99] for 2 doses, 100% [96–100] for 3 doses, and 100% [58–100] for 4 doses) and 6 or more months following vaccination (95% [71–99] for 2 doses, 87% [64–95] for 3 doses, and 100% [93–100] for 4 doses). We examined vaccine effectiveness in children starting their series of doses late in their first year or after their first birthday, and showed that catch-up schedules were also highly effective (table 4).

In a comparison of a schedule of three doses given at up to 7 months of age, with a four-dose infant schedule (three doses up to 7 months and a fourth dose at 12–16 months), the four-dose schedule significantly reduced risk of disease caused by vaccine serotypes (matched odds ratio 0, 0–0·87; table 5). We did not identify significant differences on direct comparisons between other schedules of two, three, and four doses, although small numbers of children vaccinated on some of these schedules restricted our ability to make comparisons.

	Effectiveness	95% CI
Infant schedules*		
1 dose ≤7 months	73%	43% to 87%
2 doses ≤7 months	96%	88% to 99%
3 doses ≤7 months	95%	88% to 98%
1 dose ≤7 months, 1 dose 8–11 months, 1 dose 12–16 months†	100%	88% to 100%
2 doses ≤7 months, 1 dose 12–16 months†	98%	75% to 100%
3 doses ≤7 months, 1 dose 12–16 months†	100%	94% to 100%
1 dose 7–11 months, 2 doses 12–16 months†	98%	83% to 100%
Toddler schedules*		
1 dose 12–23 months	93%	68% to 98%
2 doses 12–23 months†	96%	81% to 99%
1 dose ≥24 months†	94%	49% to 99%

* Vaccine schedules, by months of age at time of doses, are mutually exclusive. †Based on vaccination schedules recommended by the Advisory Committee on Immunization Practices.[7] We could not assess two recommended schedules (two doses 7–11 months plus one dose 12–16 months, and two doses at 24 months or later) because insufficient numbers of cases and controls were vaccinated on those schedules.

Table 4: **Effectiveness of pneumococcal conjugate vaccine against invasive pneumococcal disease caused by vaccine serotypes in children aged 3–59 months by number and timing of doses, compared with no vaccine**

Discussion

The seven-valent conjugate vaccine was protective in children 3–59 months old against disease caused by all seven serotypes contained in the vaccine, against disease caused by antibiotic-resistant strains, and against all invasive pneumococcal disease irrespective of serotype. Our results accord with findings of earlier clinical trials in which seven-valent or nine-valent conjugate vaccine formulations were given in highly controlled settings in which infants were vaccinated on three-dose or four-dose schedules.[1–4] In these clinical trials, effectiveness against disease caused by vaccine serotypes ranged from 65% in children with HIV infection in South Africa[3] to 94% in child members of a health-care system in northern California.[1] In South Africa, lower efficacy was seen in children infected with HIV than in those not infected;[3] we also recorded lower effectiveness in those with chronic illnesses than in healthy children. A trial of the nine-valent vaccine in The Gambia[4] proved its efficacy for serotypes 5, 14, and 23F; we showed that the seven-valent vaccine is effective against disease caused by all seven individual serotypes represented in the vaccine, as well as serotype 6A, which is structurally similar to vaccine serotype 6B. Our findings also show that the conjugate vaccine is highly effective for prevention of invasive disease in children who have been vaccinated on different catch-up schedules and in children who received fewer than the recommended number of doses.

Our data suggest that several schedules afford good individual protection, although we could not show protection for one dose given before 6 months of age against episodes of illness occurring after 6 months or more. The four-dose schedule recommended in the USA has disadvantages because the conjugate vaccine is expensive, and health-care providers and parents prefer that infants receive as few injections as possible.[15] Furthermore, schedules for routine infant immunisations in many parts of the world could more easily accommodate a three-dose series, with either three doses in the first 6 months of life or two doses within 6 months, followed by a booster at 1 year of age. In our study, point estimates of vaccine effectiveness for schedules with two, three, and four doses seemed very similar when assessed against no vaccination. We were unable to identify differences in protective effect of most schedules, although the risk of disease was reduced more by a schedule of three doses within 7 months, plus a booster than by three infant doses without a booster. A schedule of two doses within 7 months, plus a booster, as has been adopted for routine use in the UK and elsewhere, was highly protective compared with no vaccine, but too few children enrolled in our study were vaccinated on this schedule for us to compare its effectiveness directly with other schedules. Clinical trials of the nine-valent formulation in Africa showed that a series of three doses given early in infancy was effective against invasive disease and pneumonia.[3,4]

	Matched, adjusted odds ratio (95% CI)		
	3 doses ≤7 months, no booster*	2 doses ≤7 months, 1 dose 12–16 months*†	2 doses ≤7 months, no booster*
3 doses ≤7 months, 1 dose 12–16 months	0 (0, 0·87)‡	0 (0–10·1)	0 (0–1·54)§
3 doses ≤7 months, no booster		1·5 (0·15–14·6)	1·5 (0·54–4·35)
2 doses ≤7 months, 1 dose 12–16 months†			0·85 (0·08–9·1)

*Referent group. †Only one case and eight controls were vaccinated on this schedule, so the power to make comparisons is limited. ‡p=0·0323; for all other comparisons p>0·05. §p=0·1398.

Table 5: **Direct comparison of different vaccine schedules for risk of invasive disease caused by serotypes included in the seven-valent pneumococcal conjugate vaccine**

An important component of the success of pneumococcal conjugate vaccine has been its ability to prevent the acquisition of carriage of vaccine serotypes in the nasopharynx of vaccinated children.[10,16,17] The vaccine thereby reduces transmission of vaccine-type pneumococci, and protects unvaccinated children and adults from disease, thus producing indirect benefits from vaccination known as herd immunity.[10,16,17] Protection against pneumonia, otitis media, and carriage of vaccine-type strains might require higher antibody titres, and therefore more doses, than does prevention of invasive pneumococcal disease.[18–20] Studies have shown a high rate of production of antibodies after vaccination with two doses before 6 months of age, with a booster dose at 11 or 12 months.[21,22] The antibody response after two doses at or before 6 months of age with a booster was much the same as it was after three doses with a booster.[23]

A rise in vaccine use during our study caused an increase in herd immunity and a reduction in the number of children with vaccine-type disease available for enrolment as the study progressed. In the USA, the estimated number of cases of invasive disease in children younger than 5 years fell from an average of 17 240 per year in 1998–99 to 4454 in 2003.[24] We did not show any difference in effectiveness against vaccine serotypes with time, however, which suggests that herd effects did not confound our ability to measure specific vaccine effectiveness. Effectiveness of the vaccine against all invasive disease, without regard to serotype, diminished in that non-vaccine types accounted for a larger proportion of cases later in the study. As the amount of vaccine-type disease has fallen, a small increase has occurred in the rate of disease caused by serotypes not contained in the conjugate vaccine—in particular disease caused by 19A.[11,25] Serotype 19A was the most common cause of disease in children enrolled in our study. We previously showed that many isolates of this serotype are resistant to several antibiotics.[25] Our results indicated that conjugate vaccine did not protect against disease caused by serotype 19A, even though this serotype is structurally similar to vaccine serotype 19F. In a Finnish trial,[6] vaccination did not prevent otitis media caused by serotype 19A. Since the conjugate vaccine does not provide cross-protection against this important serotype, an antigen targeting serotype 19A should be included in future vaccine formulations. Overall, our findings indicated that vaccinated children were not at greater risk of disease caused by non-vaccine serotypes than were unvaccinated children in our study. However, vaccinated children did have a higher risk of disease caused by the pneumococcal serotype 22F.

We showed that the seven-valent conjugate vaccine was effective against disease caused by antibiotic-resistant strains; this finding lends support to clinical trial results from South Africa[3] and surveillance data from the USA, suggesting that vaccination reduces infections caused by resistant pneumococci.[26–28] The vaccine's effect on resistant infections is not surprising, since five of the seven vaccine serotypes account for most disease caused by resistant pneumococci, and that serotype 6A, a vaccine-related serotype for which the vaccine provides protection, is also commonly resistant.[29] Before the vaccine was licensed, 78% of invasive infections in the USA that were attributable to penicillin-resistant organisms were caused by serotypes contained in the seven-valent conjugate vaccine,[30] and 18 of 26 multidrug-resistant pneumococcal clones reported to cause disease worldwide were vaccine serotypes.[31]

A limitation of case-control studies is their observational nature, which can lead to bias and confounding. We took care to avoid bias in selection of controls, by using rigorous methods to locate and enrol control children. Our participation rates were acceptable. We also controlled for many possible confounders such as known risk factors for disease, and our estimates of effectiveness were not altered by access to vaccines (eg, receipt of diphtheria, tetanus, and pertussis vaccine). Nonetheless, our finding of 77% effectiveness against disease caused by non-vaccine types in children with comorbid disorders was surprising, and might indicate a chance finding or the effect of an unidentified confounding factor. The large size of our study was a strength, and allowed us to assess the effectiveness of individual vaccine serotypes and several different dosing schedules. Nonetheless, our ability to directly compare the protection provided by some schedules relative to others was limited by the small numbers of children who had been vaccinated on some schedules.

Our results indicate that the seven-valent pneumococcal conjugate vaccine has been very effective in practice in the USA. This information adds to evidence indicating that pneumococcal conjugate vaccines have

the potential to greatly reduce the 800 000 to 1 million deaths of children from pneumococcal disease every year.[32] The next challenge is to ensure that conjugate vaccines become part of routine immunisation in more places, especially in developing countries where most pneumococcal deaths in young children occur.

Contributors

All the authors participated in the design, implementation, analysis, and interpretation of the study. C G Whitney was the overall principal investigator, drafted the report, and secured funding. T Pilishvili and E R Zell oversaw data management and conducted the analysis. M M Farley, W Schaffner, A S Craig, R Lynfield, A-C Nyquist, K A Gershman, M Vazquez, N M Bennett, A Reingold, M P Glode, and A Thomas were principal investigators for individual ABCS sites and secured funding. J H Jorgensen and B Beall directed the microbiological laboratory work. A Schuchat was chief of the Respiratory Diseases Branch, overseeing ABCS activities and laboratory work and securing funding for ABCS.

Conflict of interest statement

We declare that we have no conflict of interest, apart from the following: Wyeth paid travel costs for M Farley to two meetings to present data on the epidemiology of pneumococcal disease. A–C Nyquist was a member of the Wyeth Lederle speakers bureau. E Zell owns a small amount of stock in Merck, Pfizer, and Johnson & Johnson. N Bennett serves on a Merck advisory board for zoster vaccine and was funded by Wyeth to give a presentation on pneumococcal disease.

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